Choosing catecholamine therapy for shock

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Abstract - Shock is one of the leading causes of ICU admission, and is associated with a high risk of death, whatever its cause. Adrenergic agents are the most commonly used vasopressor agents. Although the alpha-adrenergic properties of these agents raise blood pressure, they can also variably stimulate the beta-adrenergic and dopaminergic receptors. Accordingly, these agents have different haemodynamic profiles as well as different metabolic profiles. Minimal beta-adrenergic stimulation may be beneficial in preventing the decrease in cardiac output related to the increase in left ventricular afterload associated with the correction of hypotension. However, excessive beta-adrenergic stimulation (which can occur as the doses of these agents are adjusted for the vasopressor effect can have profound metabolic effects and promote arrhythmias. Whether these differences in haemodynamic and metabolic profiles impact outcome has long been undefined. Two randomized trials comparing dopamine and norepinephrine as the first vasopressor agent raised major concerns on the use of dopamine (which was associated with tachycardia and increased arrhythmic events, and may be associated with an increased risk of death, especially in the subgroup of patients with cardiogenic shock). The place of epinephrine is not well defined: although this agent is associated with tachycardia, increased incidence of arrhythmic events, and undesired metabolic effects, their relevance to outcome has not been well established, as the studies were underpowered or biased by systematic addition of dobutamine. Altogether, these studies suggest that norepinephrine may be the first-choice adrenergic agent.

Keywords - Circulatory failure, adrenergic agents, dopamine, norepinephrine, epinephrine, outcome

Introduction
Whatever its cause, shock is associated with high mortality. Both the severity and the duration of hypotension are associated with a poor outcome. Although the administration of fluids is the first line of therapy, vasopressor agents are frequently administered to keep blood pressure within an acceptable range. Even though organ perfusion is relatively independent of arterial pressure, organ blood flow becomes dependent on arterial pressure when it drops below the autoregulation threshold. However, at the microcirculatory level, the dependence of microvascular perfusion on arterial pressure is less obvious. Indeed, the microcirculatory alterations are relatively independent of arterial pressure [9,10].

What impact could vasopressor agents have on organ perfusion? In normal conditions, the addition of vasopressor agents induces arteriolar vasoconstriction and decrease microvascular blood flow. Interestingly, in experimental septic shock with profound hypotension, vasopressor agents may improve microvascular perfusion [30]. Experimental evidence also suggests that vasopressor agents limit the development of organ dysfunction [36] and prolong survival time [37], though human data is still quite limited. In a series of patients in septic shock, Albanese et al. [1] reported that correction of severe hypotension (mean arterial pressure of 51 mmHg) was associated with an increase in urine output (from 14 to 121 ml/h) and doubled creatinine clearance. Hence, even though vasopressor agents are commonly used, the benefit of correction of hypotension has not been firmly established. In addition, several issues are still largely debated. In particular, the ideal arterial pressure target has not yet been defined. In addition, it is difficult to determine when vasopressor agents should be introduced: early, before fluid resuscitation has been completed, or later, when hypovolemia has been fully corrected.

Adrenergic agents are first-line vasopressor agents. Even though their haemodynamic and metabolic effects have been investigated quite extensively, until recently only limited data on outcome have been available, so that in 2004 a Cochrane group meta-analysis was inconclusive. Accordingly, current guidelines were based mainly on these pharmacologic and haemodynamic trials, proposing norepinephrine or dopamine as first-line agents for septic shock [14], and dopamine followed by norepinephrine for cardiogenic shock [3], with epinephrine always considered to be a second-line agent. Recently, several medium- to large-size randomized controlled trials compared the effects of dopamine, norepinephrine, and epinephrine on the outcome of patients with shock. In this review, we will discuss the effects of the various adrenergic vasopressor agents.

