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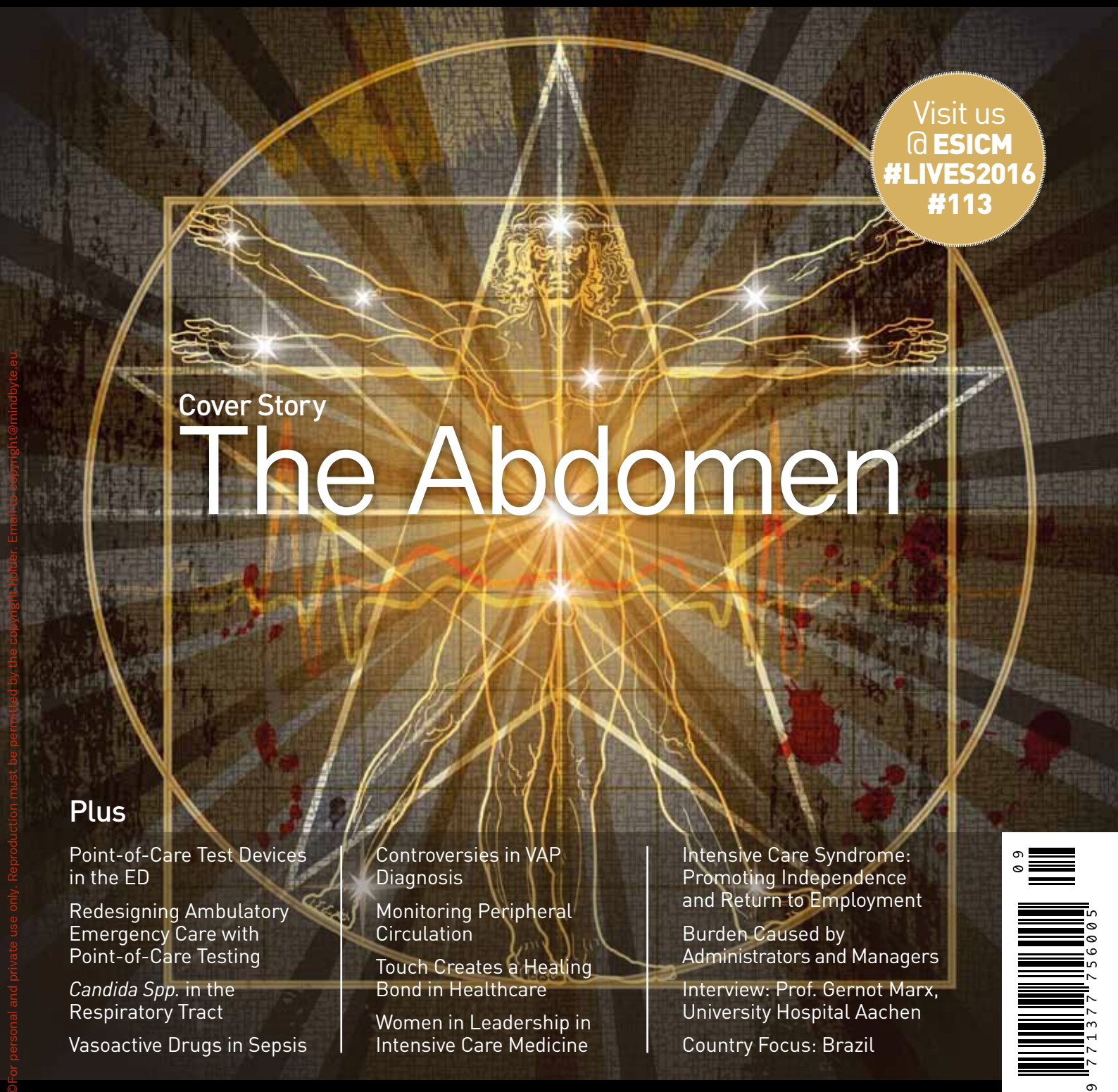

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VASOACTIVE DRUGS IN SEPSIS

In this update review on vasoactive drugs in sepsis, we focus on the most recent data regarding the type of vasopressors that should be used, the timing of infusion, the mean arterial pressure target and the alternative approaches.

