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The Right Vasopressor at the Right Time Does Early Use of Vasopressors Decrease Morbidity and Mortality in Septic Shock

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The Right Vasopressor at the Right Time

Does Early Use of Vasopressors Decrease Morbidity and Mortality in Septic Shock

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Abstract

Sepsis and septic shock is a disease process that carries a high mortality rate and is responsible for a large portion of healthcare expenditures in the United States. The Surviving Sepsis Campaign has been working to decrease the mortality of sepsis since 2001. Their mission is two-fold; providing evidence based guidelines to help direct treatment, and raising awareness to healthcare providers and patients about sepsis. A main goal in treating sepsis is to reverse the hypoperfused state by giving crystalloid fluids and administering vasopressors, specifically norepinephrine, after patients have received adequate fluids. Would modifying this treatment by giving a combination of vasopressors, instead of the current recommendation of just norepinephrine, earlier decrease the mortality of patients in septic shock?

After performing a literature search on PubMed and Google Scholar, 80 articles were found and narrowed down to a total of 32, including randomized control trials, animal trials, retrospective and prospective cohort studies and meta-analyses, were reviewed. Articles looked at norepinephrine, vasopressin, terlipressin, dobutamine, and early vasopressor use.

This literature review found that there is some evidence supporting the early use of combination vasopressor therapy, though more in-depth trials should be performed before making stronger recommendations or changing guidelines. Different patient subgroups appear to have better outcomes based on the different combinations of vasopressors. Norepinephrine continues to be a mainstay of treatment, and patients need to receive crystalloid fluids before and during administration of vasopressors.

Introduction

More than 1.7 million Americans suffer from sepsis each year.[1] Sepsis has a high mortality rate calculated between 10 and 52% with mortality increasing with disease severity.[2] Sepsis, if unnoticed and left untreated, can quickly progress into septic shock which is very severe and life threatening. Septic shock is a type of distributive shock that causes the vasculature of a body to dilate.[2] This vasodilation drops the systemic vascular resistance, thereby decreasing cardiac output and causing a hypoperfused state for the tissues of the body.[2] The Surviving Sepsis Campaign, which is a consortium of doctors and researchers formed in 2002 whose overarching goal is to reduce mortality from sepsis as well as provide guidelines for treatment, defines sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection".[3] Another group working towards understanding is Sepsis 3. Sepsis 3 is the third international consensus of what sepsis and septic shock are, and is created by a separate task force of experts to have a common definition of the disease states.[4] It defines septic shock as "a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality".[4] Septic shock is becoming more prevalent throughout the world resulting in increased costs of approximately $20 billion in the United States in 2011 alone.[4] Improving management and updating the guidelines for the care of sepsis and septic shock could help to decrease mortality in vulnerable patients and help lower healthcare costs.

The Surviving Sepsis Campaign came out with their most recent guidelines for the treatment of septic shock in 2016 but provides updates to these guidelines in order to account for new findings with the goal to continually improve care.[3] These new guidelines recommend treatment start with the goal of obtaining a Mean Arterial Pressure (MAP) of greater than

65mmHg.[3] The first step in obtaining this goal is a crystalloid fluid bolus of 30 mL/Kg within the first 3 hours of the onset of septic shock followed by more boluses of crystalloid fluid.[3] The use of norepinephrine as the first line vasopressor for fluid resistant septic shock is recommended next, followed by the addition of other vasopressors including vasopressin, epinephrine, dobutamine and dopamine.[3]

Although this is the current recommendation, there are many adverse reactions that can occur with this particular treatment regimen for septic shock. Aggressive fluid resuscitation can cause dire complications from volume overload including pulmonary edema requiring the patient to be placed on ventilator support.[5] Vasopressor use also has a downside, with many patients having a wide variety of unwanted adverse reactions including but not limited to arrhythmias, and digital and cardiac ischemia.[3,6] In light of new research, the Surviving Sepsis Campaign released an update in 2019 which includes the Hour-1 Bundle moving the use of vasopressors into the first hour of resuscitation, if clinically indicated, to help combat or preemptively treat some of the known adverse reactions.[5] Does earlier use of combination vasopressors decrease the morbidity and mortality of patients with septic shock compared to the previous standard of care of a fluid bolus followed by the use of vasopressors?

Methods

A literature search was completed using PubMed and Google Scholar. The key words included in the search were, “Sepsis”, “Septic Shock”, “Vasopressors”, “Norepinephrine”, “Vasopressin”, “Crystalloid”, and “Resuscitation.” A search of the references from these articles also produced more literature. Originally 80 articles were selected, these were further narrowed down. The vast majority of articles were published within the last 10 years. One trial was

published 11 years ago but deemed necessary due to it being viewed and used as foundational in current literature and trials. Inclusion criteria for this systematic review included evaluating conflicts of interest of the authors, evaluating study designs, and assessing the authors' interpretation of their data sets. There are five articles that evaluated norepinephrine dosing, six articles comparing the use of different doses of norepinephrine to the use of norepinephrine in combination with other vasopressors, twelve articles comparing the use of vasopressin with and without norepinephrine to the use of norepinephrine alone, seven articles that compared the use of terlipressin with and without norepinephrine to norepinephrine alone, and six articles comparing early use of vasopressors to later use. Randomized control trials, retrospective observational non-interventional studies, nested cohort studies, prospective observational studies, prospective interventional trials, meta-analyses, and animal trials were all included. Each article was reviewed individually and information was collected specifically for this review. Also reviewed were the previous and current recommendations from the Surviving Sepsis campaign to see the evolution of care.