Pharmacologic properties
Adrenergic agents increase blood pressure by stimulating alpha-adrenergic receptors located in resistive arterioles. Globally, epinephrine and norepinephrine are equipotent, so that a similar dose is required to achieve the same arterial pressure level [29]. Dopamine is less potent, as dopamine may fail to correct hypotension at the usual doses. Depending on the series, 25% [8] to 40% [19] of the patients may require the addition of another
agent, often norepinephrine. In contrast, norepinephrine is able to correct hypotension in the vast majority of patients within one hour [28]. Alpha-adrenergic receptor stimulation is also responsible for an increase in left ventricular afterload, potentially contributing to a decrease in cardiac output, and may also decrease regional blood flows, especially in skin, splanchnic, and renal beds. The impairment in splanchnic and renal perfusion does not seem to be present in septic shock [1,5,41].

In addition to the alpha-adrenergic effect, most agents can also variably stimulate beta and dopaminergic receptors, and the stimulation of the receptors is responsible for the differences in haemodynamic and metabolic effects [4].

Beta-adrenergic stimulation is responsible for the inotropic, chronotropic, and lusitropic effects of adrenergic agents. However, excessive adrenergic stimulation may trigger arrhythmic events. In addition, beta-adrenergic stimulation is associated with improvement in splanchnic perfusion [12,13,41] and in microvascular perfusion [9]. Beta-adrenergic stimulation induces important cellular effects: accelerated glycolysis and stimulation of NaKATPase, both contributing to aerobic production of lactate, an increase in blood temperature due to direct thermogenic effect. As a consequence, oxygen consumption also increases. Finally, beta-adrenergic stimulation is also associated with some immunosuppressive effects [39] in addition to directly enhancing bacterial growth [21]. The dose-effect relationship of beta stimulation is interesting: the increase in cardiac output is already present at low doses, and becomes less and less pronounced when the doses are increased further. In contrast, the metabolic effects are minimal at low doses, and increase exponentially as the dose is increased (Figure 1). As the doses of these agents are titrated according to a blood pressure goal, the beta-adrenergic stimulation is uncontrolled, and physicians often fail to realize the extent of this.

Dopaminergic receptors (both DA1 and DA2) are widely distributed throughout the kidney. DA1 receptors are found in the renal vasculature where stimulation results in vasodilation, and also in the tubules where stimulation results in increased cyclic adenosine monophosphate (cAMP) levels, promoting natriuresis and diuresis. Dopamine also stimulates DA2 receptors in the intimal and adventitial layers of the renal vasculature, and dopamine receptors in the gut and brain. Stimulation of these central DA2 receptors is thought to be the cause of the nausea sometimes associated with dopamine administration but also – and more importantly – to its endocrinologic effects. Dopaminergic stimulation suppresses prolactine release, which can markedly affect immune function. Growth hormone release is also impaired, while cortisol secretion seems to be unaffected [38].

Dopamine, norepinephrine, and epinephrine variably stimulate the beta-adrenergic receptor, while phenylephrine is deprived of this action (Table 1). Only dopamine stimulates dopaminergic receptors. As dopamine and norepinephrine have combined and relatively proportional alpha- and beta-adrenergic properties, these agents increase both cardiac output and arterial pressure. Norepinephrine predominantly increases arterial pressure together with a slight increase in or at least preserved cardiac output, and phenylephrine increases arterial pressure together with a slight decrease in cardiac output. These differences in beta-adrenergic stimulation may also lead to differences in regional perfusion.

**Does the haemodynamic or metabolic profile of these agents differ in patients with shock?**

Even though pharmacologic differences predict that the various agents may have variable haemodynamic effects according to the variable associated stimulation of beta-adrenergic and dopaminergic receptors, the impact in shock patients may be lower than expected due to decreased sensitivity of these receptors in critical conditions. The effects that are the most commonly observed are presented below and summarized in Table 2.

**Epinephrine vs norepinephrine**

Even though norepinephrine and epinephrine correct blood pressure in a similar way, their impact on cardiac output may differ. This effect may be especially important at high doses. In patients switched from dopamine to either norepinephrine and

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**Table 1. Stimulation of various adrenergic receptors by the different catecholamines**

<table>
<thead>
<tr>
<th></th>
<th>ALPHA</th>
<th>BETA</th>
<th>DOPA</th>
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<tbody>
<tr>
<td>Dopamine</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>++++</td>
<td>+</td>
<td>/-/-</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>++++</td>
<td>++++</td>
<td>/-/-</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>++++</td>
<td>/-/-</td>
<td>/-/-</td>
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</tbody>
</table>
epinephrine in a random order, epinephrine was associated with a higher cardiac output when high doses were required, while no differences were observed at low doses [11].

