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Precision fluid and vasoactive drug therapy for critically ill patients

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Abstract

There are several clinical practice guidelines concerning the use of fluid and vasoactive drug therapies in critically ill adult patients, but the recommendations in these guidelines are often based on low-quality evidence. Further, some were compiled prior to the publication of landmark clinical trials, particularly in the comparison of balanced crystalloid and normal saline. An important consideration in the treatment of critically ill patients is the application of precision medicine to provide the most effective care to groups of patients most likely to benefit from the therapy. While not currently widely integrated into these practice guidelines, this is a recognized research priority for fluid and vasoactive therapy management. The purpose of this narrative review is to illustrate the evaluation of and challenges with precision fluid and vasoactive therapies in adult critically ill patients. The paper includes a discussion of important investigations published after the release of currently available clinical practice guidelines to provide insight into how recommendations and research priorities may change future guidelines and bedside care.

Keywords

fluid therapy; albumin; normal saline; balanced crystalloids; vasoactive drugs; precision medicine

Introduction

Fluid and vasoactive drug therapies are integral components of supportive care provided to critically ill patients, but the current evidence base is insufficient to develop sophisticated clinical algorithms that would provide for a truly personalized approach to their use that considers genotypic and phenotypic characteristics (i.e., precision medicine). Bringing a personalized/precision medicine approach to the bedside treatment of patients with septic shock is complex, with several research design changes necessary to realize the enticing potential of the approach.[1] For example, most clinical trials of therapies for patients with

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septic shock have not leveraged adaptive designs with predictive and prognostic enrichment strategies.[2] Further, trials published to date have not adequately evaluated hemodynamic phenotyping, a strategy that employs several elements of a personalized/precision fluid and vasoactive drug therapy approach. The concept of hemodynamic phenotyping, which involves an algorithmic sequence of assessments to determine therapeutic management, has been employed at the bedside for a number of years due to its physiologic rationale despite a lack of strong evidence supporting its use.

The purpose of this narrative review is to provide insight into the evaluation and challenges of providing precision fluid and vasoactive therapies to adult critically ill patients. This paper discusses choice of fluid or vasoactive agent, initiation, titration, and de-escalation during the stabilization and deresuscitation phases of circulatory shock. All of these topics are research priorities for fluid resuscitation and vasopressor therapies according to the Surviving Sepsis Campaign Research Committee, including further exploring how targeted/personalized/precision medicine approaches can be applied.[3, 4] When available from published literature, the discussion will include information on genetic/genomic aspects of these therapies.

Clinical practice guidelines serve as the framework for decision-making regarding fluid and vasoactive therapies in critically ill patients. Therefore, recommendations from most recent guidelines will serve as the starting point for the discussion in this paper, recognizing that the recommendations lack the patient-specific data required for precision care. As noted throughout this paper, the majority of recommendations regarding fluid and vasoactive therapies in critical care practice guidelines are weak recommendations based on low-quality evidence. Ultimately, significant pre-clinical work coupled with novel clinical trial designs are necessary to establish the role of precision medicine approaches for fluid and vasopressor therapies in shock.[1, 5]

Data Sources and Scope

For this narrative review, a comprehensive search strategy limited to human subjects was completed in MEDLINE (Ovid) and Embase (Ovid) through to June 11, 2022. The search was repeated on September 30, 2022.

The search strategy used for the MEDLINE (Ovid) database was as follows for vasoactive therapy: (“precision medicine”[MeSH Terms]) OR “personalized medicine”[Keyword] OR “individualized medicine”[Keyword]” OR) AND “critical illness”[MeSH Terms] OR “critical care”[MeSH Terms] OR “intensive care units“[MeSH Terms]) OR “vasoconstrictor agents”[MeSH Terms] OR “cardiotonic agents”[MeSH Terms]; and for fluid therapy: (“precision medicine”[MeSH Terms]) OR “personalized medicine”[Keyword] OR “individualized medicine”[Keyword]” OR) AND “fluid therapy”[MeSH Terms] OR “isotonic solutions”[MeSH Terms] OR “albumins”[MeSH Terms])

The search strategy used for the Embase (Ovid) database was as follows for vasoactive therapy: (“personalized medicine”[MeSH Terms]) AND “critical illness”[MeSH Terms] OR “intensive care”[MeSH Terms] OR “intensive care unit“[MeSH Terms])

OR “vasoconstrictor agent”[MeSH Terms] OR “cardiotonic agent”[MeSH Terms] OR “shock”[MeSH Terms]; and for fluid therapy: (“personalized medicine”[MeSH Terms]) AND “critical illness”[MeSH Terms] OR “intensive care”[MeSH Terms] OR “intensive care unit“[MeSH Terms]) AND “fluid resuscitation”[MeSH Terms] OR “isotonic solution”[MeSH Terms] OR “crystalloid” OR “ringer lactate solution” OR “infusion fluid”[MeSH Terms] OR “albumin”[MeSH Terms]).

Title and abstract screening for the search results was conducted. Articles considered for the review had to explicitly focus on precision/personalized medicine using fluids or vasoactive agents in critically ill patients.

This paper will discuss initial endpoints for resuscitation, but due to low quality evidence and the breadth of content in this article, an in-depth discussion of monitoring techniques will not be provided. Readers interested in currently available monitoring techniques are referred to the expert panel report of a European Society of Intensive Care Medicine task force,[6] which was unable to provide recommendations using GRADE methodology due to an insufficient evidence base.[7] This paper does provide recommendations for groups of patients in mixed medical-surgical intensive care units (ICUs) most likely to benefit from specific approaches, rather than studies limited to patients with single system diseases (e.g. liver, heart, kidney) or injuries often treated in specialized ICU settings or in non-ICU settings.

Clinical Practice Guidelines

Since 2020, there are four guidelines published with recommendations for the choice of fluid and vasoactive drug administration specific to critically ill patients.[9-12] All four of these guidelines have strong recommendations against using starch products. It is worth noting, though, that task force decision-making occurred prior to the publication of two large randomized investigations comparing balanced salt solutions to normal saline; the Balanced Solution versus Saline in Intensive Care Study (BaSICS) and Plasma-Lyte 148 versus Saline (PLUS) trials.[13, 14] Two of the most recent guidelines are from the Surviving Sepsis Campaign; one concerning sepsis and septic shock and the other concerning the management of COVID-19 in critically ill adults.[9, 10] Apart from the recommendation against starch products, there are only four strong recommendations in these two guidelines regarding fluids and vasoactive agents: crystalloids as first-line fluid for resuscitation (sepsis and septic shock), norepinephrine as first-line over other vasopressors (sepsis and septic shock), and recommending against using dopamine when norepinephrine is available for shock (COVID-19). All of the remaining recommendations for fluids and vasoactive agents are “weak” recommendations (i.e. “suggest” statements).

The most recent guidelines relative to choice of intravenous fluids (no recommendations for vasoactive agents) in critically ill patients was a compilation of recommendations by the French Society of Anaesthesia and Intensive Care Medicine and the French Society of Emergency Medicine.[11] The guidelines include a strong recommendation not to use hypertonic saline as a first-line therapy for hemorrhagic shock. There was strong agreement based on expert opinion not to use gelatin products for patients with sepsis or septic shock.

Another guideline promulgated by a panel of the Society of Critical Care Medicine includes fluid recommendations for adults with acute and acute-on-chronic liver failure in the ICU setting.[12] The guidelines only have strong recommendations against using starch products for initial fluid resuscitation and for using norepinephrine as the first-line vasopressor for fluid-resistant patients.