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Sepsis and especially septic shock is associated with arterial vasodilation refractory to fluid challenge. The use of vasoactive drugs is strongly recommended by the Surviving Sepsis Campaign (Dellinger et al. 2013) and the European consensus on circulatory shock management and monitoring (Cecconi et al. 2014).

Which Vasopressor Should be Used?

Arterial vasoconstrictive response is mediated by three physiological pathways involving α1-adrenergic receptors, V1a agonist receptors and angiotensin receptors. To date most studies have examined the use of catecholamines (i.e. dopamine, norepinephrine and epinephrine). De Backer et al. (2012) compared survival in patients with septic shock treated with dopamine or norepinephrine in a meta-analysis that included 2,768 patients. In randomised trials dopamine was associated with an increased risk of death (relative risk (RR) 1.12; 95% confidence interval (CI) 1.01–1.20; p=0.035) and cardiac arrhythmias (RR 2.34; 95% CI 1.46 –3.77; p=0.001). The most recent meta-analysis focusing on vasopressors in patients with septic shock analysed data from 32 trials including 3544 patients and compared six vasopressors, alone or in combination (Avni et al. 2015). Compared to dopamine (866 patients, 450 events), norepinephrine (832 patients, 376 events) was associated with a decrease in all-cause mortality (RR 0.89; 95% CI 0.81-0.98), corresponding to an absolute risk reduction of 11% and a number of patients needed to be treated of 9 to avoid one death. Compared to dopamine, norepinephrine was associated with a lower risk of major adverse events and cardiac arrhythmias.

Epinephrine was compared with norepinephrine in two double-blind randomised controlled trials, and did not demonstrate a better survival in patients with septic shock (Annane et al. 2007; Myburgh et al. 2008). Of note, both trials were underpowered, which led the Surviving Sepsis Campaign experts to recommend that epinephrine "may be added to, or substituted, for norepinephrine when an additional agent is needed to maintain adequate blood pressure (grade 2B, weak recommendation based on moderate level of evidence)" (Dellinger et al. 2013).

Catecholamines are associated with an increased risk of cardiac arrhythmias (Asfar et al. 2014) and pro-inflammatory side effects (Andreis and Singer, 2016). A high catecholamine load is associated with a high mortality rate (Dünser et al. 2009a). These data prompted some authors to assess an alternative approach using V1a agonists. The largest trial, published by Russell et al. (2008), compared the administration of norepinephrine versus a combination of low dose of vasopressin plus norepinephrine in 778 patients with septic shock. Overall, there was no difference in survival rate. However, in the a priori defined strata of less severe patients, the vasopressin-treated patients experienced a lower mortality rate and lower renal replacement therapy requirements. The reasons for this beneficial effect in this subgroup of patients with septic shock is unclear, but could be attributed to the so-called "decatecholaminisation effect" (Asfar et al. 2016), as norepinephrine weaning was faster in this subgroup and may have improved patients' outcome by reducing norepinephrine side effects. A recent meta-analysis in patients with septic shock by Oba et al. (2014) showed that norepinephrine and norepinephrine plus low-dose vasopressin was associated with a decreased mortality rate in patients treated with the combination, compared with dopamine (Odds ratio (OR) 0.80 [95% CI 0.65-0.99], 0.69 [0.48-0.98], respectively). In the VANISH trial vasopressin was compared to norepinephrine in terms of renal outcome in patients with septic shock (Gordon et al. 2016). Unfortunately, early administration of vasopressin was not associated with a better renal outcome. However, the confidence interval included a potential clinically important benefit for vasopressin. Efficacy of selepressin, a new V1a agonist, is currently being assessed in patients with septic shock in the Selepressin Evaluation Programme for Sepsis-Induced Shock - Adaptive Clinical Trial (SEPSIS-ACT) that aims to recruit 1800 patients, NCT02508649 (clinicaltrials.gov/ct2/show/NCT02508649).