Their metabolic profile may also differ. Levy et al. [18] first noticed that, compared to a combination of norepinephrine and dobutamine titrated to reach the same arterial pressure and cardiac output, epinephrine was associated with a transient increase in arterial lactate levels and in gastric PCO2, suggesting impaired gastric perfusion. Other trials confirmed the impairment in splanchnic perfusion with epinephrine compared to norepinephrine [11,25]. However this effect may be transient, as no differences could be observed at 24 hours [18]. In two randomized trials [2,29], each including around 300 patients with septic shock, epinephrine administration was associated with an increase in heart rate and lactate levels and a decrease in arterial pH that lasted two days. Similar results were recently observed in a small series of patients with cardiogenic shock [20]. The increase in lactate levels is of uncertain origin. Even though tissue hypoxia cannot be ruled out, other causes need to be considered, as beta-adrenergic stimulation promotes aerobic glycolysis [15,17].

Finally, epinephrine significantly increases heart rate, while it remain stable with norepinephrine [20,29]. This epinephrine-induced tachycardia is often neglected, but it increases myocardial oxygen demand, which can be particularly unfavourable in patients with ischemic cardiac disease. Furthermore, due to uncontrolled beta stimulation, epinephrine may induce more arrhythmias than norepinephrine. Some trials [20,29] observed a significant increase in arrhythmic events while another [2] failed to do so. Differences in vasopressor doses, the addition of dobutamine, and patient-related factors may play an important role. In a population of patients with cardiogenic shock, the incidence of arrhythmic events increased markedly with epinephrine [20].

**Dopamine vs norepinephrine**

The differences in cardiac output during dopamine or norepinephrine administration may be less pronounced in critically ill patients. While some trials have effectively observed that myocardial contractility is greater when patients receive dopamine compared to norepinephrine [22,35], other trials have found that cardiac output remained unchanged when patients were switched from one agent to the other [11].

Because dopaminergic stimulation is expected to improve splanchnic perfusion, several investigators focused their attention on this region. Compared to norepinephrine, dopamine was associated with either altered or unchanged splanchnic blood flow and gastric PCO2 [11,24].

A final, often neglected, consideration is that dopamine induces tachycardia more than norepinephrine [8,31]. Furthermore, the incidence of arrhythmias also significantly increases in patients receiving dopamine compared to norepinephrine [8,31].

**Phenylephrine vs other agents**

There is only limited data that looks at the effects of phenylephrine. In six patients with septic shock, Rademaker et al. [33] reported that switching from norepinephrine to phenylephrine was associated with a decrease in cardiac output, splanchnic blood flow, and increased gastric PCO2. These effects were reversed when they were switched back to norepinephrine. These data suggested that the small beta-adrenergic effect associated with norepinephrine was associated with a better systemic and splanchnic perfusion. Using a similar design, in a series of 15 patients with septic shock, Morelli et al. [27] observed that the switch to phenylephrine induced an increase in arterial lactate

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**Table 2. Principal haemodynamic and metabolic effects of the various adrenergic vasopressor agents**

<table>
<thead>
<tr>
<th></th>
<th>DOPAMINE</th>
<th>NOREPINEPHRINE</th>
<th>EPINEPHRINE</th>
<th>PHENYLEPHRINE</th>
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<tbody>
<tr>
<td>Heart rate</td>
<td>↑↑</td>
<td>↔</td>
<td>↑↑↑</td>
<td>↔↑↓</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>↑↑</td>
<td>↑</td>
<td>↑↑↑</td>
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<tr>
<td>Splanchnic blood flow</td>
<td>↔↑↑</td>
<td>↑</td>
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<td>↓</td>
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<tr>
<td>Gastric PCO2 gap</td>
<td>↔↑↑</td>
<td>↔</td>
<td>↑↑</td>
<td>↑</td>
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<tr>
<td>Temperature</td>
<td>↔</td>
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<td>↑↑</td>
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<tr>
<td>Glucose</td>
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<tr>
<td>Lactate</td>
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<tr>
<td>pH</td>
<td>↔</td>
<td>↔</td>
<td>↑↑</td>
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<tr>
<td>Hypothalamo-pituitary axis</td>
<td>Altered</td>
<td>↔</td>
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Symbols: ↓ decreased; ↑ increased; ↔ unaffected, minimally affected, or unpredictable effects. The number of arrows indicates the magnitude of the effect.
levels, a decrease in splanchnic perfusion, and a decrease in urinary output that was reversed when patients were switched back to norepinephrine. However, these data were not confirmed in a small randomized trial that included 32 patients [26]. In that trial, patients receiving norepinephrine or phenylephrine reached a similar cardiac index and a similar level of gastric PCO2. Given the small size of the randomized trial, individual confounding factors may play a major role. Accordingly, safety issues regarding the use of phenylephrine still persist.