Precision Medicine Concepts Applicable to both Fluid and Vasoactive Drug Therapy

There are new conceptual models of critical illness being proposed that have the potential to allow for true precision care. Sepsis is currently considered to be a syndrome based on signs and symptoms; however, a new translational conceptual model of critical illness has been proposed that is based on biologic descriptors. This new model would not only consider traditional factors such as age and comorbidities, but also information such as physiologic, genomic, transcriptomic, proteomic and metabolomic profiling, which could be used to provide patient-specific therapeutic interventions including fluids and vasoactive drugs during different physiologic states.[15]

Subphenotyping has been used in a variety of critical care disorders, including sepsis, to identify potentially meaningful treatment-responsive patient subgroups.[16] This approach seeks to identify group characteristics (based on a variety of potential information sources such as clinically-available data or transcriptomics) that distinguish the group from other groups of patients with the same phenotype.[16] For example, genome-wide gene expression profiling established two transcriptomic sepsis response signatures (subphenotypes) with differential mortality risk.[17, 18] Sepsis response signature 1 represents a relatively immunosuppressed subphenotype with higher mortality, while sepsis response signature 2 is a more immunocompetent subphenotype.[18] Few studies have evaluated medication response/outcome differences between subphenotypes in septic shock. A recent study that developed and validated subphenotypes of sepsis provides a good example of how phenotypic profiling may guide choice of fluid therapy in the future. The retrospective study included patients with suspected infections that were divided into a training cohort of 12,473 patients from 2014-2017 and a validation cohort of 8256 from 2018-2019. Modeling of vital signs occurred during the first 8 hours of hospitalization to develop and validate these cohorts. Four sub-phenotypes were identified with one group of hypotensive patients found to have lower mortality with balanced crystalloids versus normal saline (OR, 0.39; 95% CI, 0.23-0.67) based on a secondary analysis of the SMART investigation. While this study is more hypothesis generating in need of confirmation by prospective trials, it does reveal the possibility of a more personalized approach to care.[19, 20] In another study, investigators found a differential mortality effect of corticosteroids by sepsis response signature subphenotype, but outcomes did not differ based on sepsis response signature between patients allocated to early adjunctive vasopressin compared with norepinephrine monotherapy.[21] Future studies should evaluate differential treatment effects of other fluids, vasopressor drugs, and treatment approaches by shock subphenotype.[16]

Hemodynamic phenotyping involves an algorithmic sequence of assessments to determine therapeutic management. The use of hemodynamic phenotyping for the treatment of shock has been in practice for many years, notably with the “early goal-directed therapy” protocol sequentially evaluating central venous pressure, mean arterial blood pressure, and central venous oxygen saturation to guide treatment in septic shock.[22] Although the specific “early goal-directed therapy” protocol was subsequently not found to be superior to standard care, many elements of the protocol were components of the standard of care at the time of subsequent studies.[23] Elements of hemodynamic phenotyping for fluid and vasoactive agent use are suggested by the Surviving Sepsis Campaign guidelines, as exampled by the statements “For adults with sepsis or septic shock, we suggest using dynamic measures to guide fluid resuscitation, over physical examination, or static parameters alone” and “For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, we suggest either adding dobutamine to norepinephrine or using epinephrine alone.”[10] A novel hemodynamic phenotyping approach in septic shock is currently under evaluation in the ANDROMEDA-SHOCK-2 study, which includes algorithmic assessment of pulse pressure, diastolic blood pressure, fluid responsiveness, capillary refill time, and echocardiographic evidence of cardiac dysfunction with corresponding therapeutic interventions.[24] The findings from this study evaluating whether this specific hemodynamic phenotyping and treatment approach improves patient outcomes compared with standard care are anxiously awaited.

Fluid Therapy

The traditional categorization of commercially available resuscitation fluids for critically ill patients is a dichotomous choice between crystalloid or colloid products, but this approach belies important clinical differences not only between, but also within each of these categories. In more recent clinical practice guidelines, recommendations concerning choice of fluid have begun to reflect these recognized differences allowing for a somewhat more nuanced approach to the goal of providing precision care. For example, as stated in the French Society of Anaesthesia and Intensive Care Medicine and the French Society of Emergency Medicine guidelines, “Due to the arrival of new fluids and the publication of large-scale clinical trials, it is now possible to have a somewhat more precise vision of their prescription specificities, but numerous questions remain unanswered.”[11] The implications of these large-scale trials are discussed in this paper, but until more evidence is available allowing for a truly personalized approach, the only option is to provide effective and safe treatment regimens for groups of patients based on similar unifying characteristics.

Fluid Resuscitation Monitoring and Endpoints

Current clinical practice guidelines suggest the use dynamic measures of fluid responsiveness over static measures or isolated findings on physical examination recognizing that no single clinical parameter will assess volume status. The guidelines also suggest the adjunctive use of serum lactate concentrations (if elevated and taking into consideration other causes of elevation) in patients with sepsis or septic shock and capillary refill time in patients with septic shock. The initial endpoint associated with this monitoring is to achieve a mean arterial pressure (MAP) ≥65 mm Hg. The guidelines recognize

the limitations of performing more advanced hemodynamic monitoring in resource poor settings. In the latter settings, dynamic measures to assess fluid responsiveness could include passive leg raising or fluid boluses titrated to MAP in conjunction with assessments of capillary refill time and lactate concentrations (if available). In settings that have access to more invasive dynamic monitoring, echocardiography should allow for a more precision approach to care. Additional dynamic measurements of stroke volume, stroke volume variation, and pulse pressure variation may be useful when specialized equipment and personnel are available.

There are more questions than answers related to volume resuscitation and ideal endpoints for individual patients. This is illustrated by research priorities identified by a research committee of the Surviving Sepsis Campaign.[3, 4] Thirteen gaps in need of future research were identified including questions related to individualization of fluid, variables to titrate fluids, timing of fluid administration, and variables to trigger resuscitation and deresuscitation. There is research underway attempting to fill some of these gaps and allow for more precision care by evaluating the trajectories of hemodynamic data over time. For example, there is a database study that evaluated 761 patients presenting to an emergency department with data indicating a high risk of septic shock. Fluid responsiveness of the patients was assessed relative to changes in mean arterial pressure (MAP) time series from 15 minutes before to 2 hours after a fluid bolus. This clustering of MAP values demonstrated that responsiveness during the two-hour period after fluid boluses occurred approximately 25% of the time. Using an increase in MAP of at least 10 mm Hg to define fluid responsiveness, there was variation in the clusters relative to the presence and duration of responsiveness.[25] Another database study involving an emergency department that evaluated systolic blood pressure data also revealed dynamic changes over time with implications for fluid and vasopressor therapies.[26]

Colloids

Three large randomized clinical trials serve as the basis for the most of the recommendations in clinical practice guidelines regarding albumin versus crystalloid fluids in critically ill patients; Saline versus Albumin Fluid Evaluation (SAFE),[28] Albumin Italian Outcome Sepsis (ALBIOS),[29] and Early Albumin Resuscitation for Sepsis and Septic Shock Amount and Rate of Fluid Administration (EARSS).[30] The results of the latter study have only been published in abstract form or as part of a systematic review. The populations in all three trials were heterogeneous medical and surgical ICU patients, although as indicated by their titles ALBIOS focused on patients with sepsis while EARSS with a fixed dose albumin regimen focused on patients with sepsis and septic shock. Additionally, all three trials were pragmatic with non-albumin fluids left to clinician discretion. Since none of the trials detected overall between-group differences for the primary mortality endpoint, the focus tends to be on subgroup analyses that did demonstrate statistically significant differences; lower adjusted mortality with albumin in patients with severe sepsis in SAFE (fluid titration based on clinical parameters) and in patients with septic shock and hypoalbuminemia in ALBIOS (titrating albumin to a serum concentration of at least 3 g/dL), and higher adjusted mortality with albumin in patients with traumatic brain injury (TBI) in SAFE.