Background

Norepinephrine

Surviving Sepsis Campaign has recommended norepinephrine as the first-line vasopressor in their guidelines since 2008.[6] Their recommendation for this intervention has only increased in strength since the first guidelines were published due to their analyses of recent trials and studies.[3,7] The goal of treatment associated with adding a vasopressor is to attain a MAP greater than 65mmHg.[3,5-7] MAP is an important measurement of the pressure at the level of the organs and if it falls too low the organs are not perfused.[3] If an organ is not perfused, the cells

start to die, and the tissues and organs are not able to function.[3] A MAP below 65mmHg is associated with the hypoperfusion of organs and higher mortality since inadequate amounts of oxygen is being delivered.[3] Norepinephrine is a catecholamine that is both an alpha and beta 1 agonist.[8] It acts as a strong alpha agonist causing vasoconstriction, which increases systemic resistance and, in turn, blood pressure.[8] It also acts as a weak beta 1 agonist, having inotropic and chronotropic effects.[8] Adverse reactions include arrhythmias, bradycardia, peripheral vascular insufficiency and peripheral ischemia.[8]

Norepinephrine is an effective vasopressor, especially in patients that are severely hypoperfused. A prospective observational study by Chen et al followed 372 patients with acute kidney injuries from septic shock.[9] The study tracked the amount and frequency of the vasopressors they received and patients' 90 day mortality after dialysis was started.[9] The study found no statistical difference in mortality rates between the norepinephrine group when compared to the non norepinephrine group, which included the use of other vasopressors such as dopamine, dobutamine, epinephrine, isoproterenol and milrinone.[9] Even though there was no significant change in mortality, this study did find that patients receiving norepinephrine spent a statistically significant less amount of time on dialysis compared to the non norepinephrine group.[9] This is particularly interesting since the norepinephrine group was comprised of more severely ill patients with significantly higher Sequential Organ Failure Assessment (SOFA) scores.[9] SOFA scores are a measurement tool used in intensive care units (ICU) to help predict mortality based on the function of organ systems, including cardiovascular, respiratory, hepatic, neurologic, renal and coagulation.[2]

Similarly, a meta-analysis reviewed 14 studies including a total of 2811 patients who received vasopressors for septic shock.[10] Oba and Loan looked at the benefit and effectiveness of different vasopressors in septic shock.[10] They concluded that norepinephrine and norepinephrine with low dose vasopressin can decrease 28 day mortality when compared to patients receiving dopamine alone.[10] In their analysis, they concluded that dopamine should not be completely ruled out as a treatment option as it may have a place in treating patients with a low risk of arrhythmias.[10] Another meta-analysis of 43 randomized control trials with a total of 5767 patients in septic shock evaluated the effects of vasopressors on adverse reactions and 28 day mortality.[11] Cheng et al found more incidences of arrhythmias with dopamine, 26.01%, epinephrine, 22.98%, norepinephrine with dobutamine, 20.6%, as compared to norepinephrine alone, 8.33%, and vasopressin, 1.67%.[11] In this analysis there was a decrease in mortality when adding dobutamine to norepinephrine.[11] The combination therapy of norepinephrine and vasopressin was associated with shortened hospital stays for patients.[11] Finally, the analysis found that when terlipressin was added to norepinephrine it decreased ICU mortality for patients with sepsis compared to the use of other vasopressors in similar patients.[11] Based on these studies norepinephrine continues to be an effective vasopressor and is justified as the first line treatment in the Hour-1 Bundle for combating hypoperfusion and its associated complications for patients with septic shock as stated in the guidelines.[3,9,10,11]

Not covered in the most recent Surviving Sepsis Campaign's guidelines is the recommended dosing of norepinephrine to attain the MAP goal. Per UpToDate, the recommended dose to treat septic shock is 0.01-3 mcg/kg/min.[8] There does not appear to be a consensus for dosing, though many studies are showing high doses of norepinephrine is

associated with increases in morbidity and mortality. Many studies and trials are trying to pinpoint what should be considered a high and low dose.

There has been much speculation and debate about how much norepinephrine is too much. A retrospective study by Chou et al out of China in 2011 reported that doses greater than 0.3mcg/kg/min significantly increased mortality for patients.[12] The higher dosage showed a mortality of 93.5% compared to 66.4% ($p<0.001$) for patients receiving less than 0.3mcg/kg/min.[12] This study had a high overall mortality, which was attributed to the high prevalence of severe acute kidney injury documented by a drastic decrease in average urine output, 0.3 L/24hrs, and elevated serum creatinine, 4.8+/-4.1 mg/dL.[12] The researchers followed the patients for 60 days after treatment, noting that 97.5% of the patients died before 60 days and 2% dying after the 60 days, leaving only .5% as survivors.[12] The main focus of Chou et al's study was looking at the results of continuous renal replacement therapy (CRRT) in critically ill patients receiving high doses of vasopressors.[12] Patients who did not require CRRT were not included in this study. Crystalloid fluid therapy is not mentioned, and it is unknown if this played any role in this retrospective observational study.

On a similar note, Martin et al performed a retrospective, non-interventional, observational study looking at ICU patient charts over a 4 year period and evaluated their 90 day mortality.[13] The study showed that a norepinephrine dose of greater than 1mcg/kg/min is linked to higher mortality, up to 90%, for patients experiencing septic shock.[13] The higher dose was associated with higher mortality compared to lower doses of norepinephrine, but interestingly the link between higher mortality and high doses of norepinephrine had death occurring during the

infusion.[13] If patients survived the original high dose infusion of norepinephrine, the mortality rate remained consistent with other, lesser dosages.[13]

Defining what is considered a high dose of norepinephrine has been difficult to determine. Auchet et al conducted a retrospective observational study looking for predictors of mortality in patients experiencing septic shock.[14] They found a high predictive value of mortality when high dose norepinephrine is given to a patient who already has a high SOFA score.[14] This study looked at the total doses of vasopressors divided by the total time they were given and came out with a weight based mean dose.[14] Their data showed a weight based mean dose of 0.75 mcg/kg/min, as the high dose, has a good predictive value of mortality with a sensitivity of 73% and a specificity of 74%.[14] They also looked at maximum dosage given, and most survivors in this study had received a maximum dose of less than 2.3 mcg/kg/min at some point during their care.[14] The max dose had a smaller predictive value compared to the weight based mean dose.[14] This study did have a smaller 90 day mortality rate, 60%, compared to other high dose norepinephrine studies.[14]