Impact on outcome
To what extent can these differences in pharmacologic properties affect outcome? The available data only allow a comparison of dopamine, norepinephrine, and epinephrine.

Epinephrine vs norepinephrine
Data from observational studies were inconclusive, mainly because a minority of patients received epinephrine and this was often combined with other drugs, as it is often used as second-line agent. Two recent randomized trials that included 610 patients shed some light on this issue.

In a multi-centre trial in France, Annane et al. [2] compared the effects of epinephrine and norepinephrine in septic shock. These agents were administered in a blind fashion to achieve a mean arterial pressure of at least 70 mmHg. In addition, dobutamine in the norepinephrine group (or its placebo, if the patient was randomized in the epinephrine group) was administered at a dose of 5 mcg/kg/min. This dose was stopped when mean arterial pressure reached 70 mmHg, or increased if the cardiac index was lower than 2.5 L/min.m². This study aimed at demonstrating a 20% absolute reduction in 28-day mortality, from 60% to 40%. Although the trial was scheduled to include 340 patients, the trial was stopped after the inclusion of 330 patients. There was no significant difference in mortality rates at Day 28: 64 (40%) deaths occurred in the epinephrine group and 58 (34%) deaths in the norepinephrine group (p=0.31; relative risk 0.86, 95% CI 0.65–1.14). There was no significant difference in secondary outcome, with a 90-day mortality of 52% in the epinephrine group vs 50% in the norepinephrine group (p=0.73). Adjustment for potential confounding factors did not alter the results. Dobutamine or its placebo was used in 76% of the patients at baseline, 64% at Day 1 and 38% at Day 2, with no difference either in the proportion of patients treated or in dose between the groups, indicating that the investigators perceived the haemodynamic effects to be similar. There were no differences in adverse events, including the rate of arrhythmic events.

Overall, these results suggest that no obvious difference in outcome can be detected between epinephrine and norepinephrine plus dobutamine. Several comments should be made here. First, although there was a 6% absolute (15% relative) reduction of mortality at Day 28 in the norepinephrine group, the trial was totally underpowered to detect such a difference (5,000 patients should have been included). Second, the investigators randomized 330 patients among the 1,591 patients screened, which may represent a selection bias (as also reflected by the lower-than-expected mortality rate in the patients included in the trial). Third, inclusion criteria allowed up to 24 hours of therapy with open-label vasopressor agents before inclusion in the trial, and exposure to other drugs for a significant time may have confounded the results. Theoretically, some patients allocated to one investigational drug may have received the other study drug in an open-label fashion before inclusion. Finally, dobutamine was added in all patients at baseline without any evidence of low cardiac index, and was continued until a mean arterial pressure of 70 mmHg was achieved. As a result, the use of dobutamine was uncommonly high in this trial, and this may have masked some of the differences between the two agents.

A second randomized trial was performed in Australia and New Zealand by Myburgh et al. [29]. The primary outcome of the trial was haemodynamic success, defined as time to achieve the mean arterial pressure goal, while 28-day and 90-day survival were also reported. The authors included patients the attending physician had decided to have their blood pressure increased, which included shock patients (of various origins, but mostly septic shock) as well as patients with subarachnoid haemorrhage (in whom forced hypertension was induced as part of triple-H therapy). The authors randomized 280 patients (among the 636 assessed) to receive either norepinephrine or epinephrine, without adjudication of other agents. Haemodynamic success was similar with both agents, with a time to reach mean arterial pressure goal of 40 vs 35 hours, respectively (p=0.26). There were no differences in 28-day mortality (26% vs 23%, p=0.48). It is interesting to note that the trial drug has had to be stopped prematurely much more frequently in the epinephrine group than in the norepinephrine group (13% vs 3%, p=0.002). The results of this trial are quite difficult to interpret, due to the conjunction of the high exclusion rate for intolerance to the study agent and by the inclusion of non-shocked patients (resulting in a global mortality of only 25%).

