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LESS IS MORE IN INTENSIVE CARE

Less is more: catecholamine-sparing strategies in septic shock

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Noradrenaline, a catecholamine, is the first line agent for the management of septic shock [1] and has been shown to be superior to dopamine [2] and equivalent to adrenaline [3] and vasopressin [4]. High doses of catecholamines are frequently required to reverse shock [5, 6]. While the presence of circulatory shock remains a strong and independent predictor of mortality [7], the use of catecholaminergic agents to reverse shock is associated with adverse events—tachyarrhythmias, thermogenic, metabolic and excess vasoconstriction resulting in tissue ischemia [2, 8]. These adverse effects have led to an interest in adjunctive therapies and catecholamine minimization strategies.

Optimal fluid resuscitation

The first step is optimizing fluid resuscitation. While guidelines recommend optimal filling prior to initiation of vasopressor support [1], the precise endpoints for fluid resuscitation remain unclear. In resource-limited settings in Africa, fluid boluses significantly increased 48-h mortality in critically ill children with impaired perfusion [9]. A positive fluid balance in patients with sepsis is associated with increased mortality [10].

Blood pressure targets

The 2016 Surviving Sepsis guidelines recommend a target of mean arterial pressure (MAP) of 65 mmHg in patients with septic shock requiring vasopressors [1]. A randomized trial comparing MAP targets of 65–75 mmHg with 80–85 mmHg reported no improvement in mortality and a higher rate of arrythmias in the higher target group. In the subgroup of patients with chronic hypertension, the higher target group required less renal replacement therapy (RRT) [8]. A study in the septic ICU population has shown that the odds of mortality and kidney injury increased with hypotension exposure (defined as MAP < 65 mmHg) [7]. Maintaining an MAP > 65 mmHg would be prudent and in accord with the guidelines [1]. Appropriate MAP targets in the later stages of septic shock, and how these could be individualized is currently unknown.

Non-catecholamine vasoconstrictors—vasopressin and analogues

Vasopressin acts as a potent vasoconstrictor via V1a receptors on vascular smooth muscle. The use of vasopressin as an adjunctive therapy in septic shock is associated with reductions in noradrenaline requirements, but has not been associated with improved outcomes [4, 11]. Other vasopressin analogues, such as terlipressin and selepressin, used as adjunctive therapy, result in catecholamine sparing, but no improvement in outcomes [12].

Methylene blue

The use of methylene blue for shock reversal in vasoplegic states has demonstrated short-term improvement in systemic hemodynamics, but is not associated with mortality benefits [13].

Corticosteroids and angiotensin

Three adjunctive therapies have been shown to improve the resolution of shock in sepsis—hydrocortisone, hydrocortisone/fludrocortisone combination, and angiotensin [5, 6, 14]. In health, the actions of angiotensin, hydrocortisone, and aldosterone are linked through complementary and intersecting biological mechanisms. Both hydrocortisone and the combination of hydrocortisone and fludrocortisone have been shown to reverse circulatory shock, reduce the requirement for pressor therapy,

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and result in improved patient centered outcomes. At doses of hydrocortisone used in septic shock, plasma cortisol concentrations approximate 3500 mmol/L, which would be anticipated to be sufficient to activate the mineralocorticoid receptor [15]. Whether fludrocortisone has independent catecholamine, sparing effects is unclear. A factorial design study that compared hydrocortisone plus fludrocortisone with hydrocortisone alone in septic shock did not demonstrate any difference in vasopressor free days between the two groups [16].

Angiotensin II (AT II), part of the Renin–Angiotensin–Aldosterone System, is a product of the enzymatic cleavage of Angiotensin I via the Angiotensin Converting Enzyme and acts via Angiotensin Type 1 Receptor. Its principal action is peripheral vasoconstriction, along with volume expansion, mediated through sodium and water retention (via aldosterone and direct actions on the renal tubules).

Recently, human synthetic stable AT-II has been investigated in critically ill patients with vasodilatory and septic shock. In a Phase III trial(ATHOS-3) by Khanna and colleagues [14], there was a mean reduction of 0.03 ug/kg/h of background vasopressor usage in norepinephrine equivalents, while AT II was administered over a 48-h interventional period of the trial. In addition, more than 70% of patients assigned to AT-II incremented their MAP to at least 75 mmHg or 10 mmHg more than baseline. The trial was not powered to show a reduction in mortality.