Because the administration of albumin has not been shown to reduce crude mortality when resuscitating patients with sepsis or septic shock in resource poor settings, an isotonic crystalloid solution is a reasonable resuscitation fluid of choice.[10] Even in settings where albumin is available, its use should be avoided when resuscitating patients with severe TBI as defined by a Glasgow Coma Scale score of 3 to 8. However, albumin is a reasonable alternative to crystalloids in patients with septic shock and hypoalbuminemia titrating albumin to a serum concentration of at least 3 g/dL, particularly in patients not responding to initial crystalloid therapy.[29] Albumin is a reasonable first-line option in subgroups of patients with acute, or acute-on-chronic liver failure or cirrhosis requiring fluid resuscitation, again titrating to a serum albumin concentration of at least 3 g/dL.[12]

Crystalloids

There is no uniform definition of a balanced crystalloid solution, but this terminology typically describes a solution with concentrations of electrolytes that reflect normal physiological concentrations in the blood, with some descriptions also referring to near-normal blood pH, a strong ion difference close to normal plasma bicarbonate concentration (i.e., buffered), osmolality, or tonicity.[31] Although different formulations of balanced crystalloids have been available for decades, the traditional choice of crystalloid resuscitation fluid for critically ill patients was either lactated Ringer's or normal saline. The situation began to change when animal, observational, and crossover studies involving critically ill patients documented adverse effects of chloride ion such as decreased kidney blood flow and glomerular filtration rate.[32-36] Subsequent to these studies were five large randomized trials that are changing the previous colloid versus crystalloid debate to a balanced crystalloid versus normal saline debate.[13, 14, 20, 37, 38] Of these randomized trials, none of the studies evaluating mortality as a primary outcome found a statistically significant difference between groups, although in the Isotonic Solutions and Major Adverse Renal Events Trial (SMART) there were lower odds (14.3% vs 15.4%, adjusted OR, 0.9; 95% CI, 0.82-0.99) in the balanced crystalloid group of a composite endpoint of major adverse kidney events within 30 days (MAKE30).[20] Additionally, a subsequent secondary analysis of SMART that was limited to patients with a diagnosis of sepsis found reductions with balanced crystalloids not only in adjusted odds ratios (aOR) for MAKE30 (35.4% vs. 40.1%; aOR, 0.78; 95% CI, 0.63-0.97), but also in number of vasopressor-free days (20 vs. 19 days; aOR, 1.25; 95% CI, 1.02-1.54), renal replacement therapy-free days (20 vs. 19 days; aOR, 1.35; 95% CI, 1.08-1.69), and 30-day in-hospital morality (26.3% vs. 31.2%; aOR, 0.74; 95% CI, 0.59-0.93).[39]

In conjunction with the publication of the PLUS trial was the first of a number of systematic reviews and meta-analyses.[40] This systematic review included six trials with a low risk of bias, the five major randomized studies listed above and one small study in trauma patients with only 46 evaluable patients.[38] The risk ratio (RR) for 90-day mortality was in favor of balanced crystalloids, albeit with the confidence interval crossing one (RR, 0.96; 95% CI, 0.91-1.01; I^2, 12.1%). Using vague priors (a statistical term in which the baseline effectiveness is considered neutral and highly variable) in a Bayesian meta-analysis, the authors concluded that the posterior probability of balanced crystalloids reducing mortality was 89.5%. The point estimates showed lower mortality in patients with sepsis (RR, 0.93;

95% CI, 0.86-1.01; I^2, 22.3%), but higher mortality in patients with TBI (RR, 1.26; 95% CI, 0.98-1.60; I^2, 20.2%) in patients receiving balanced crystalloids. There were no significant differences detected between groups for renal replacement therapy, vasopressor-free days, or ventilator-free days. Similar overall results were found in two additional systematic reviews with meta-analyses when limiting study inclusion to randomized studies.[41, 42]

Differences in study design (e.g. blinding, crossover vs. parallel group) is always a consideration when comparing the results of several trials, but there are some particular issues that have been the subject of discussion, particularly in light of the BaSICS and PLUS investigations. A recent paper summarized the more common concerns mentioned by skeptics for the overall lack of statistically significant differences noted between balanced crystalloids and normal saline in the large randomized trials.[43] These concerns along with more detailed explanations are listed in Table 1.

The importance of the patient population under study and the administration of non-study fluids was the subject of a secondary analysis of 90-day mortality using the BaSICS data in which there was a categorization of patients based on type of admission and fluid administration in the 24 hours prior to enrollment.[44] Using hierarchical logistical Bayesian modeling the investigators found that the probability of benefit [odds ratios (OR) and 89% credible intervals (CrI)] of balanced crystalloid over normal saline increased if patients received only balanced crystalloid prior to study enrollment (probability of benefit, 0.92; OR, 0.78, 89% CrI, 0.56-1.03). This was primarily a function of unplanned admissions for sepsis (probability of benefit, 0.96; OR, 0.70, 89% CrI, 0.50-0.97) and planned admissions (probability of benefit, 0.97; OR, 0.79, 89% CrI, 0.65-0.97). Further evidence of the importance of the enrolled patient population is exemplified by a planned *a priori* secondary analysis of the SMART trial that was focused on patients with TBI.[45] While the proportion of patients who died during the study period was similar in the balanced crystalloid and normal saline groups (16% vs. 14%, respectively, adjusted OR, 1.03; 95% CI, 0.60-1.75; P=0.91), patients in the balanced crystalloid group had a worse outcome with respect to total mortality or discharge to another facility (adjusted OR, 1.38; 95% CI, 1.02-1.86; P=0.04). This worse outcome in patients with TBI receiving balanced crystalloid solutions is consistent with the results of a previous multicenter observational study comparing lactated Ringer's to normal saline in which patients receiving lactated Ringer's had higher adjusted mortality (hazard rate, 1.78; 95% CI, 1.04-3.04).[46] The reasons for worse outcomes with the balanced crystalloids vs. normal saline is uncertain, but the discussion sections of these trials allude to the osmolarity differences between the two solutions. There is currently no adequately powered randomized trial comparing iso-oncotic (i.e., 4% or 5%) albumin to a balanced crystalloid solution for sepsis resuscitation, although one known by the acronym "ABC-Sepsis" is currently in progress.[47] There is one randomized trial comparing a 20% albumin solution to a balanced crystalloid in patients with cirrhosis and sepsis, but with only 50 patients in each group the study was under-powered to detect a significant difference in 28-day mortality (P=0.57).[48] While the albumin led to more rapid reversal of hypotension, there was no significant difference in shock reversal at 48 hours (P=0.35) and adverse effects led to the discontinuation of albumin in 22% of patients, 12% due to pulmonary edema.

Together, these data suggest that the subset of critically ill patient must be considered when developing a precision fluid therapy regimen, despite the overall lack of differences in crude mortality between normal saline and balanced crystalloid solutions in published trials. Balanced crystalloid solutions of similar composition to those used in the previously cited trials should be avoided in patients with severe TBI due to the potential to increase mortality. Otherwise, presuming the cost difference between normal saline and balanced crystalloid solutions is not an issue, balanced crystalloids are particularly appealing when resuscitating the subset of patients with reduced or fluctuating kidney function.[49]

Fluid Dosing

The proposed initial resuscitation dosing strategies for fluids are almost as controversial as recommendations concerning the type of fluid administered. The guidelines by the Surviving Sepsis Campaign for sepsis and septic shock have a weak recommendation based on low-quality of evidence that patients with sepsis-induced hypoperfusion or septic shock should receive at least 30 mL/kg of intravenous crystalloid fluid within the first three hours of resuscitation.[10] These guidelines further state there is insufficient evidence to make a recommendation on the use of restrictive versus liberal fluid strategies in the first 24 hours of resuscitation in patients with ongoing signs of hypoperfusion and volume depletion after initial resuscitation. The basis for the 30 mL/kg figure is average fluid volumes administered in sepsis trials and lacks a personalized approach.[50] Fluid boluses of 4 mL/kg are usually adequate for assessing fluid responsiveness.[51] Concerns with the one-size-fits-all 30 mL/kg approach were first raised with publication of the FEAST study, in which children with severe infection in a more resource scarce setting who did not receive a fluid bolus had lower mortality.[52] Prospective validation of the recommended volume is required to confirm this strategy in all comers with sepsis or septic shock.

There is particular concern with the fixed 30 mL/kg volume recommended in clinical practice guidelines in subgroups of patients at increased risk of fluid overload such as those with heart failure, chronic kidney or liver disease, or extreme obesity. The current Surviving Sepsis Campaign guideline refers to a retrospective cohort study involving patients with sepsis or septic shock that did not detect harm with administration of a fixed 30 mL/kg volume in these “volume sensitive” high-risk patients.[50] However, this cohort study and others with similar findings are limited by residual confounding due to their observational design.[50, 53, 54] In patients with high-risk comorbidities, it is reasonable to administer crystalloids in 500 mL boluses with close monitoring to determine if additional doses are necessary.[55] Additionally, early administration of vasopressors should be considered in these subgroups.[55]

Studies in patients with sepsis and septic shock evaluating biomarkers associated with shedding of the endothelial glycocalyx layer have sought to determine if potential harm may occur from fluid resuscitation strategies or if these biomarkers serve to guide the amount of volume resuscitation required.[56-60] At present, conflicting results as well as trial design limits the conclusions that can be drawn.