"we suggest starting norepinephrine after one hour of aggressive fluid resuscitation"

According to the latest published data, norepinephrine is still the first line vasopressor in patients with septic shock.

When to Start?

By definition, septic shock is defined as circulatory impairment associated with hypotension refractory to fluid resuscitation. This definition immediately raises two questions related to the amount of fluid resuscitation and the timing of vasoactive drug initiation. The Surviving Sepsis Campaign recommends in its bundle of resuscitation an amount of 30 mL/Kg (Dellinger et al. 2013). However, this strong recommendation is based on a low level of evidence (grade 1C). The timing of vasoactive drug initiation and amount of fluid resuscitation were recently shown to be strongly associated with mortality in a retrospective study in patients with septic shock (Waechter et al. 2014). The lowest mortality rate was observed for a minimum one litre of fluids administered within the first hour after shock onset and when the vasoactive drug was started within 1-6 hours after the fluid resuscitation. A very early administration of vasoactive drugs within the first hours after hypotension recognition was associated with a higher mortality rate.

Similarly, Bai et al. (2014) reported in a retrospective cohort the effects of early versus late norepinephrine administration. Every one hour of administration delay during the first 6 hours was associated with a 5.3% increase in mortality. The 28-day mortality rate was significantly higher when norepinephrine administration was started ≥ 2 hours after septic shock onset. Finally, Lee et al. (2014) reported in a retrospective study including 594 patients with septic shock that a high proportion of fluid received within the first 3 hours was associated with a high survival rate.

According to the latest published data, we suggest starting norepinephrine after one hour of aggressive fluid resuscitation with at least 1-2 litres of fluids.

Which Mean Arterial Pressure Level Should We Target?

Organ perfusion pressure in shock states is driven by mean arterial pressure both in pressure-regulated organs (i.e. brain, kidney and heart) as well as in non-pressure-regulated organs. The optimal mean arterial pressure target for every patient is unknown and an individualised approach is necessary. As suggested by the Surviving Sepsis Campaign recommendations, the mean arterial pressure target may be set to higher threshold in patients with cardiovascular comorbidities such as chronic hypertension (Dellinger et al. 2013).

Mean Arterial Pressure Target and Mortality

Based on observational studies (Dünser et al. 2009b; Varpula et al. 2005), a threshold of 60 to 65mmHg of mean arterial pressure appears suitable in patients with septic shock. Below these values the mortality rate increases proportionally to the time spent under the threshold. Interestingly, above the threshold of 70 mm Hg, in a retrospective study, Dünser et al. (2009a) did not report any relationship between mean arterial pressure level and mortality in patients with septic shock, but showed a significant relation between catecholamine load and mortality rate. Finally, the Sepsispam trial assessed two levels of mean arterial pressure (65 to 70 mm Hg versus 80 to 85 mm Hg) in patients with septic shock and did not demonstrate beneficial effect on survival (Asfar et al. 2014). However, patients treated with the higher mean arterial pressure target experienced more cardiac arrhythmias probably due to the higher load of catecholamines.

Mean Arterial Pressure and Kidney Function

The kidney circulation is highly autoregulated. Dünser et al. (2009a) reported that, in patients with septic shock, higher target pressures were associated with better renal outcome. In an observational study, Badin et al. (2011) reported that, in patients with septic shock and initial renal function impairment, those who maintained their mean arterial pressure between 72 to 82 mm Hg within the first day of septic shock, had a better renal outcome at day 3. Similarly, Poukkanen et al. (2013) reported in a multicentre study, including 423 patients with severe sepsis, that hypotensive episodes below 73 mm Hg were associated with worse renal outcome. The Sepsispam trial did not report any beneficial effect on kidney function in the overall studied population (Asfar et al. 2014). However, in the a priori defined strata of patients with chronic hypertension, patients who were treated with the higher mean arterial pressure target had less occurrence of renal failure.