At this stage, the issue of the superiority of one agent over the other has not yet been solved, as both trials were underpowered.

Dopamine vs norepinephrine
Several observational data suggest that dopamine may be associated with a worse outcome [8, 23, 34]. In particular, the large Sepsis Occurrence in Acutely Ill Patients (SOAP) observational trial [34] included 1,058 patients in shock, among whom 375 (35%) received dopamine. Patients treated with dopamine had higher ICU (42.9% vs 35.7%, p=0.021), 30-day (44.5% vs 36.9%, p=0.013), and hospital (49.9% vs 41.7%, p=0.011) mortality rates than other patients in shock. These results remain significant after adjustment for other covariates. Similar results were found in the subgroup of patients with septic shock, although significance was marginally lost. Dopamine use was also identified by multivariate analysis as a factor independently associated with increased risk of death (odds ratio: 1.67 [1.19–2.35], p=0.003).

Using a propensity score to limit the influence of confounding factors, Boulain et al. [6] observed that mortality was higher in the septic patients receiving dopamine than in those receiving norepinephrine (28-day mortality of 62% vs 41%, respectively;
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...p=0.006). However, these results were challenged by another large observational study conducted by Povoa et al. [32]. The authors included 458 patients in septic shock, half of these receiving dopamine. Hospital mortality rates were higher in patients receiving norepinephrine than in those receiving dopamine (52% vs 39%, p=0.002). This difference in mortality rate was further exacerbated when the authors analysed patients treated with norepinephrine and dopamine as the sole vasopressor agent (47% vs 20%, p<0.001). This last analysis was confounded by the fact that patients treated with dopamine and requiring a second vasopressor agent were excluded, while this did not occur in the norepinephrine group, as norepinephrine can almost always correct hypotension. Hence, these patients may have had a higher shock severity, associated with a marked increase in mortality rates [19,34]. Altogether, these trials signalled that dopamine may be associated with an increased risk of death compared to norepinephrine, though confounding factors may play a role.

Based on the results of the observational SOAP trial [34], we conducted a large multi-centre double-blind randomized trial investigating the effects of dopamine and norepinephrine as the first-line vasopressor agent in shock [8]. Patients in shock were randomized to receive either dopamine (maximal dose: 20 mcg/kg/min) or norepinephrine (maximal dose: 0.19 mcg/kg/min); if needed, an open-label infusion of norepinephrine (or epinephrine) could be added, without dose limitation. The target blood pressure was left to the discretion of the attending physician, with a recommended mean arterial pressure of 65 mmHg. Based on the results of the SOAP observational trial, we estimated that 765 patients should be included in each group to demonstrate a 15% relative reduction in 28-day mortality. Of the 1,679 patients, 858 received dopamine and 821 received norepinephrine. There were no differences between the two groups at baseline. Septic shock was the main cause of shock (n=1044, 63%), followed by cardiogenic shock (n=280, 17%) and hypovolemic shock (n=263, 16%). Even though hypotension was similarly corrected in both groups, the addition of open-label norepinephrine was more common in the dopamine group than in the norepinephrine group (26% vs 20%, p<0.01). On the other hand, dobutamine use was less frequent in the dopamine group than in norepinephrine group (20% vs 28%, p<0.01), while the doses, when used, were slightly higher in the dopamine group (11 vs 9 mcg/kg/min, p<0.01).