The rate of fluid administration is another consideration. The BaSICS trial, comparing balanced crystalloids and normal saline, formally evaluated the effect of infusion rate on

mortality as part of a factorial design.[61] This arm of the study did not detect a difference in 90-day survival, regardless of slow versus rapid infusion (333 mL/hour vs. 999 mL/hour, respectively) of crystalloid fluid. Similarly, a retrospective study involving 49,331 with sepsis in 149 hospitals in New York found that time to completion of the initial bolus fluid dosing was not associated with mortality, but as pointed out by the investigators, this finding is prone to confounding due to sicker patients likely receiving fluids sooner and having an increased likelihood of death.[62] These findings should not be interpreted as negating the importance of prompt fluid administration, particularly in patients with sepsis and septic shock where delays in resuscitation of more than two hours increase mortality.[63]

Deresuscitation

As discussed earlier, there are some advocates for individualizing fluid administration with an emphasis on limiting the amount fluid administered by giving smaller boluses of fluid with early initiation of vasopressors.[55] Another approach focuses on the post-resuscitation phases of hemodynamic support. Preliminary data support the potential benefits of limiting fluid administration volumes during the stabilization and deresuscitation phases of shock in conjunction with diuretics to remove excess fluid during the deresuscitation phase. Both early and post-resuscitation fluid restrictive approaches have their basis in investigations demonstrating the importance of the endothelium for maintaining homeostasis as highlighted above,[64] and clinical studies showing the adverse clinical outcomes of overly aggressive fluid administration.[65] In a recent systematic review with meta-analysis of observational studies involving critically ill patients, the adjusted RR for mortality increased by a factor of 1.19 (95% CI, 1.11-1.28) for each liter of positive fluid balance.[66] The authors of one modeling study suggest that there should be a maximum amount of fluid administered between 6 to 10 liters, with 8 liters being optimal.[67] A survey of critical care specialists suggests that this message of the importance of limiting and removing fluid (“deresuscitation”) is becoming widespread with 95% of respondents recognizing the need to address fluid overload.[68]

Since publication of the 2021 Surviving Sepsis Campaign guideline, the Conservative versus Liberal Approach to Fluid Therapy in Septic Shock (CLASSIC) trial was published.[69] This randomized trial enrolled 1554 patients with onset of shock within 12 hours before screening who received at least one liter of intravenous fluid. As expected, patients in the restrictive vs. standard fluid group received less fluid in the ICU [median of 1798 mL (interquartile range, 500 to 4366) vs. median of 3811 ml (interquartile range, 1861 to 6762), respectively]. However, there was no significant difference detected between groups for the primary outcome of 90-day mortality (42.3% vs. 42.1, adjusted absolute difference, 0.1 percentage points; 95% confidence interval, −4.7% to 4.9%; P = 0.96). Similarly, there were no significant between-group differences detected for serious adverse events, days alive without life support, or days alive and out of hospital. Another multicenter feasibility study known as the Restrictive Fluids Versus Standard Care in Adults with Sepsis in the Emergency Department (REFACED) trial was recently published that lends support to a future adequately powered trial to detect a between-group mortality difference less than 5%.[70]

While large-scale randomized investigations have not demonstrated a survival advantage for restricted compared to liberal fluid regimens, there remain concerns regarding excessive fluid administration. These concerns have prompted calls for resuscitation based on precision care for individual patients rather than a simple restricted versus liberal dichotomous breakdown.[71] Notably, in a pre-post study of a multi-professional diuretic approach as a component of deresuscitation, the diuresis approach was associated with lower cumulative fluid balance and lower mortality.[72] This focus on optimizing clinical outcomes associated with fluid administration has been termed fluid stewardship, analogous to antimicrobial stewardship when dealing with infectious diseases.

Studies are beginning to evaluate clinical decision-making rules for fluid resuscitation in sepsis and septic shock that consider individual phenotypic considerations. They provide recommendations for fluid administration that change during the resuscitation and deresuscitation phases. For example, in one analysis of data from 335 units at 208 hospitals, the investigators developed a fluid management strategy for days 1, 3 and 5 after ICU admission for patients with sepsis, and predicted a longer survival time with the observed regimens if the dynamic treatment model was instituted.[73] In another study involving patients in 25 tertiary care teaching hospitals in China, modeling revealed five phenotypes of septic shock with a need for differential timing of deresuscitation by class.[74] Adaptive platform trial design may be the optimal method to prospectively evaluate such decision support tools aimed at precision fluid resuscitation.[2, 75]

Vasoactive Drug Therapy

Vasopressors are utilized in patients with circulatory shock when intravenous fluids are not indicated or fail to restore effective tissue and organ perfusion.[6] Commonly used vasoactive medications for the treatment of circulatory shock include catecholamines (e.g., norepinephrine, epinephrine, dobutamine), vasopressin, and angiotensin II. Each vasoactive agent has unique clinical pharmacology resulting in differential pharmacodynamic effects and outcomes in circulatory shock.[10, 76-78] Despite decades of bedside use and investigation, there is high practice variability with vasopressors across continents and within the United States.[79, 80] Importantly, vasopressor practice variability, at least partially, contributes to unexplained heterogeneity in septic shock trial control group mortality.[81] As such, there is an urgent need to define the optimal approach to selection, dose titration, and escalation of vasopressor therapy.[3, 4] A precision medicine approach to vasopressor therapy may offer a pathway towards achieving this goal.

Achieving an initial MAP ≥65 mm Hg is the recommended therapeutic target for vasopressor dosage titration in most patients.[6, 10, 77] Nevertheless, patient-specific factors can be considered in therapeutic decision-making regarding MAP targets and corresponding vasopressor dosages. In the average patient with septic shock, targeting a MAP of 80-85 mm Hg failed to improve outcomes compared with a MAP target of 65-70 mm Hg, but the higher MAP target more frequently caused new-onset atrial fibrillation.[82] However, in the stratum of patients with chronic hypertension allocated to the higher MAP target, there was a lower frequency of renal insufficiency without a higher risk for adverse effects. Additionally, in a study of patients aged 65 years or older with vasodilatory shock, compared

with usual care, a MAP target of 60-65 mm Hg resulted in lower vasopressor exposure without a between-group mortality difference detected.[83] Therefore, if achieving an initial MAP ≥65 mm Hg fails to restore effective perfusion in a patient with chronic hypertension and vasodilatory shock, increasing the MAP target can be trialed.[6] Contrastingly, if adequate perfusion is achieved with a MAP target ≥65 mm Hg in an elderly patient with vasodilatory shock, decreasing the MAP target to 60-65 mm Hg can be trialed. Importantly, in patients with uncontrolled bleeding without severe TBI, a MAP target of 50-60 mm Hg is recommended until hemostasis is achieved and patients with severe TBI should have a MAP ≥80 mm Hg maintained.[6, 8]

Possible predictive/drug-responsive components of a precision medicine vasopressor regimen for patients with circulatory shock include pharmacogenetic/pharmacogenomic information and biomarkers (in addition to the previously introduced concepts of subphenotyping and hemodynamic phenotyping).[1] Pharmacogenetic/pharmacogenomic approaches to medication management have led to therapeutic breakthroughs in a number of non-critical care settings. Yet, the utility of incorporating pharmacogenomic information into therapeutic decision-making in shock remains to be elucidated. Studies have identified genetic polymorphisms within vasopressor pathways with therapeutic potential in circulatory shock.[84-94] (Table 2) Genetic information may also assist in identifying patients most at risk for adverse effects of vasoactive agents. A genetic polymorphism was associated with the development of serious adverse events from vasopressin and norepinephrine in patients with septic shock.[90] However, trials have not evaluated therapeutic regimen adjustments based on genetic polymorphism information. Further, the turnaround time for genotype information must be drastically improved for the data to influence bedside management of vasopressor therapy in shock.