According to the latest published data, regarding the effects of mean arterial pressure on mortality, a target of 65 mm Hg is reasonable as suggested by the Surviving Sepsis Campaign recommendations.

Regarding the prevention of kidney failure occurrence, a higher mean arterial pressure target may be recommended in patients with chronic hypertension. However, this should be weighted with the cardiovascular side effects due to the increase in catecholamine load.

Which Inotropic Agent Should We Add?

Haemodynamics targets may not be achieved despite aggressive fluid resuscitation and early vasopressor initiation. Myocardial failure, due to a complex combination of haemodynamic, genetic, molecular, metabolic, and structural alterations is frequent and may often explain this situation. It occurs early in septic shock, but is often silent, as 15 to 50% of patients have overt cardiac failure (Antonucci et al. 2014). Cardiac failure may worsen oxygen delivery to peripheral organs. To maintain the balance between oxygen delivery and oxygen uptake, it is recommended to monitor central venous oxygen or mixed venous oxygen saturations with a target of 70% and 65% respectively (Dellinger et al. 2013 ; Cecconi et al. 2014). Adequate oxygen administration, red blood cells transfusions, fluid challenge to increase cardiac preload and finally inotropic drugs could be used. The Surviving Sepsis Campaign recommends the use of a dobutamine test, up to 20 µg/Kg/min, when cardiac filling pressures are high, associated with myocardial failure, and/or when there are persistent signs of low peripheral perfusion despite adequate fluids and pressure resuscitation (Dellinger et al. 2013).

To date only few data from small randomised control trials with limited outcome are available, making it difficult to come to a conclusion about the role of dobutamine in the treatment of patients with septic shock (Levy et al. 1997; Seguin et al. 2002).

Other inotrope agents have been used to support cardiac function, including phosphodiesterase inhibitors, such as milrinone or enoximone, and calcium sensitisers, such as levosimendan. In addition to their inotropic effects, these drugs also have arterial vasodilatation properties and may worsen hypotension in patients with septic shock. However, these drugs may reduce the catecholamine load and participate in the so-called "decatecholaminisation effect" of patients with septic shock. In addition, extra haemodynamic properties, such as immunomodulator and anti-oxidative effects of levosimendan (Asfar et al. 2016; Hasslacher et al. 2011), are of potential interest and may also improve survival in patients with septic shock. In a recent meta-analysis, Zangrillo et al. (2015) showed a significant decreased mortality in patients with severe sepsis or septic shock treated by levosimendan (59/125 [47%]) as compared with standard inotropic treatment, dobutamine (74/121 [61%]) (risk difference = − 0.14, risk ratio = 0.79 [0.63-0.98], p = 0.03,

numbers needed to treat = 7). The Levosimendan for the Prevention of Acute oRgan Dysfunction in Sepsis (LeoPARDS) trial is a multicentre randomised control trial, performed in the United Kingdom, aimed at comparing levosimendan for 24 hours versus placebo within 24 hours of septic shock onset (Orme et al. 2014). The recruitment of patients is now completed. The results will probably help us to better delineate levosimendan indications.

Dobutamine remains the first line inotropic drug according to the Surviving Sepsis Campaign recommendations. However, this statement may be challenged by the results of the LeoPARDS trial assessing levosimendan efficacy.

Conclusion

We have focused on the recent literature related to the use of vasoactive drugs in patients with septic shock. Recent publications have improved our knowledge regarding norepinephrine, which is still the first line vasoactive drug. To date, the Surviving Sepsis Campaign guidelines (Dellinger et al. 2013) are still relevant. The ongoing trials related to the use of vasoactive drugs in patients with septic shock may alter these recommendations. ■

Conflict of Interest

Simon Bocher declares that he has no conflict of interest. François Beloncle declares that he has no conflict of interest. Pierre Asfar declares that he has no conflict of interest.

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