A nested cohort study in the Dexmedetomidine for Sepsis in Intensive Care Unit Randomized Evaluation (DESIRE) trial by Yamamura et al considered a high dose of norepinephrine as greater than 416 mcg/kg/week.[15] This dose averaged out to 0.04 mcg/kg/min though they were looking at total norepinephrine given over the first week of treatment, not just individual doses.[15] Both arms of the study, a high dose and a low dose group, received boluses of crystalloid fluids before starting vasopressors.[15] The high dose group did require higher doses of supplemental vasopressors (dobutamine and vasopressin), required more crystalloid fluid both in day 1 and day 2 of treatment, and had less ventilator free days when compared to the low dose

group.[15] There was no difference in mortality between the two groups.[15] Again, this study looked at total norepinephrine dose over a week not individual doses, but based on their graphs the highest dosage was given on day 2 of treatment with approximately 300 mcg/kg/day given, which averages out to a dose of 0.2 mcg/kg/min.[15] This amount is still well below the high doses used in other studies that considered at least 1 mcg/kg/min as its high dose.[12-15] Chen et al looked at patients with acute kidney injuries from septic shock, vasopressors they received, and 90 day mortality after dialysis was started.[9] The study showed norepinephrine may have a detrimental effect on severely ill patients with acute kidney injury following septic shock, but survivors who received norepinephrine tended to spend less time on dialysis.[9] The researchers also found that this increase in mortality was dose dependent and also took into account an increase in adverse effects associated with higher doses of norepinephrine.[9] There is a lack of agreement as to what constitutes a high dose of norepinephrine, but it is observed that higher doses are linked to increased risks of adverse effects that are tied to higher mortality.[9,12-14] There is no consensus on what constitutes a high dose of norepinephrine but there is sufficient evidence that higher mortality is associated with elevated doses of norepinephrine, but what constitutes a high or low dose is not the only factor to consider when looking at norepinephrine use.

With higher mortality and morbidity associated with higher dose norepinephrine, are there certain patient populations that affect the pharmacokinetics and pharmacodynamics of norepinephrine and require different doses or combinations of vasopressors? A retrospective cohort study performed by Bauman et al did a 2 year review of 159 patients in septic shock who required vasopressors.[16] This study found that racial differences can affect how a patient will respond to different vasopressors.[16] The data showed that with similar severity of sepsis and

similar pre-vasopressor treatments, African Americans require higher doses of norepinephrine when compared to Caucasians, 21.08 mcg/hr versus 12.37 mcg/hr ($p<0.01$) respectively.[16] This study looked at total doses[16] and did not show weight based dosing, which is how norepinephrine is normally dosed. They also found that the African American patients had a statistically significant higher prevalence of pre-existing hypertension, 68.3% versus 31.7% ($p=0.007$), and end stage renal disease, 85.7% versus 14.3%($p=0.011$), when compared to similar Caucasian patients.[16] The source of the infections that caused the patients to go into septic shock were also significantly different.[16] Bloodstream infections were more frequent in African Americans, 8.2% versus 0.6% $p=0.017$, while abdominal infections were more prevalent in Caucasians, 13.8% versus 10.7% $p=0.008$.[16] Though severity of septic shock was comparable between the two groups, source of infection and preexisting conditions may alter how the disease progresses therefore changing the treatment. That said, racial differences and medical histories appear to play a role in how a patient responds to treatment.

Norepinephrine is very effective as a first line vasoconstrictor in the treatment of septic shock.[3] There is no upper limit of dosing listed in the guidelines, and there does appear to be a risk of increased morbidity and mortality associated with higher dose infusions of norepinephrine.[3,9,12-15] The use of other vasopressors, like vasopressin, in conjunction with or apart from norepinephrine, have been studied to see if there are better treatment plans available that could decrease these risks in patient populations. There is evidence that when patient situations and patient populations are considered there are different combinations of treatment options that may increase the likelihood of a positive outcome.

Vasopressin

The current Surviving Sepsis Campaign guidelines weakly recommend adding vasopressin to norepinephrine to either increase MAP to the target goal or to decrease the norepinephrine dosage that is tied to higher mortality.[3] Vasopressin is an antidiuretic hormone analog that binds to arginine vasopressin (AVP) receptors.[17] There are two types of AVP receptors, V1 and V2. V1 increases systemic vascular resistance, and V2 increases aquaporin production in the renal tubule increasing water reabsorption, both of these work to increase tissue perfusion.[17] While vasopressin treatment has shown to increase MAP, there are multiple reasons to be cautious and why this is only a weak recommendation.[3,17] Adverse effects include atrial fibrillation, ischemic heart disease, myocardial infarction, limb ischemia, hyponatremia, renal insufficiency, increased serum bilirubin, and decreased platelet count.[3,17] Vasopressin can be used as part of a combination therapy with norepinephrine or potentially as an initial monotherapy, though there are concerns about adverse reactions when using vasopressin alone or in combination therapies and how timing of administration affects these effects.