A number of biomarkers have been associated with vasopressor response and outcomes. The effect of low blood and intracellular pH causing lower catecholamine response has been known for over 60 years.[95] Recent data have also shown an association between lower arterial pH and lower vasopressin response.[96] Separate from its effect on pH, several studies showed higher lactate concentrations were associated with lower response to catecholamine-adjunctive vasopressin and angiotensin II.[96-99] Further, higher lactate concentration at vasopressin initiation was associated with higher mortality.[99] Renin is a novel perfusion marker that may be superior to lactate, with higher concentrations correlating with hypoperfusion and greater angiotensin II response.[100, 101] In a subgroup analysis of a study comparing angiotensin II to placebo in patients with vasodilatory shock, patients with higher renin concentrations allocated to angiotensin II had lower mortality.[101] Angiopoietin-2 is another novel biomarker that is part of the endothelial cell activation signaling pathway, which destabilizes endothelial cell junctions leading to increased vascular permeability.[102, 103] Higher angiopoietin-2 concentrations have been associated with higher fluid overload, more organ dysfunction, and higher mortality.[104] In a subgroup analysis of a study comparing norepinephrine plus vasopressin to norepinephrine monotherapy in septic shock, patients allocated to norepinephrine plus vasopressin with low angiopoietin-2 concentrations had lower mortality than patients who had high angiopoietin-2 concentrations.[104] Contrastingly, a mortality difference was not detected by angiopoietin-2 concentration in patients allocated to the norepinephrine monotherapy arm. Further, the

p-value for heterogeneity of treatment effect across angiopoietin-2 subgroups was not significant, decreasing the credibility of this subgroup analysis.[105] Thus, while plasma angiopoietin-2 concentrations have been suggested as a predictive biomarker for vasopressor response, further evaluation is required.[106] Additionally, patients with biomarkers suggesting low oxygen delivery (e.g., low central venous oxygen saturation and/or high veno-arterial carbon dioxide tension difference) despite adequate hemoglobin concentration should be considered for inotrope initiation.[107] However, despite their theoretical rationale and established ability to increase oxygen transport, inotropes have not been demonstrated as beneficial in critically ill patients with septic shock nor those with cardiac dysfunction (including cardiogenic shock).[10, 108-112] Lastly, vasopressor-related data may also represent predictive/drug-responsive biomarkers for other vasoactive agents.[1, 113, 114] Studies have shown norepinephrine-equivalent catecholamine dose at the time of adjunctive vasopressin, angiotensin II, and epinephrine initiation was associated with adjunctive vasopressor response.[99, 115, 116] Further, patients with vasodilatory shock receiving catecholamines and vasopressin had higher odds of response to angiotensin II compared with patients receiving catecholamines without vasopressin.[98] These preliminary data provide impetus to use the outlined biomarkers to develop a precision vasopressor regimen, and their use should be incorporated into the design of prospective trials.

Conceptually, precision vasopressor therapy can be implemented in a variety of ways. One approach is to only undertake vasopressor decisions (e.g., particular vasoactive agent initiation or drug-specific dosage titration) in patients with a high predicted likelihood of success (representing a subphenotype). This approach could use a single predictive/drug-responsive component (such as pharmacogenetic/pharmacogenomic information or a biomarker) to guide therapy, or incorporate multiple known and purported components into clinical prediction models to recommend specific vasoactive therapy decisions. Results of prediction model approaches have been mixed; one artificial intelligence algorithm predicted optimal fluid and vasopressor dosage better than bedside clinician actions, but a machine learning algorithm failed to adequately predict vasopressin response.[117, 118] Another precision vasopressor therapy approach is to start multiple vasoactive agents with different mechanisms of action at the same time, and use patient-specific predictive/drug-responsive component(s) (e.g., renin concentration) to subsequently adjust the vasopressor regimen. This initial “broad spectrum” approach followed by vasoactive “de-escalation” is similar to the approach with antimicrobials employed in many intensive care units.[119, 120] While the “broad spectrum” and “de-escalate” approach to vasopressor decision-making has theoretical rationale, it has not been evaluated in studies, and the benefits and risks to the approach are currently unknown. Future studies should compare the outlined precision vasopressor therapy approaches to each other and to standard care in order to determine if a precision vasopressor approach can improve patient outcomes in circulatory shock.

Summary and Conclusion

While clinical practice guidelines for critically ill patients provide clinicians with recommendations to optimize care, current guidelines pertaining to fluid administration have yet to incorporate more recent trials evaluating balanced crystalloids and normal saline. Furthermore, these guidelines have been unable to fully integrate precision medicine

into fluid and vasoactive therapy recommendations; however, this is a recognized research priority. Evaluation of clinical trial subgroups, biomarkers, hemodynamic measures, and genomics/genetics that identify patients based on unifying characteristics can provide insights into a more personalized approach, but not all are ready for implementation into daily practice. Further research evaluating precision medicine approaches with or without clinical prediction models as compared to standard of care will help determine the role for personalized therapy in critically ill patients.

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REFERENCES

1. Seymour CW, Gomez H, Chang C-CH, et al. Precision medicine for all? Challenges and opportunities for a precision medicine approach to critical illness. Crit Care 2017;1:257.
2. Bhatt DL, Mehta C. Adaptive Designs for Clinical Trials. N Engl J Med 2016;1:65–74.
3. Coopersmith CM, De Backer D, Deutschman CS, et al. Surviving Sepsis Campaign: Research Priorities for Sepsis and Septic Shock. Crit Care Med 2018;8:1334–56.
4. Lat I, Coopersmith CM, De Backer D. The Surviving Sepsis Campaign: Fluid Resuscitation and Vasopressor Therapy Research Priorities in Adult Patients. Crit Care Med 2021;4:623–35.
5. Shah FA, Meyer NJ, Angus DC, et al. A Research Agenda for Precision Medicine in Sepsis and Acute Respiratory Distress Syndrome: An Official American Thoracic Society Research Statement. Am J Respir Crit Care Med 2021;8:891–901.
6. Cecconi M, De Backer D, Antonelli M, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med 2014;12:1795–815.
7. Atkins D, Eccles M, Flottorp S, et al. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group. BMC Health Serv Res 2004;1:38.
8. Spahn DR, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. Crit Care 2019;1:98.
9. Alhazzani W, Evans L, Alshamsi F, et al. Surviving Sepsis Campaign Guidelines on the Management of Adults With Coronavirus Disease 2019 (COVID-19) in the ICU: First Update. Crit Care Med 2021;3:e219–e34.
10. Evans L, Rhodes A, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Crit Care Med 2021;11:e1063–e143.
11. Joannes-Boyau O, Le Conte P, Bonnet MP, et al. Guidelines for the choice of intravenous fluids for vascular filling in critically ill patients, 2021. Anaesth Crit Care Pain Med 2022;3:101058.
12. Nanchal R, Subramanian R, Karvellas CJ, et al. Guidelines for the Management of Adult Acute and Acute-on-Chronic Liver Failure in the ICU: Cardiovascular, Endocrine, Hematologic, Pulmonary, and Renal Considerations. Crit Care Med 2020;3:e173–e91.
13. Zampieri FG, Machado FR, Biondi RS, et al. Effect of Intravenous Fluid Treatment With a Balanced Solution vs 0.9% Saline Solution on Mortality in Critically Ill Patients: The BaSICS Randomized Clinical Trial. JAMA 2021;9:1–12.
14. Finfer S, Micallef S, Hammond N, et al. Balanced Multielectrolyte Solution versus Saline in Critically Ill Adults. N Engl J Med 2022;9:815–26.

