



# Vasopressors in real-life: are they all equivalent?

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Sepsis remains a major health problem, with an estimated incidence of 19 million per year worldwide (1) and a mortality rate ranging from 15 to more than 60% (2-4), corresponding to an about 5.3 million of deaths per year.

Hypotension is a hallmark of circulatory dysfunction in septic shock (5). Indeed, a need for vasopressors to maintain a mean arterial pressure (MAP)  $\geq 65$  mmHg is required to diagnose septic shock according to current definition (5,6).

When fluid resuscitation alone is insufficient to restore an adequate tissue perfusion, vasopressor administration is recommended. Current international guidelines recommend norepinephrine as first-line vasopressor agent to treat hypotension, while vasopressin, epinephrine, dopamine and phenylephrine are all considered second choices (7).

Norepinephrine is an endogenous catecholamine with a strong stimulating activity on  $\alpha$ -adrenergic receptors and a modest on  $\beta$ -receptors (8). Accordingly, it has a potent vasoconstrictor together with a modest positive inotropic and chronotropic effect.

As prolonged exposure to norepinephrine (and catecholamines in general) may have several deleterious effects such as myocardial ischemia and arrhythmias (9,10), alternative agents have been investigated for their efficacy and safety as compared with norepinephrine. Several randomized trials comparing different vasopressors in septic shock has been published, showing no clear benefit of one agent over another, with the possible exception of improved survival and reduced incidence of arrhythmias with norepinephrine as compared with dopamine (11-13).

Dr. Vail and colleagues recently published results of a study investigating the effect of a 2011 national norepinephrine shortage in United States on outcome of patients admitted for septic shock during the same period (14). In their study, they found that the most frequent alternative vasopressor was phenylephrine, a pure  $\alpha$ -adrenergic agonist (15). Interestingly, patients admitted to hospitals affected by norepinephrine shortage, had a higher in-hospital mortality, as compared with periods before and after the shortage.

Although there were some limitations intrinsic to the observational trials, results of this study remains particularly interesting because it allows to test the effect of a therapeutic strategy in a real-world context, i.e., outside the controlled conditions of a RCT (16).

These findings may have several explanations. A simple explanation might be that norepinephrine shortage led to a delay in treatment of septic shock, or to a tighter selection of patients who would receive norepinephrine, with associated worsening of outcome (17).

Another possibility is physicians' and nurses' lack of familiarity with alternative vasopressors. It is well known that experience is critical for good outcome of medical procedures (18). Experience with drug use is also crucial, as we can better foresight the effect of a certain dose in a certain condition, as well as possible side effects. On the contrary, use of unfamiliar drugs may lead to unexpected effects with possible detrimental results (i.e., excessive hypertension or hypotension with vasoactive medications).

This underline the need for novel therapeutic strategies to be tested in real-life setting, and the importance of large, multicenter, pragmatic trials. Indeed, there are several examples of strategies which showed positive results when tested in small, tightly controlled, single-center trials, while proved ineffective or even detrimental in large RCTs (19).

Finally, we should consider that alternative vasopressors have different pharmacological effects as compared with norepinephrine. The most frequently used vasopressor in Vail and colleagues' study was phenylephrine. Phenylephrine is a pure  $\alpha$ -adrenergic agonist, which increases blood pressure through peripheral vasoconstriction, frequently at the cost of a reduced cardiac output through increased afterload (15,20). Furthermore, experimental and clinical data suggests that pure  $\alpha$ -adrenergic agonists have detrimental effects on regional blood flow of critical districts, such as renal and gastrointestinal (21,22). On the contrary, the effect of norepinephrine on  $\beta$ -receptors lead to an increase in cardiac output even in the face of increased afterload, thereby allowing to a better preservation of blood flow to vital organs (15,20). The study by Vail *et al.* does not provide hemodynamic data. However, we can speculate that target MAP remained the same throughout the shortage period, and was maintained with alternative vasopressors use. Thus, these results underline that, although MAP remains a critical parameter, it should not be the only targeted parameter when managing critically ill patients with shock. While maintenance of adequate MAP should be pursued in the early resuscitation phase, subsequent management should also consider additional parameters such as cardiac output and tissue perfusion variables (23,24).

Other alternative vasopressors used in the study by Vail *et al.* and currently recommended as alternative by guidelines were epinephrine, dopamine, and vasopressin (7). Meta-analyses of RCTs suggested that dopamine is associated with worse outcome than norepinephrine, possibly because of the increased myocardial oxygen consumption due to the greater increase in heart rate, or cardiac arrhythmia (7). Epinephrine does not seem to be associated with increased mortality as compared with norepinephrine. However, there are some evidences of decreased splanchnic perfusion, hyperlactatemia, and increase in drug-related adverse events associated with epinephrine use, which is therefore considered a second-line agent (7). Vasopressin is the most attractive alternative agent, as there are some evidences of a possible beneficial effect on kidney function, though an improvement in clinical outcome has not been established (7). It is worth noting that, in the

study by Vail *et al.*, physicians working in hospitals with norepinephrine shortage preferred to use phenylephrine, instead of vasopressin. Possible explanation for this might be the relatively recent introduction of vasopressin as an alternative vasopressor, as compared with phenylephrine [which has been introduced in clinical practice some 60 years ago (15)], and the fear for cardiac and mesenteric ischemia associated with vasopressin administration. As new practices may take years before becoming widespread adopted, it is not surprising that clinicians preferred to rely on an agent that was still more familiar. Regardless of second-line vasopressor chosen, however, study by Vail and colleagues highlight that, despite neutral results from RCTs, as of today alternative vasopressors might be not as effective and safe as norepinephrine.

To summarize, the study by Vail *et al.* allow us to draw several important conclusions:

- (I) Drug shortages should be considered public health crises which require prompt interventions as they can negatively affect patients' outcome, even when alternative drugs are available;
- (II) Although available trials on vasopressors use in septic shock did not report differences in clinical outcomes, data from real-world practice suggest that some differences between vasopressors may exist outside the closed controlled environment of clinical trials;
- (III) Despite search for alternative agents, norepinephrine remains the best vasopressor to treat hemodynamic derangements in septic shock and probably in others types of shock (25).

Public health authorities should focus on developing management strategies to face a drug shortage crisis, while the search for alternative agents should continue.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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