One of the potential adverse effects of vasopressin use is cardiac ischemia, which is normally diagnosed with a 12 lead electrocardiogram (ECG) and elevated troponin and CK-MB levels. Mehta et al performed a prospective sub study as part of the VASST study.[18] They specifically looked at troponin levels, CK-MB levels, and 12 lead ECGs as markers for cardiac ischemia in the 121 patients who received either a low dose of vasopressin, 01-0.3 U/min, or norepinephrine, 5-15 mcg/min, after already receiving 5 mcg/min of norepinephrine.[18] There was no difference in the elevation of troponin and CK-MB levels between the two groups in this substudy.[18] The only difference between the two groups on the 12 lead ECG was that the norepinephrine monotherapy group had a higher presence of Q waves, 26% versus 18% p=0.039,

compared to the vasopressin group.[18] Q waves can be a sign of cardiac ischemia. There was no statistical difference in the presence of ST segment elevation, ST segment depression or T-wave inversion.[18] There was no correlation found during this study with the presence of cardiac ischemia and increased mortality.[18] Although cardiac ischemia is a concern with the use of vasopressin, vasopressin paired with norepinephrine does not appear to be more responsible at causing cardiac ischemia when compared to the use of norepinephrine alone. Making sure that the patient does not already have a history of acute coronary syndrome or severe heart failure is vital before administration.

Russell et al performed the Vasopressin and Septic Shock Trial (VASST) to see if a low dose infusion of vasopressin administered in combination with norepinephrine decreased mortality compared to patients being treated with norepinephrine alone.[19] They analyzed 778 patients who had been randomized into the trial.[19] VASST looked at 0.01-0.03 U/min infusions of vasopressin given with 5 mcg/min of norepinephrine compared to patients receiving only norepinephrine at 5-15 mcg/min.[19] There was no significant change in mortality at 28 days, 35.4% versus 39.3%(p=0.26), or at 90 days, 43.9% versus 49.6% (p=0.11) between the vasopressin and norepinephrine groups respectively.[19] There was also no statistical difference between the amount or severity of adverse reactions between the two groups, 10.3% in the vasopressin group and 10.5% in the norepinephrine group (p=1.00).[19] Though not statistically significant, there were more incidences of cardiac arrests in the norepinephrine group and more incidences of digital ischemia in the vasopressin group.[19] It is important to note that the study did exclude patients if they had a known history of acute coronary syndrome or severe heart failure since these conditions are both known to worsen with vasopressin administration.[19] An

interesting aspect about this study was that the baseline MAP for patients studied was between 72-73 mmHg, already in the target range of 65-75mmHg.[19] The authors note that as the study progressed it became more of a norepinephrine sparing study as opposed to unresponsive to norepinephrine study as originally intended.[19] The VASST study found that combination therapy is not superior to norepinephrine monotherapy.[19] VASST evaluated the use of low doses of vasopressin in patients who had already achieved the MAP goal[19], but the authors cede that there are other doses and other times that vasopressin could and should be administered to promote positive treatment results.

One such instance is higher dose vasopressin combination therapy may be more effective than low dose vasopressin monotherapy at treating septic shock. Torgersen et al performed a randomized control open label trial to compare and determine effective dosing of vasopressin.[20] The two doses used were 0.033 and 0.067 U/min as part of combination therapy with norepinephrine at a dose of at least 0.6 mcg/kg/min.[20] Patients were given the combination therapy for a total of 48 hours.[20] This was a small study with 50 total patients randomized.[20] The researchers noted that the patients in the higher dose group had a greater reduction in norepinephrine doses at 48 hours 0.22 +/- 0.16 mcg/kg/min in the high dose vasopressin group and 0.4 +/- 0.31 mcg/kg/min in the low dose group (p=0.006).[20] Troponin levels were also significantly lower in the higher dose vasopressin group 0.22 +/-0.41 mg/dL compared to 1.77 +/- 4.8 mg/dL (p=0.03).[20] Another adverse reaction of vasopressin is a fall in platelet counts. In this study the low dose vasopressin group had a statistically significant drop (p=0.02) in platelets while the high dose group did have a drop, although it was not statistically significant (p=0.18).[20] Mortality rates were not affected between the two treatment groups, ICU mortality was 40% in

the low dose versus 52% in the high dose (p=0.57), and 28 day mortality was 52% (p=1) for both groups.[20] Vasopressin as used in combination therapy appears to be more effective in higher doses at increasing and maintaining MAP, thereby decreasing the amount of norepinephrine needed.[20] The adverse reactions were also decreased in the higher dose vasopressin group compared to the low dose group.[20] Dosing of vasopressin does appear to affect its effectiveness in reversing hypoperfusion in septic shock. Another important factor that health care providers should consider as it could change how well a patient responds to vasopressin is the timing of administration.

Russel et al reevaluated their data from the VASST study after the new Sepsis 3 criteria came out, evaluating it based on the new criteria for sepsis.[21] The Sepsis 3 criteria requires that septic shock be identified when a patient displays "persistent hypotension requiring vasopressors to maintain a MAP greater than 65 mmHg and having a serum lactate greater than 2 mmol/L despite adequate volume resuscitation."[4,21] Bringing in the new requirement for a lactate greater than 2 mmol/L reduced the sample size from VASST, but the new sample still showed no significant difference in mortality for the norepinephrine plus vasopressin group compared to the norepinephrine alone group.[21] The researchers did find that patients that were treated according to the older inclusion criteria who had a lactate level less than or equal to 2 mmol/L had a significantly lower mortality in the vasopressin group compared to the norepinephrine group at both 28 days, 27.2% versus 36.6% (p=0.086), and at 90 days, 35.6% versus 47.9% (p=0.036).[21] This reanalysis of the data exposes a subset of patients that may benefit from early combination therapy.

Since the VASST trial reanalysis exposed a subset of patients that may benefit from the combination therapy of norepinephrine and vasopressin[21] Sacha et al performed a retrospective review looking to identify other predictors of that could show which patients might benefit from the combination therapy.[22] This review looked at 938 ICU patient charts to evaluate who responded to vasopressin by achieving a MAP greater than 65mmHg at 6 hours post vasopressin infusion.[22] The researchers noted a 45% response rate to a fixed dose, 0.03 U/min, of vasopressin.[22] The group of patients that responded to vasopressin had a decrease in mortality, 56.6% versus 71.7% ($p<0.001$)[22], and a decrease in the dosage of norepinephrine needed.[22] They also noted that patients with a lactate of less than or equal to 1.4 mmol/L were more likely to respond to vasopressin ($p<0.001$).[22] Vasopressin is effective overall but it is shown to be even more effective when patients are not already in a state of severe septic shock.