15. Maslove DM, Tang B, Shankar-Hari M, et al. Redefining critical illness. Nature Med 2022;6:1141–48.
16. Reddy K, Sinha P, O'Kane CM, Gordon AC, Calfee CS, McAuley DF. Subphenotypes in critical care: translation into clinical practice. Lancet Respir Med 2020;6:631–43.
17. Burnham KL, Davenport EE, Radhakrishnan J, et al. Shared and Distinct Aspects of the Sepsis Transcriptomic Response to Fecal Peritonitis and Pneumonia. American Journal of Respiratory and Critical Care Medicine 2017;3:328–39.
18. Davenport EE, Burnham KL, Radhakrishnan J, et al. Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study. The Lancet Respiratory Medicine 2016;4:259–71. [PubMed: 26917434]
19. Bhavani SV, Semler M, Qian ET, et al. Development and validation of novel sepsis subphenotypes using trajectories of vital signs. Intensive Care Med 2022.
20. Semler MW, Self WH, Wanderer JP, et al. Balanced Crystalloids versus Saline in Critically Ill Adults. N Engl J Med 2018;9:829–39.
21. Antcliffe DB, Burnham KL, Al-Beidh F, et al. Transcriptomic Signatures in Sepsis and a Differential Response to Steroids. From the VANISH Randomized Trial. Am J Respir Crit Care Med 2019;8:980–86.
22. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;19:1368–77.
23. The PRISM Investigators. Early, Goal-Directed Therapy for Septic Shock — A Patient-Level Meta-Analysis. N Engl J Med 2017;23:2223–34.
24. Kattan E, Bakker J, Estenssoro E, et al. Hemodynamic phenotype-based, capillary refill time-targeted resuscitation in early septic shock: The ANDROMEDA-SHOCK-2 Randomized Clinical Trial study protocol. Rev Bras Ter Intensiva 2022;34:1–11. [PubMed: 35674525]
25. Gu Q, Prasad V, Heldt T. Characterizing Fluid Response and Sepsis Progression in Emergency Department Patients. 2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). 23-27 July 2019. Available from https://ieeexplore.ieee.org/document/8856521. Accessed September 28, 2022.
26. Prasad V, Lynch JC, Filbin MR, Reisner AT, Heldt T. Clustering Blood Pressure Trajectories in Septic Shock in the Emergency Department. 2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). 23-27 July 2019. Available from https://ieeexplore.ieee.org/document/8857191. Accessed September 28, 2022.
27. Annane D, Siami S, Jaber S, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. JAMA 2013;17:1809–17.
28. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004;22:2247–56.
29. Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med 2014;15:1412–21.
30. Patel A, Laffan MA, Waheed U, Brett SJ. Randomised trials of human albumin for adults with sepsis: systematic review and meta-analysis with trial sequential analysis of all-cause mortality. BMJ 2014;g4561. [PubMed: 25099709]
31. Semler MW, Kellum JA. Balanced Crystalloid Solutions. Am J Respir Crit Care Med 2019;8:952–60.
32. Raghunathan K, Shaw A, Nathanson B, et al. Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis. Crit Care Med 2014;7:1585–91.
33. Singh P, Okusa MD. The role of tubuloglomerular feedback in the pathogenesis of acute kidney injury. Contrib Nephrol 2011;12–21. [PubMed: 21921605]
34. Wilcox CS. Regulation of renal blood flow by plasma chloride. J Clin Invest 1983;3:726–35.
35. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA 2012;15:1566–72.

36. Shaw AD, Raghunathan K, Peyerl FW, Munson SH, Paluszkiewicz SM, Schermer CR. Association between intravenous chloride load during resuscitation and in-hospital mortality among patients with SIRS. Intensive Care Med 2014;12:1897–905.
37. Semler MW, Wanderer JP, Ehrenfeld JM, et al. Balanced Crystalloids versus Saline in the Intensive Care Unit. The SALT Randomized Trial. Am J Respir Crit Care Med 2017;10:1362–72.
38. Young JB, Utter GH, Schermer CR, et al. Saline versus Plasma-Lyte A in initial resuscitation of trauma patients: a randomized trial. Ann Surg 2014;2:255–62.
39. Brown RM, Wang L, Coston TD, et al. Balanced Crystalloids versus Saline in Sepsis. A Secondary Analysis of the SMART Clinical Trial. Am J Respir Crit Care Med 2019;12:1487–95.
40. Hammond NE, Zampieri FG, Tanna GLD, et al. Balanced Crystalloids versus Saline in Critically Ill Adults — A Systematic Review with Meta-Analysis. NEJM Evidence 2022;2:EVIDoa2100010.
41. Beran A, Altorok N, Srour O, et al. Balanced Crystalloids versus Normal Saline in Adults with Sepsis: A Comprehensive Systematic Review and Meta-Analysis. J Clin Med 2022;7.
42. Dong W-H, Yan W-Q, Song X, Zhou W-Q, Chen Z. Fluid resuscitation with balanced crystalloids versus normal saline in critically ill patients: a systematic review and meta-analysis. Scand J Trauma Resusc Emerg Med 2022;1:28.
43. Kopp BJ, Lenney M, Erstad BL. Balanced Salt Solutions for Critically Ill Patients: Nonplused and Back to Basics. Ann Pharmacother 10600280221084380.
44. Zampieri FG, Machado FR, Biondi RS, et al. Association between Type of Fluid Received Prior to Enrollment, Type of Admission, and Effect of Balanced Crystalloid in Critically Ill Adults: A Secondary Exploratory Analysis of the BaSICS Clinical Trial. Am J Respir Crit Care Med 2022;12:1419–28.
45. Lombardo S, Smith MC, Semler MW, et al. Balanced crystalloid vs saline in adults with traumatic brain injury: secondary analysis of a clinical trial. J Neurotrauma 2022.
46. Rowell SE, Fair KA, Barbosa RR, et al. The Impact of Pre-Hospital Administration of Lactated Ringer's Solution versus Normal Saline in Patients with Traumatic Brain Injury. J Neurotrauma 2016;11:1054–9.
47. Cafferkey J, Ferguson A, Grahamslaw J, et al. Albumin versus balanced crystalloid for resuscitation in the treatment of sepsis: A protocol for a randomised controlled feasibility study, “ABC-Sepsis”. J Intensive Care Soc 0:17511437221103692.
48. Maiwall R, Kumar A, Pasupuleti SSR, et al. A randomized-controlled trial comparing 20% albumin to plasmalyte in patients with cirrhosis and sepsis-induced hypotension [ALPS trial]. J Hepatol 2022.
49. Toporek AH, Semler MW, Self WH, et al. Balanced Crystalloids versus Saline in Critically Ill Adults with Hyperkalemia or Acute Kidney Injury: Secondary Analysis of a Clinical Trial. Am J Respir Crit Care Med 2021;10:1322–25.
50. Kuttab HI, Lykins JD, Hughes MD, et al. Evaluation and Predictors of Fluid Resuscitation in Patients With Severe Sepsis and Septic Shock. Crit Care Med 2019;11:1582–90.
51. Nasa P, Wise R, Elbers PWG, et al. Intravenous fluid therapy in perioperative and critical care setting-Knowledge test and practice: An international cross-sectional survey. J Crit Care 2022;154122. [PubMed: 35908420]
52. Maitland K, Kiguli S, Opoka RO, et al. Mortality after Fluid Bolus in African Children with Severe Infection. N Engl J Med 2011;26:2483–95.
53. Liu VX, Morehouse JW, Marelich GP, et al. Multicenter Implementation of a Treatment Bundle for Patients with Sepsis and Intermediate Lactate Values. Am J Respir Crit Care Med 2016;11:1264–70.
54. Khan RA, Khan NA, Bauer SR, et al. Association Between Volume of Fluid Resuscitation and Intubation in High-Risk Patients With Sepsis, Heart Failure, End-Stage Renal Disease, and Cirrhosis. Chest 2020;2:286–92.
55. Marik PE, Byrne L, van Haren F. Fluid resuscitation in sepsis: the great 30 mL per kg hoax. J Thorac Dis 2020;Suppl 1:S37–s47. [PubMed: 32148924]
56. Saoraya J, Wongsamita L, Srisawat N, Musikatavorn K. The effects of a limited infusion rate of fluid in the early resuscitation of sepsis on glycocalyx shedding measured by plasma syndecan-1: a randomized controlled trial. J Intensive Care 2021;1:1.