At 28 days, mortality rates were 52.5% in the dopamine group and 48.5% in the norepinephrine group (odds ratio: 1.17 [0.97-1.42], p=0.07). The Kaplan-Meier survival curves provided the same information. Interestingly, a predefined subgroup analysis observed a significant increase in mortality rate in patients with cardiogenic shock. This difference may be related to the dopamine-induced tachycardia and increase in arrhythmic events. It is also interesting to note that there were no differences in the incidence of other adverse events. Although mortality differences in the entire population failed to reach statistical significance, this study raises serious concerns about the safety of dopamine therapy, since dopamine was associated with more arrhythmias and with an increased rate of death in the subgroup of patients with cardiogenic shock, compared to norepinephrine.

Several comments should be made on this trial. First, this is one of the largest trials conducted in patients with shock (including the three relevant subgroups). In addition, external validity of this trial is important, as most of the screened patients were included (1,679/2,011, or 83%), optimizing external validation of the data. Second, the 8% relative reduction in mortality in norepinephrine group is lower than expected, the study was powered to detect a 15% difference, and an effect of this magnitude can thus be excluded. Third, exposure to investigational drugs was maximized: open-label vasopressor prior to randomization was allowed for a maximum of four hours, and 85% of the patients effectively received the trial drug as the first vasopressor agent without prior use of any other vasopressor agent. In addition, the study drug was the last to be weaned, and the study drug was resumed if a new shock episode occurred within 28 days of inclusion.

Similar findings were observed in a single-centre randomized trial published a short time later by Patel et al. [31]. These authors randomized 252 patients in septic shock to receive either dopamine (up to a dose of 20 mcg/kg/min) or norepinephrine (up to a dose of 20 mcg/min); the sample size was computed to detect an absolute difference of 20% in 28-day mortality. The time allowed for open-label use of vasopressor agents prior to randomization was a maximum of 6 hours. If blood pressure was not corrected with these maximal doses or if arrhythmias developed, vasopressin and, if needed, phentylephrine were added. The pressure target was a mean arterial pressure of > 60 mmHg or a systolic arterial pressure of > 90 mmHg. The two groups were comparable at baseline. The mortality rate in the dopamine group was 50% (67/134) as compared to 43% (51/118) in the norepinephrine group (P=0.282). Kaplan-Meier survival curves reported similar information. Importantly, the incidence of arrhythmic events was markedly increased in the dopamine group compared to the norepinephrine group.

Interestingly, these two large randomized trials comparing dopamine and norepinephrine as the first vasopressor agent found a similar trend in improved outcome in the norepinephrine groups compared to the dopamine groups. In addition, both trials reported an increased incidence of arrhythmic events with dopamine. Three meta-analyses have been published, covering the same trials but providing slightly differing results [7,16,40]. In a meta-analysis that included 2,043 patients with any type of shock, Vasu et al. [40] reported that the aggregated risk of death was significantly lower for patients receiving noradrenaline compared to patients randomized to dopamine (RR: 0.91 [0.83-0.99], P=0.028). Although Havel et al. [16] observed a slightly different result (RR: 0.95 [0.87-1.03], p=0.21), these authors evaluated outcome at last follow-up, which ranged from ICU to 12 months, depending on the trial. In addition to increasing heterogeneity, this also decreased the number of patients available for analysis to 1,400. Focusing on patients with septic shock only, De Backer et al. [7] observed in 1,408 patients that the aggregated risk of death was also higher with dopamine.
compared to norepinephrine (RR: 1.10 [1.01-1.20], P=0.035). These results suggest that norepinephrine should be preferred over dopamine for the treatment of shock.

Conclusions
Adrenergic vasopressor agents are used for their alpha-adrenergic properties to correct hypotension in shock states. However, their variable beta-adrenergic and sometimes dopaminergic properties can lead to significant differences in their haemodynamic and metabolic effects, especially at high doses. Although observational studies suggest that differences in outcome may be observed among the different agents, confounding factors have played a role. Recent randomized trials raised major concerns on the use of dopamine, which was associated with tachycardia and increased arrhythmic events, and may be associated with an increased risk of death, especially in the subgroup of patients with cardiogenic shock. The place of epinephrine is not well-defined. Although this agent is associated with tachycardia, increased incidence of arrhythmic events, and undesired metabolic effects, their relevance to outcome has not been well established, as the studies were underpowered or biased by the systematic addition of dobutamine. Altogether, these studies suggest that norepinephrine may be the first-choice adrenergic agent.

References
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