In addition to lactate levels, there are other potential predictors of vasopressin response. Nascente et al performed a small prospective interventional study with 18 patients.[23] The study included patients in septic shock who had already received crystalloid fluid boluses and norepinephrine, the patients then received a vasopressin dose of 0.04 U/min and infused patients for 1 hour followed by 48 hours of observation.[23] The evaluators obtained sidestream dark field imagery of the sublingual microvasculature and compared three images; one from before treatment, another from 1 hour after the initial vasopressin infusion, and the last from 2 hours after the infusion.[23] The researchers reported that 50% of the patients had microvascular response to vasopressin and classified these patients as responders.[23] Both groups, the responders and nonresponders, had a decrease in the norepinephrine dose required to maintain a MAP greater than 65 mmHg during the 1 hour infusion of vasopressin.[23] However, the study found that the

nonresponders had a need for a significant increase in norepinephrine dosing after the cessation of the vasopressin infusion to maintain a MAP of 65 mmHg or greater.[23] The responders did not have a similar need for an increase in norepinephrine.[23] The researchers also found that patients who are receiving higher doses of norepinephrine before the administration of vasopressin are more likely to have a microcirculatory response to vasopressin, specifically patients receiving norepinephrine doses above 0.38 mcg/kg/min.[23] They assigned a predicted probability of 53% with a sensitivity of 78% and a specificity of 77%.[23] Although this study helped to predict who would respond to vasopressin combination therapy, there were many shortcomings that make drawing definitive conclusions challenging including a restrictively small sample size with no randomization nor control. The study looked only at the results of the infusion of vasopressin for a short period of time and no long term effects were followed.[23] Predicting who will respond to the combination therapy is very important, providers do not want to waste valuable time and risk adverse reactions if it is known a patient will not respond to the therapy. More studies need to be completed and analyzed to strengthen current guidelines and recommendations.

Studies are finding that there are patients who respond with the addition of vasopressin to norepinephrine and those who do not respond. Timing may be a confounder affecting who responds. Hammond et al performed a prospective open label trial testing if early dosing of norepinephrine with vasopressin decreased morbidity and mortality compared to norepinephrine monotherapy.[24] Over two separate 4 month periods, the evaluators added patients who were in septic shock and had received at least 30mL/kg fluid bolus in the previous 4 hours of treatment into the study.[24] In the first 4 month period patients were treated with norepinephrine starting at 5mcg/min.[24] The primary outcome of the study was to find the amount of time needed to achieve

a MAP of 65 mmHg and then maintain it for 4 hours. In the norepinephrine monotherapy portion, a failure was considered an inability to achieve or maintain a MAP of 65 mmHg with a dose of up to 15mcg/min.[24] In the second study period, patients were started on 5mcg/min of norepinephrine and then given vasopressin at a dose of 0.04 U/min within 4 hours of starting the norepinephrine.[24] Norepinephrine was then titrated up to achieve and maintain the MAP goal.[24] If unable to achieve or maintain the MAP with a norepinephrine dose of 15 mcg/min, the dual therapy was considered a failure.[24] A total of 82 patients, 41 in each group were analyzed.[24] Both groups had elevated lactate levels, greater than 4 mmol/L.[24] They found that early use of vasopressin decreased the time it took for patients to reach and maintain a MAP greater than 65mmHg when compared to the norepinephrine monotherapy group, 5.7 hrs versus 7.6 hrs ($p=0.058$).[24] Vasopressin was used as a secondary vasopressor in 46% of the patients in the monotherapy group.[24] In this study, the adding of vasopressin to norepinephrine within 4 hours of onset of septic shock was more effective at achieving and maintaining the MAP goal.[24] The researchers did not show any difference in mortality, hospital stay length, or new onset of arrhythmias between the two groups.[24] It also appears that elevated lactate levels did not affect the effectiveness of vasopressin in this study.[24]

A small retrospective cohort analysis performed by Reardon et al looked at early versus late delivery of vasopressin in septic shock.[25] Early delivery was defined as less than 4 hours after the start of norepinephrine.[25] The dose of vasopressin in this review was 0.04 U/min.[25] The researchers found a significant decrease in the number of new onset arrhythmias noted in the early administration group compared to the late group, 37.1% versus 63.9% ($p<0.001$) respectively.[25] The most common new arrhythmia was atrial fibrillation with rapid ventricular

response.[25] There was no noticeable difference between the amount and duration of norepinephrine used.[25] Another finding, though not statistically significant, was a trend of elevating troponin ($p>0.05$) and CK-MB ($p>0.05$) in the late administration of vasopressin.[25] These studies demonstrate that the early use of combined norepinephrine and vasopressin is able to achieve targeted MAP goals earlier than norepinephrine monotherapy.[24,25] Early combination therapy also shows a decrease in adverse effects like the amount of arrhythmias and possibly a decrease in cardiac ischemia when compared to late use of vasopressin.[24,25]

Vasopressin combination therapy has been shown to lower the risks of cardiac problems,[24,25] though dosing may affect its effectiveness.[26] Russell, Wellman, and Walley evaluated mortality rates between norepinephrine and combination therapy of norepinephrine and vasopressin, looking at rates both before and after the VASST study was performed at their hospital.[26] This retrospective matched cohort study found that before the VASST trial, combination therapy of norepinephrine and vasopressin had a higher 28 day mortality rate compared to norepinephrine alone, 60.8% versus 46.2% ($p=0.009$).[26] After the trial the mortality rates of patients receiving combination therapy were comparable to the monotherapy patients, 31.2% and 26.9%.[26] Since this is a retrospective cohort study, they did not find a cause for this change in mortality. The authors speculate that it could have been due to a decrease in the amount of initial vasopressin given after the VASST study, 0.032 U/min post VASST and 0.036 U/min ($p=0.001$) pre VASST.[26] Another possible cause could have been that benefits of treatment outweighed any adverse events, which they did not assess. Also postulated is that the providers may have been more aware of the guidelines of when to use vasopressin and when not to based on the severity and circumstances of the patient.[26] Either way, it is very interesting that

the mortality rates changed after the study, and that habits of prescribing vasopressin changed as well.