57. Inkinen N, Pettilä V, Lakkisto P, et al. Association of endothelial and glycocalyx injury biomarkers with fluid administration, development of acute kidney injury, and 90-day mortality: data from the FINNAKI observational study. Ann Intensive Care 2019;1:103.
58. Puskarich MA, Cornelius DC, Tharp J, Nandi U, Jones AE. Plasma syndecan-1 levels identify a cohort of patients with severe sepsis at high risk for intubation after large-volume intravenous fluid resuscitation. J Crit Care 2016;125–29.
59. Macdonald S, Bosio E, Shapiro NI, et al. No association between intravenous fluid volume and endothelial glycocalyx shedding in patients undergoing resuscitation for sepsis in the emergency department. Sci Rep 2022;1:8733.
60. Saoraya J, Wongsamita L, Srisawat N, Musikatavorn K. Plasma syndecan-1 is associated with fluid requirements and clinical outcomes in emergency department patients with sepsis. Am J Emerg Med 2021;83–89.
61. Zampieri FG, Machado FR, Biondi RS, et al. Effect of Slower vs Faster Intravenous Fluid Bolus Rates on Mortality in Critically Ill Patients: The BaSICS Randomized Clinical Trial. JAMA 2021;9:830–38.
62. Seymour CW, Gesten F, Prescott HC, et al. Time to Treatment and Mortality during Mandated Emergency Care for Sepsis. N Engl J Med 2017;23:2235–44.
63. Leisman DE, Doerfler ME, Schneider SM, Masick KD, D'Amore JA, D'Angelo JK. Predictors, Prevalence, and Outcomes of Early Crystalloid Responsiveness Among Initially Hypotensive Patients With Sepsis and Septic Shock. Crit Care Med 2018;2:189–98.
64. Hippensteel JA, Uchimido R, Tyler PD, et al. Intravenous fluid resuscitation is associated with septic endothelial glycocalyx degradation. Crit Care 2019;1:259.
65. Silversides JA, Fitzgerald E, Manickavasagam US, et al. Deresuscitation of Patients With Iatrogenic Fluid Overload Is Associated With Reduced Mortality in Critical Illness. Crit Care Med 2018;10:1600–07.
66. Messmer AS, Zingg C, Müller M, Gerber JL, Schefold JC, Pfortmueller CA. Fluid Overload and Mortality in Adult Critical Care Patients-A Systematic Review and Meta-Analysis of Observational Studies. Crit Care Med 2020;12:1862–70.
67. Shahn Z, Shapiro NI, Tyler PD, Talmor D, Lehman L-wH. Fluid-limiting treatment strategies among sepsis patients in the ICU: a retrospective causal analysis. Critical Care 2020;1:62.
68. Silversides JA, McAuley DF, Blackwood B, Fan E, Ferguson AJ, Marshall JC. Fluid management and deresuscitation practices: A survey of critical care physicians. J Intensive Care Soc 2020;2:111–18.
69. Meyhoff TS, Hjortrup PB, Wetterslev J, et al. Restriction of Intravenous Fluid in ICU Patients with Septic Shock. N Engl J Med 2022;26:2459–70.
70. Jessen MK, Andersen LW, Thomsen M-LH, et al. Restrictive Fluids Versus Standard Care in Adults with Sepsis in the Emergency Department (REFACED) – a Multicenter, Randomized Feasibility Trial. Acad Emerg Med.
71. Virág M, Leiner T, Rottler M, Ocskay K, Molnar Z. Individualized Hemodynamic Management in Sepsis. J Pers Med 2021;2:157.
72. Bissell BD, Laine ME, Thompson Bastin ML, et al. Impact of protocolized diuresis for deresuscitation in the intensive care unit. Critical Care 2020;1:70.
73. Zhang Z, Zheng B, Liu N. Individualized fluid administration for critically ill patients with sepsis with an interpretable dynamic treatment regimen model. Sci Rep 2020;1:17874.
74. Ma P, Liu J, Shen F, et al. Individualized resuscitation strategy for septic shock formalized by finite mixture modeling and dynamic treatment regimen. Crit Care 2021;1:243.
75. van Haren F Personalised fluid resuscitation in the ICU: still a fluid concept? Crit Care 2017;Suppl 3:313. [PubMed: 29297387]
76. Hollenberg SM. Vasoactive drugs in circulatory shock. Am J Respir Crit Care Med 2011;7:847–55.
77. Levy B, Bastien O, Bendjelid K, et al. Experts' recommendations for the management of adult patients with cardiogenic shock. Ann Intensive Care 2015;1:17.
78. Bauer SR, MacLaren R, Erstad BL. Shock Syndromes. In: DiPiro JT, Yee GC, Posey L, Haines ST, Nolin TD, Ellingrod V eds. Pharmacotherapy: A Pathophysiologic Approach. 12th ed. New York, NY: McGraw-Hill, 2022.

79. Abril MK, Khanna AK, Kroll S, McNamara C, Handisides D, Busse LW. Regional differences in the treatment of refractory vasodilatory shock using Angiotensin II in High Output Shock (ATHOS-3) data. J Crit Care 2019;188–94. [PubMed: 30553989]
80. Vail EA, Gershengorn HB, Hua M, Walkey AJ, Wunsch H. Epidemiology of Vasopressin Use for Adults with Septic Shock. Ann Am Thorac Soc 2016;10:1760–67.
81. de Grooth H-J, Postema J, Loer SA, Parienti J-J, Oudemans-van Straaten HM, Girbes AR. Unexplained mortality differences between septic shock trials: a systematic analysis of population characteristics and control-group mortality rates. Intensive Care Med 2018;3:311–22.
82. Asfar P, Meziani F, Hamel JF, et al. High versus low blood-pressure target in patients with septic shock. N Engl J Med 2014;17:1583–93.
83. Lamontagne F, Richards-Belle A, Thomas K, et al. Effect of Reduced Exposure to Vasopressors on 90-Day Mortality in Older Critically Ill Patients With Vasodilatory Hypotension: A Randomized Clinical Trial. JAMA 2020;10:938–49.
84. Adefurin A, Ghimire LV, Kohli U, et al. Genetic variation in the α1A-adrenergic receptor and phenylephrine-mediated venoconstriction. Pharmacogenomics J 2015;4:310–15.
85. Sofowora GG, Dishy V, Landau R, et al. Alpha 1A-adrenergic receptor polymorphism and vascular response. Clin Pharmacol Ther 2004;6:539–45.
86. Shibata K, Hirasawa A, Moriyama N, Kawabe K, Ogawa S, Tsujimoto G. α1a-Adrenoceptor polymorphism: pharmacological characterization and association with benign prostatic hypertrophy. Br J Pharmacol 1996;6:1403–08.
87. Leineweber K, Heusch G. β1- and β2-Adrenoceptor polymorphisms and cardiovascular diseases. Br J Pharmacol 2009;1:61–69.
88. Nakada TA, Russell JA, Boyd JH, et al. beta2-Adrenergic receptor gene polymorphism is associated with mortality in septic shock. Am J Respir Crit Care Med 2010;2:143–9.
89. Nakada TA, Russell JA, Wellman H, et al. Leucyl/cystinyl aminopeptidase gene variants in septic shock. Chest 2011;5:1042–49.
90. Anantasit N, Boyd JH, Walley KR, Russell JA. Serious adverse events associated with vasopressin and norepinephrine infusion in septic shock. Crit Care Med 2014;8:1812–20.
91. de Denus S, Dubé MP, Fouodjio R, et al. A prospective study of the impact of AGTR1 A1166C on the effects of candesartan in patients with heart failure. Pharmacogenomics 2018;7:599–612.
92. He J, Gu D, Kelly TN, et al. Genetic variants in the renin-angiotensin-aldosterone system and blood pressure responses to potassium intake. J Hypertens 2011;9:1719–30.
93. Yang Y, Tian T, Lu J, He H, Xing K, Tian G. A1166C polymorphism of the angiotensin II type 1 receptor gene contributes to hypertension susceptibility: evidence from a meta-analysis. Acta Cardiol 2017;2:205–15.
94. Nakada TA, Russell JA, Boyd JH, et al. Association of angiotensin II type 1 receptor-associated protein gene polymorphism with increased mortality in septic shock. Crit Care Med 2011;7:1641–8.
95. Weil MH, Houle DB, Brown EB Jr., Campbell GS, Heath C. Vasopressor agents; influence of acidosis on cardiac and vascular responsiveness. Calif Med 1958;6:437–40.
96. Bauer SR, Sacha GL, Siuba MT, et al. Association of Arterial pH With Hemodynamic Response to Vasopressin in Patients With Septic Shock: An Observational Cohort Study. Crit Care Explor 2022;2:e0634.
97. Sacha GL, Lam SW, Duggal A, et al. Predictors of response to fixed-dose vasopressin in adult patients with septic shock. Ann Intensive Care 2018;1:35.
98. Wieruszewski PM, Wittwer ED, Kashani KB, et al. Angiotensin II Infusion for Shock: A Multicenter Study of Postmarketing Use. Chest 2021;2:596–605.
99. Sacha GL, Lam SW, Wang L, Duggal A, Reddy AJ, Bauer SR. Association of Catecholamine Dose, Lactate, and Shock Duration at Vasopressin Initiation With Mortality in Patients With Septic Shock. Crit Care Med 2022;4:614–23.
100. Jeyaraju M, McCurdy MT, Levine AR, et al. Renin Kinetics Are Superior to Lactate Kinetics for Predicting In-Hospital Mortality in Hypotensive Critically Ill Patients. Crit Care Med 2022;1:50–60.

