

Hemodynamics for Adults

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Most of the hemodynamic recommendations below are similar to those published in Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021.¹ Ultimately, adult patients with COVID-19 who require fluid resuscitation or hemodynamic management of shock should be treated and managed as adult patients with septic shock.

Recommendation

- For adults with COVID-19 and shock, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using dynamic parameters, capillary refill time, and/or lactate levels over static parameters to assess fluid responsiveness (**BIIa**).

Rationale

In a systematic review and meta-analysis of 13 randomized clinical trials in intensive care unit (ICU) patients without COVID-19 ($n = 1,652$), the use of dynamic assessment to guide fluid therapy reduced mortality (risk ratio 0.59; 95% CI, 0.42–0.83), ICU length of stay (weighted mean difference -1.16 days; 95% CI, -1.97 to -0.36), and duration of mechanical ventilation (weighted mean difference -2.98 hours; 95% CI, -5.08 to -0.89).² The dynamic parameters used in these trials included stroke volume variation, pulse pressure variation, and stroke volume change after a passive leg raise or fluid challenge. Passive leg raising followed by assessment of pulse pressure variation and stroke volume variation appears to predict fluid responsiveness with the greatest accuracy.³ The static parameters included some components of early goal-directed therapy (e.g., central venous pressure, mean arterial pressure [MAP]).

In patients who did not have COVID-19, resuscitation therapies for shock, as indicated by serum lactate levels, were summarized in a systematic review and meta-analysis of 7 randomized controlled trials ($n = 1,301$).⁴ When compared with therapy guided by central venous oxygen saturation levels, therapy directed by early lactate clearance was associated with a reduction in mortality (relative ratio 0.68; 95% CI, 0.56–0.82), shorter ICU stay (mean difference -1.64 days; 95% CI, -3.23 to -0.05), and shorter duration of mechanical ventilation (mean difference -10.22 hours; 95% CI, -15.94 to -4.50).

Recommendation

- For acute resuscitation in adults who have COVID-19 and shock, there is insufficient evidence for the Panel to recommend either for or against the use of balanced crystalloids, such as Ringer's lactate solution, over normal saline.

Rationale

The composition of sodium, potassium, and chloride found in balanced crystalloids, such as Ringer's lactate solution, is similar to the composition found in extracellular fluid. The use of balanced crystalloids may prevent hyperchloremic metabolic acidosis, which has been associated with administration of large quantities of normal saline.⁵ Observational data have suggested an association between normal saline and acute kidney injury and higher risk of death,⁶ and many Panel members with experience in acute fluid resuscitation use balanced crystalloids.

A pragmatic randomized trial compared the use of balanced and unbalanced crystalloids for intravenous fluid administration in critically ill adults without COVID-19 ($n = 15,802$).⁷ The rate of the composite

outcome of death, new renal-replacement therapy, or persistent renal dysfunction was lower in the balanced crystalloids arm than in the unbalanced crystalloids arm (OR 0.90; 95% CI, 0.82–0.99; $P = 0.04$). A secondary analysis compared outcomes in a subset of patients with sepsis ($n = 1,641$).⁸ Compared to treatment with unbalanced crystalloids, treatment with balanced crystalloids resulted in fewer deaths (aOR 0.74; 95% CI, 0.59–0.93; $P = 0.01$) and more days free of vasopressors and renal replacements.

A subsequent meta-analysis of 21 non-COVID-19 randomized controlled trials ($n = 20,213$), which included the pragmatic trial cited above,⁷ compared balanced crystalloids to 0.9% saline for resuscitation in critically ill adults and children.⁹ The meta-analysis reported nonsignificant differences between the treatment arms for hospital mortality (OR 0.91; 95% CI, 0.83–1.01) and acute kidney injury (OR 0.92; 95% CI, 0.84–1.00). In a trial of more than 11,000 patients who were in the ICU and required fluid resuscitation, the use of balanced fluids, compared with the use of normal saline, did not reduce mortality at 90 days.¹⁰ Similarly, in a large trial of critically ill adults in Australia and New Zealand, the use of balanced crystalloids for fluid therapy, compared with the use of normal saline, did not reduce the incidence of acute kidney injury or the risk of death at 90 days.¹¹

Recommendation

- For acute resuscitation in adults with COVID-19 and shock, the Panel **recommends against** the initial use of **albumin (BI)**.