With changing the dosing and timing of vasopressin and norepinephrine combination therapy, it has shown to be superior to norepinephrine monotherapy at reversing the hypoperfused patient in septic shock.[20-25] Vasopressin is effective as an adjunctive vasopressor and vasopressin may be just as effective as norepinephrine if used as monotherapy. The vasopressin versus norepinephrine as initial therapy in septic shock (VANISH) trial evaluated the use of vasopressin as monotherapy compared to norepinephrine.[27] This was a double blinded, randomized clinical trial with vasopressin doses up to 0.06 U/min and norepinephrine doses up to 12 mcg/min.[27] Open label use of norepinephrine was used as a supplement vasopressor when patients were maxed out on study medication and still had not reached a MAP of 65 mmHg.[27] They also tested giving hydrocortisone versus a placebo to patients, creating a total of 4 arms to this study.[27] There were 408 patients who were analyzed from the initial 421 who were randomized.[27] They noted no difference in mortality between the groups that received norepinephrine, 27.5%, and vasopressin, 30.9%, at 28 days.[27] The patients treated with vasopressin had a lower rate of needing renal replacement therapy, 25.4% versus 35.3%.[27] Also of note is that the use of vasopressin compared to norepinephrine did not affect the amount of new onset organ failure or the amount of organ failure free days.[27] The total amount of open label norepinephrine use was lower in the vasopressin group when compared to the norepinephrine group, while MAP measurements had no significant difference between the two groups.[27] Initial vasopressin monotherapy did not improve or worsen mortality compared to norepinephrine monotherapy and was just as effective at maintaining MAP.

Vasopressin is currently recommended as an adjunctive medication for patients not reaching or maintaining a MAP goal of 65 mmHg on norepinephrine alone.[3] There is evidence showing that there are patient populations that may benefit from the addition of vasopressin to norepinephrine in a combination therapy.[20-25] There is also an indication from the evidence collected that the earlier the combination therapy is started, the more effective the treatment is at fighting the hypoperfused state.[20-25] Along with the support for combination therapy of vasopressin and norepinephrine, there is data that validates that initial monotherapy of vasopressin is as effective as norepinephrine monotherapy.[27] Vasopressin is not the only antidiuretic hormone analog, terlipressin is another analog that may be effective in reversing the hypoperfusion associated with septic shock and may not carry the same risks of adverse effects as vasopressin.

Terlipressin

Terlipressin is a long acting antidiuretic hormone analog that is selective for the V1 receptor. Terlipressin is currently unavailable in the United States, but it is in a phase 3 clinical trial for hepatorenal syndrome type 1.[28] Terlipressin is used elsewhere in the world for treatment of hepatorenal syndrome and hemorrhaging esophageal varicies.[29,30]

Terlipressin has been used in animal studies and has shown its effectiveness as a vasopressor in the treatment of septic shock. Ishikawa et al gave bolus injections of terlipressin to sheep that were in septic shock.[29] The two study arms consisted of a single 1mg bolus and a 1mg bolus followed by two sequential boluses of 0.5mg every 2 hours.[29] They found that terlipressin was able to return the MAP to the target level but caused decreased coronary and mesenteric blood flow, as well as worsening hyperlactatemia and hypokalemia.[29] Kampmeier et

al compared giving terlipressin at 2 mcg/kg/hr either as first line vasopressor, or as a second line after norepinephrine exceeded dosing of 0.5 mcg/kg/min and a 0.9% sodium chloride infusion.[30] This study used sheep that were put into septic shock and the intervention period was only 24 hours.[30] There was no difference in 24 hr mortality, change in norepinephrine, or fluid requirements.[30] The animal studies showed that terlipressin is an effective tool to increase MAP in septic shock and reverse the hypoperfused state, but that there were also possible serious and severe adverse effects that need to be further evaluated.[29,30]

Two studies evaluated the effectiveness of terlipressin compared to norepinephrine as initial monotherapy in septic shock. Adverse effects were more serious and prevalent in these studies,[31,32] confirming what was found in the animal trials.[29,30] Choudhury et al discovered that terlipressin had more incidences of adverse effects, 40.5% versus 21.4% ($p=0.06$), compared to norepinephrine.[31] 28 day mortality was comparable between terlipressin, 73.8%, and norepinephrine, 85.7% ($p=0.17$). [31] Lui et al also found the terlipressin group did have a higher percentage of serious adverse effects, 30% compared to the 11.65% in the norepinephrine group ($p<0.01$).[32] Digital ischemia was found to be the singular significantly increased adverse effect in the terlipressin group, 12.6% versus 0.35% ($p<0.0001$).[32] These two studies illustrate that there can be increased morbidity with the use of terlipressin monotherapy, when compared to norepinephrine monotherapy.[31,32]

Even with the increased adverse effects, terlipressin was still shown to be effective in animal studies[29,30]and appears to be an effective vasopressor for humans in septic shock. Choudhury et al performed a randomized open label trial comparing terlipressin to norepinephrine as a first line vasopressor for patients with cirrhosis and septic shock who are

unresponsive to fluid boluses after 2 hours.[31] This was a small study with a total of 84 patients.[31] The researchers found that patients in the terlipressin group were able to obtain a MAP greater than 65 mmHg within 48 hours; better than the norepinephrine group, 95.2% versus 71.4% (p=0.003).[31] Something else of note, though not statistically significant, is that the terlipressin group had a higher lactate clearance (p=0.06) and improved tissue perfusion compared to the norepinephrine group.[31] Lactate clearance was able to help predict mortality.[31] Lactate clearance decline noted at 12 hours was statistically significant in patients who died compared to patients who survived at 28 days, 58% versus 4% (p=0.01).[31] The terlipressin group also had a trend towards reversing acute kidney injuries on day 5, 37.5% versus 8.3% (p=0.08).[31] Also noted in the study was that patients in the norepinephrine group had a significantly higher incidence of variceal bleeding compared to the terlipressin group, 9.5% versus 0% (p=0.01).[31] This information may help to identify patient populations that would benefit from the use of terlipressin as opposed to norepinephrine.