Concerns regarding renal vasoconstriction and hypoxia with AT-II were not borne out by a post hoc analysis of ATHOS-3 trial data. In patients with acute kidney injury requiring RRT at study drug initiation, 28-day survival and MAP response were higher, and the rate of RRT liberation was greater in the Angiotensin II group as compared to placebo [17].

Miscellaneous therapies for catecholamine sparing

Extracorporeal blood purification techniques for septic shock have been shown to improve hemodynamic status resulting in reductions in catecholamine requirements, but robust data from clinical trials showing improvements in outcome are lacking [18].

In conclusion, although pooled analysis of data from a systematic review and meta-analysis of RCTS of various non-catecholaminergic vasopressor suggest that treatment with non-catecholaminergic agents improves survival in vasodilatory shock (34% vs. 39%, risk ratio = 0.88, 95% CI = 0.79–0.98, $p = 0.02$), no individual agent has been shown to be associated with improved survival [13]. There is a growing body of evidence to recommend early initiation of pressor therapy based on clinical trials [19].

Table 1 Top 10 research questions on vascular responsiveness in septic shock

Research focus	Key questions
Biological mechanisms	
1. Biology of vascular responsiveness	Elucidating the role of endocrine biomarkers—cortisol, aldosterone and angiotensin and their metabolite biochemistry and their associations with shock reversal and mortality
2. Genomic mechanisms	Understanding the interaction between endocrine biomarkers, their receptor expressions and corticosteroid supplementation
3. Racial variability in response to catecholamines	Racial variability in catecholamine responsiveness has been reported in clinical studies. This question needs to be investigated at a biological level studying catecholamine receptor density, receptor expression and dose response relationships amongst various ethnic groups
4. Genetic variability in response to catecholamines	Delineate the role of catechoamine receptor polymorphisms in vascular responsiveness in septic shock
Clinical focus questions	
5. Developing clinical prediction models for shock reversal	Amalgamation of databases from clinical trials to understand patient demographics, disease severity, hemodynamic data sets, vasopressor dosing, timing of shock reversal and outcome to develop prediction models
6. Guidelines for resuscitation targets for septic shock	Pressure indices Flow indices Microcirculatory parameters
7. Comparisons of catecholamine vs. non-catecholamine pressor agents in septic shock	A head to head comparison in a randomized controlled trial of catecholamine vs. non-catecholaminergic agents in septic shock
8. Identifying the optimal timing for adding a second pressor agent in the management of shock	Determining the dosage and MAP targets at which a second pressor needs to be added
9. Weaning of pressors	Determining the optimal discontinuation sequence of pressors
10. Delineating the role of fludrocortisone	A robust clinical trial comparing hydrocortisone vs. hydrocortisone plus fludrocortisone in patients with septic shock

While catecholamine therapy is associated with adverse effects, there is no high-quality evidence to recommend the use of non-catecholaminergic pressors over catecholamines. In a large epidemiological study in the United States, conducted during a period of norepinephrine shortage, the most commonly administered alternative vasopressor for septic shock was phenylephrine. Hospitalisation for septic shock during periods of norepinephrine shortage was associated with higher in-hospital mortality [20].

The field of vascular responsiveness and shock reversal is hampered by several uncertainties. We outline the top 10 research questions in this area for the next decade (Table 1). Future research focusing on understanding biology of vascular responsiveness, intersection of steroid and angiotensin pathways, deciphering optimal and individualized targets for resuscitation, genetic and racial variability in responses to catecholamines, head-to-head comparisons of the efficacy of catecholamine vs. non-catecholamine pressor agents on mortality, optimal norepinephrine dosage at which to initiate additional pressor therapy in the face of escalating pressor requirements, determining the discontinuation sequence during pressor wean and delineating the role of fludrocortisone will guide the rational management of septic shock.

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Compliance with ethical standards

Conflicts of interest
The authors do not have any financial conflict of interest in association with this manuscript.

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