101. Bellomo R, Forni LG, Busse LW, et al. Renin and Survival in Patients Given Angiotensin II for Catecholamine-Resistant Vasodilatory Shock. A Clinical Trial. Am J Respir Crit Care Med 2020;9:1253–61.
102. David S, Kümpers P, van Slyke P, Parikh SM. Mending leaky blood vessels: the angiopoietin-Tie2 pathway in sepsis. J Pharmacol Exp Ther 2013;1:2–6.
103. Ziegler T, Horstkotte J, Schwab C, et al. Angiopoietin 2 mediates microvascular and hemodynamic alterations in sepsis. J Clin Invest 2013;8:3436–45.
104. Fisher J, Douglas JJ, Linder A, Boyd JH, Walley KR, Russell JA. Elevated Plasma Angiopoietin-2 Levels Are Associated With Fluid Overload, Organ Dysfunction, and Mortality in Human Septic Shock. Crit Care Med 2016;11:2018–27.
105. Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ 2010;c117. [PubMed: 20354011]
106. Russell JA. Vasopressor therapy in critically ill patients with shock. Intensive Care Med 2019;11:1503–17.
107. De Backer D Detailing the cardiovascular profile in shock patients. Crit Care 2017;3:311.
108. Tacon CL, McCaffrey J, Delaney A. Dobutamine for patients with severe heart failure: a systematic review and meta-analysis of randomised controlled trials. Intensive Care Med 2012;3:359–67.
109. Koster G, Bekema HJ, Wetterslev J, Gluud C, Keus F, van der Horst IC. Milrinone for cardiac dysfunction in critically ill adult patients: a systematic review of randomised clinical trials with meta-analysis and trial sequential analysis. Intensive Care Med 2016;9:1322–35.
110. Léopold V, Gayat E, Pirracchio R, et al. Epinephrine and short-term survival in cardiogenic shock: an individual data meta-analysis of 2583 patients. Intensive Care Med 2018;6:847–56.
111. Antcliffe DB, Santhakumaran S, Orme RML, et al. Levosimendan in septic shock in patients with biochemical evidence of cardiac dysfunction: a subgroup analysis of the LeoPARDS randomised trial. Intensive Care Med 2019;10:1392–400.
112. Sato R, Ariyoshi N, Hasegawa D, et al. Effects of Inotropes on the Mortality in Patients With Septic Shock. J Intensive Care Med 2021;2:211–19.
113. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001;3:89–95.
114. Ammar MA, Ammar AA, Wieruszewski PM, et al. Timing of vasoactive agents and corticosteroid initiation in septic shock. Ann Intensive Care 2022;1:47.
115. Khanna A, English SW, Wang XS, et al. Angiotensin II for the Treatment of Vasodilatory Shock. N Engl J Med 2017;5:419–30.
116. Ammar MA, Limberg EC, Lam SW, et al. Optimal norepinephrine-equivalent dose to initiate epinephrine in patients with septic shock. J Crit Care 2019;69–74.
117. Komorowski M, Celi LA, Badawi O, Gordon AC, Faisal AA. The Artificial Intelligence Clinician learns optimal treatment strategies for sepsis in intensive care. Nat Med 2018;11:1716–20.
118. Scheibner A, Betthauser KD, Bewley AF, et al. Machine learning to predict vasopressin responsiveness in patients with septic shock. Pharmacotherapy 2022;6:460–71.
119. Chawla LS, Ostermann M, Forni L, Tidmarsh GF. Broad spectrum vasopressors: a new approach to the initial management of septic shock? Crit Care 2019;1:124.
120. Wieruszewski PM, Khanna AK. Vasopressor Choice and Timing in Vasodilatory Shock. Crit Care 2022;1:76.

Table 1.

Explanations for lack of differences noted between balanced crystalloids and normal saline solutions in large randomized trials.*

Issue	Explanation
Patients	Patients in the SMART investigation (the only study with a positive primary outcome in favor of balanced crystalloids) were unplanned admissions mostly via the emergency department, while most of the other large RCTs had substantial numbers of patients admitted to the ICU following operative procedures
Infusion rate	There was no standardization of the rates of fluid administration across the large RCTs and only one of these trials (BaSICS) evaluated a slow vs. fast infusion rate with no difference noted in overall mortality
Intervention fluid and deresuscitation strategies	Apart from randomization to balance crystalloid or normal saline, there was no standardization with respect to the use of study fluids or the manner in which fluids were initiated (e.g. bolus vs. infusion) or de-escalated during the stabilization or deresuscitation stages of treatment
Alterations in pH	There are strong ion differences not only between balanced crystalloids and normal saline, but also between balance crystalloids following intravenous administration
Use of vasoactive agents	All aspects of vasopressor and other vasoactive medication administration were based on physician discretion
Chloride administration	There were differences in the RCTs with respect to both the amount of chloride administered and the resultant serum chloride concentrations
Electrolytes other than chloride	Electrolyte concentrations of balanced crystalloids vary depending on the specific solution and this may be impactful (e.g. solution tonicity in patients with traumatic brain injury)
Non-study fluid administration	There was no standardization of non-study fluid type, initiation, rate of administration, or total volume administered

* Adapted from Kopp BJ, Lenney M, Erstad BL. Balanced salt solutions for critically ill patients: nonplused and back to basics. Ann Pharmacother. 2022 Apr. doi:10.1177/10600280221084380

SMART, isotonic Solutions and Major Adverse Renal Events Trial; RCTs, randomized controlled trials; ICU, intensive care unit; BaSICS, Balanced Solution versus Saline in Intensive Care Study

Table 2.

Potential genetic polymorphism targets within vasopressor pathways

Vasopressor	Receptor/Protein	SNP, Genotype	Outcomes Relevant to Shock
Catecholamines	α_{1a}-adrenoreceptor (ADRA1A)	rs1048101, Arg347Cys (formerly termed Arg492Cys)	Similar *in vitro* and *in vivo* agonist activity as other genotypes[84-86]
		Other ADRA1A SNPs	No difference detected between genotypes for *in vivo* phenylephrine-induced vasoconstriction. Some indication for genotype variants of SNPs rs574647 and rs1079078 having increased and decreased, respectively, *in vivo* sensitivity to phenylephrine-induced vasoconstriction.[84]
	β_1-adrenoreceptor (ADRB1)	rs1801253, Arg389Gly	Lower *in vitro* agonist activity, attenuated *in vivo* dobutamine-induced chronotropy and inotropy[87]
	β_2-adrenoreceptor (ADRB2)	rs1042717, AA genotype	Higher mortality, more organ dysfunction, higher heart rate, and higher norepinephrine dose requirement in septic shock[88]
Vasopressin (and analogues)	Vasopressin receptor 1a (AVPR1A)	rs10877970, rs1495027, and rs3803107	No difference detected between genotypes for mortality in septic shock[89]
	Vasopressin receptor 1b (AVPR1B; also known as V3 receptor)	rs28418396, AA genotype	Lower area under the vasopressin plasma concentration-time curve, more frequent serious adverse events, and higher mortality in septic shock[90]
	Leucyl/cystinyl aminopeptidase (LNPEP)	rs4869317, TT genotype	Higher plasma vasopressin clearance and higher mortality in septic shock[89]
Angiotensin II	Angiotensin II type 1 receptor (AGTR1)	rs5186, A1166C	Higher agonist activity, higher susceptibility to hypertension, and higher renin activity with angiotensin receptor antagonist in heart failure.[91-93] No difference detected between genotypes for mortality in septic shock.[94]
	Angiotensin II type 1 receptor-associated protein (AGTRAP)	rs11121816, GG genotype	Higher mortality, lower mean arterial pressure, and higher heart rate in septic shock.[94]

SNP = single nucleotide polymorphism