Liu et al performed a randomized double blinded control trial that compared terlipressin to norepinephrine use as the initial vasopressor for the treatment of septic shock.[32] The study had two treatment groups. Patients who were still hypotensive despite adequate fluid resuscitation were given either terlipressin at 20-160 mcg/hr or norepinephrine at 4-30 mcg/min.[32] The study was stopped after 50% recruitment due to interim results falling into the futility region for the study.[32] There were 526 patients that were analyzed for this study.[32] They found no difference in mortality between the terlipressin and norepinephrine groups, 40% versus 38% (p=0.633).[32] Both groups had similar improvement in their 7 day SOFA scores, decreasing by 7 in the terlipressin group and 6 in the norepinephrine group (p=0.123).[32] Days without vasopressors were also very

similar, 14.66 days for terlipressin and 15.5 days for norepinephrine (p=0.424).[32] Terlipressin appears to work as effectively as norepinephrine at reversing the hypoperfused state, and may be a better choice for first line treatment with certain patient populations, this should be tempered with the fact that more adverse effects were noted with terlipressin and it is still not cleared to be used on humans in the United States.[31,32]

Vasopressin is recommended as an adjunct to norepinephrine according to Surviving Sepsis Campaign guidelines.[3] With terlipressin being a long acting, selective V1 agonist it may be a better medication to use as in combination with norepinephrine instead of vasopressin. Xiao et al executed a small randomized control trial that tested low dose terlipressin, 1.3 mcg/kg/hr, after the patients had received norepinephrine 0.5 mcg/kg/min compared to patients receiving only norepinephrine to maintain a MAP greater than 65 mmHg.[33] There were 32 patients enrolled.[33] This study found that the terlipressin group had a steady decline in the amount of norepinephrine needed after 2 hours compared to the norepinephrine monotherapy group which needed continued dosage increases in order to maintain a perfused state.[33] The MAP in the terlipressin group continued to be maintained above 65mmHg whereas the norepinephrine monotherapy group started to drop after 2 hours.[33] The 6 hour resuscitation goal of maintaining MAP above 65 mmHg was achieved at a higher rate in the terlipressin group compared to norepinephrine group, 73.3% versus 47.1% ($p<0.01$).[33] The 7 day survival was also significantly better in the terlipressin group, 66.7% versus 23.5% ($p<0.01$) in the norepinephrine group.[33] Serious adverse reactions occurred in 47% of the patients in the combination therapy group and 82.3% of the norepinephrine monotherapy group. Higher incidences of acute renal failure and adult respiratory distress syndrome occurred in the norepinephrine monotherapy group, which

likely helped curb the mortality rate in the terlipressin group.[33] A continuous low dose infusion of terlipressin appears to improve patient outcomes and has lower adverse effect rates, though this was a very small study and only followed for 7 day mortality.[33]

Terlipressin as combination therapy with norepinephrine has some support showing that it is more effective than norepinephrine monotherapy,[33] terlipressin is also as effective as vasopressin and norepinephrine combination therapy at treating septic shock.[34] Morelli et al conducted the continuous terlipressin versus vasopressin infusion in septic shock (TERLIVAP) randomized control pilot study looking at combination therapy of terlipressin 1.3 mcg/kg/hr plus norepinephrine compared to vasopressin 0.03 U/min plus norepinephrine compared to a monotherapy treatment of norepinephrine 15mcg/min.[34] This was a small study with 15 patients in each group.[34] They looked at results for each patient up to 60 hours after initiation and switched from use of vasopressin and terlipressin to norepinephrine after 48 hours.[34] The terlipressin group had a significantly lower requirement for norepinephrine during and after the infusion of terlipressin when compared to both the vasopressin combination therapy and the norepinephrine monotherapy group ($p<0.001$).[34] There was no significant difference in mortality between these groups during the duration of the study, 46.67% for terlipressin, 53.33% for vasopressin, and 66.67% for norepinephrine ($p=0.533$) but it is important to remember patients were only followed for 60 hours.[34] There was also a statistically insignificant difference in the amount of new onset arrhythmias, 0% in terlipressin, 6.67% in vasopressin and 26.67% in the norepinephrine ($p=0.054$) groups respectively.[34] The norepinephrine and vasopressin groups both had statistically significant ($p<0.05$) increases in heart rate compared to the terlipressin combination therapy group.[34] The norepinephrine group had a statistically significant ($p<0.05$)

decrease in pH compared to the terlipressin group.[34] Norepinephrine use had more patients requiring renal replacement therapy, 53.3% compared to 26.7% in the terlipressin and 33.3% in the vasopressin groups, though this was not statistically significant ($p=0.293$).[34] Although many results showed benefits, terlipressin did cause adverse effects. Terlipressin did have a statistically significant drop in platelet count from baseline over time compared to vasopressin and norepinephrine ($p<0.001$).[34] Terlipressin also had a statistically significant ($p<0.05$) decrease in hemoglobin compared to the norepinephrine monotherapy group.[34] This study provides some evidence that low dose continuous infusion of terlipressin in combination with norepinephrine is as effective as norepinephrine monotherapy and vasopressin with norepinephrine combination therapy at increasing MAP for patients in septic shock.[34] Due to the small nature, limited study drug treatment window, and short duration of patient follow up, further studies will be needed to add strength to any treatment plan recommending to add terlipressin as a combination therapy for septic shock.