Rationale

A meta-analysis of 20 non-COVID-19 randomized controlled trials ($n = 13,047$) that compared the use of albumin or fresh-frozen plasma to crystalloids in critically ill patients found no difference in all-cause mortality between the treatment arms.¹² In contrast, a meta-analysis of 17 non-COVID-19 randomized controlled trials ($n = 1,977$) that compared the use of albumin to crystalloids in patients with sepsis reported a reduction in mortality among the patients who received albumin (OR 0.82; 95% CI, 0.67–1.0; $P = 0.047$).¹³ Given the higher cost of albumin and the lack of a definitive clinical benefit, for acute resuscitation in adults with COVID-19 and shock, the Panel **recommends against** the initial use of **albumin (BI)**.

Recommendation

- For adults with COVID-19 and shock, the Panel recommends **norepinephrine** as the first-choice vasopressor (**AI**).

Rationale

Due to its vasoconstrictive effects, norepinephrine increases MAP with little change to heart rate and less increase in stroke volume than dopamine. Dopamine increases MAP and cardiac output, primarily due to increases in stroke volume and heart rate. Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in patients with septic shock. Dopamine may be particularly useful in patients with compromised systolic function, but it causes more tachycardia and may be more arrhythmogenic than norepinephrine.¹⁴ Dopamine may also influence the endocrine response via the hypothalamic pituitary axis and have immunosuppressive effects.¹⁵ A systematic review and meta-analysis of 11 non-COVID-19 randomized controlled trials that compared vasopressors used to treat patients with septic shock found that norepinephrine use resulted in lower all-cause mortality (risk ratio 0.89; 95% CI, 0.81–0.98) and a lower risk of arrhythmias (risk ratio 0.48; 95% CI, 0.40–0.58) than dopamine use.¹⁶ Although the beta-1 activity of dopamine would be useful in patients with myocardial dysfunction, the greater risk of arrhythmias limits its use.^{17,18}

Recommendation

- For adults with COVID-19 and shock, the Panel recommends titrating vasoactive agents and targeting a MAP of 60 to 65 mm Hg over targeting a higher MAP (**BI**).

Rationale

A meta-analysis of individual patient data from 2 non-COVID-19 randomized controlled trials (n = 894) compared higher versus lower blood pressure targets for vasopressor therapy in adult patients with shock.¹⁹ The study reported no significant differences between the higher-target and lower-target arms for 28-day mortality (OR 1.15; 95% CI, 0.87–1.52), 90-day mortality (OR 1.08; 95% CI, 0.84–1.44), myocardial injury (OR 1.47; 95% CI, 0.64–3.56), or limb ischemia (OR 0.92; 95% CI, 0.36–2.10). The risk of arrhythmia was increased in the higher-target arm (OR 2.50; 95% CI, 1.35–4.77).

Similarly, the 65 trial, a randomized controlled trial in patients without COVID-19 (n = 2,463), reported no significant difference in mortality between patients that received vasopressor therapy guided by a target MAP of 60 to 65 mm Hg and those that received treatment guided by a higher, standard-of-care target MAP (41% vs. 43.8%; relative risk 0.93; 95% CI, 0.85–1.03).²⁰ Given the indication of improved outcome with lower MAP targets (and no firm indication of harm), the Panel recommends titrating vasoactive agents and targeting a MAP of 60 to 65 over targeting a higher MAP (**BI**).

Additional Recommendations for Adults With COVID-19 and Shock

- The Panel **recommends against** using hydroxyethyl starches for intravascular volume replacement in adult patients with COVID-19 and sepsis or septic shock (**AI**).
- As a second-line vasopressor, the Panel recommends adding either **vasopressin** (up to 0.03 units/min) (**BIa**) or **epinephrine** (**BIb**) to norepinephrine to raise MAP to the target or adding **vasopressin** (up to 0.03 units/min) (**BIa**) to decrease the norepinephrine dose.
- The Panel **recommends against** using **low-dose dopamine** for renal protection (**AI**).
- The Panel recommends using **dobutamine** in adult patients with COVID-19 who show evidence of cardiac dysfunction and persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents (**BII**).
- The Panel recommends that all adult patients with COVID-19 who require vasopressors have an arterial catheter placed as soon as practical, if resources are available (**BIII**).
- For adult patients with refractory septic shock who have completed a course of corticosteroids to treat COVID-19, the Panel recommends using low-dose corticosteroid therapy (“shock-reversal”) over no corticosteroid therapy (**BIa**).
 - A typical corticosteroid regimen in septic shock is intravenous hydrocortisone 200 mg once daily administered either as an infusion or in intermittent doses. The duration of hydrocortisone therapy is usually a clinical decision.
 - Adult patients who are receiving corticosteroids for COVID-19 are receiving sufficient replacement therapy and do not require additional hydrocortisone.

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