Antidiuretic hormone analogs, terlipressin and vasopressin, have been shown to be effective at counteracting the hypoperfusion caused by septic shock.[20-25,27,31-34] There is some evidence to support the use of these antidiuretic hormone analogs as either combination therapy with norepinephrine early in septic shock [20-25,33,34] or as a first line vasopressor in specific patient populations.[27,31-33] The early use of these medications is associated with a quicker response of reaching the MAP goal and maintaining it, but more studies are needed.[24,33]

Early Pressors

The Surviving Sepsis Campaign modified its most recent guidelines to include a new Hour-1 Bundle, which now includes a rapid bolus of 30 mL/kg crystalloid infusion along with

giving vasopressors during or after the bolus to help achieve and maintain a MAP of 65 mmHg.[5] This is a change from the 2016 guidelines, which had the bolus given in the first 3 hours followed by subsequent boluses and then the use of vasopressors.[3] There is data to support that earlier use of the combination therapy of norepinephrine with vasopressin [20-25] and norepinephrine with terlipressin [33,34] improves outcomes. This evidence that early use of norepinephrine is an effective way to combat hypoperfusion but there can be detrimental effects if given too early or too late.[37]

Hamzaoui et al performed a prospective observational study which looked at the use of early norepinephrine defined as given at some point before 6 hours after the onset of septic shock in 105 patients.[35] They found that in severe shock, early use of norepinephrine was effective at obtaining the MAP goal and increasing preload and contractility of the heart.[35] Bai et al performed a small retrospective non-interventional study that also showed early administration of norepinephrine to be beneficial.[36] This study classified early administration of norepinephrine to be within 2 hours of the onset of septic shock.[36] The lowest mortality, 27.5%, was associated with administration of norepinephrine at or before the 1 hour mark after the onset of septic shock.[36] Mortality increased with each hour of delay with mortality reaching 65% if norepinephrine was administered after the initial 6 hours.[36] They also noted a decrease in the total duration and dosage of norepinephrine as well as a decrease in total crystalloid fluids needed for the early group compared to the late group.[36] Early vasopressors with fluid was found to be beneficial in this study and indications show the earlier the administration the better for patient success.

Health care providers must be careful because not enough fluid can also be detrimental for patients. Martin et al found that there was a higher mortality rate associated with earlier norepinephrine use.[13] This study found survivors received more fluid overall during treatment compared to non-survivors, but due to the retrospective nature of this study it is unknown why there is this descrepency.[13] Too little crystalloid fluid in a patient before starting vasopressors is also found to be an issue by Waechter et al.[37] This is another retrospective observational study that looked at 18 years of ICU patient charts from 24 hospitals analyzing 2,849 total patients. A large influencer in increased mortality in this study was low amounts of fluid infused during the 1-6 hour period after the onset of shock.[37] They noticed higher mortality rates when less than 500 mL of crystalloid fluid was given within the first hour after onset of septic shock.[37] Mortality increased when given a low volume of fluid, less than 500 mL, 6.3% to 7.5% compared to a moderate, 1.7 L, and large, 3.7 L, amount of infused fluid.[37] Also found in the higher mortality was an association between the decrease in fluid and vasopressors given with-in the first hour.[37] They hypothesized that this is due to both treatment outcomes being the same, MAP greater than 65mmHg, and therefore there is a decrease in prescribed fluids once that goal is achieved.[37] Waechter et al found higher mortality in septic patients if they were given vasopressors in the first hour of shock or after six hours after the onset of shock.[37] They also found that patients who received a low volume of fluid from 1 to 6 hours after the onset, median of 0.5 L, had a higher mortality.[37] Giving vasopressors before an adequate amount of crystalloid fluid is administered can be detrimental to patients.

Decreasing the amount of crystalloid fluid used in resuscitation of septic shock patients is one reason for early vasopressor administration. Intravenous fluid administration is not

completely benign and can cause problems with fluid overload. Finding the appropriate amount of fluid to administer before starting vasopressors is a balancing act. McDonald et al looked at altering the standard approach with a limited fluids approach.[38] The restricted fluid resuscitation in suspected sepsis associated hypotension (REFRESH) was a pilot prospective randomized open label trial that looked at decreasing the initial crystalloid fluid given with the addition of vasopressors earlier in treatment.[38] The two arms of this study consisted of the standard bolus of 30 mL/kg administered within the first 3 hours, another bolus of 1L followed by boluses of 500 mL, followed by vasopressors to achieve a MAP of 65mmHg versus the restricted fluid arm which started vasopressors right away to achieve a MAP of 65 mmHg with fluid boluses of 250 mL up to 1 L being administered as needed along with a maintenance fluid dose of 150mL/hr.[38] This protocol was from onset until 6 hours post randomization.[38] This small pilot study of 99 patients showed no increased mortality, 8% in the restricted group versus 6% in the standard care.[38] The restricted care had less total time receiving vasopressors compared to the standard care, 21 hours versus 33 hours ($p=0.13$), though it is not a statistically significant decrease in time.[38]

Ranjit et al performed a pilot study that also looked at restricted fluid and early norepinephrine use compared to the established standard of care in pediatrics.[39] This study looked at limiting fluid after the initial 30mL/kg bolus by infusing norepinephrine at 0.05-0.1 mcg/kg/min or continuing with fluid boluses up to 40 mL/kg and then using vasopressors.[39] The study compared 27 patients who were placed in the early norepinephrine group and then the authors used charts from 41 previous treated patients to make the data set for the current standard of care group.[39] They noted a decrease in the volume of crystalloid fluid received in the early

vasopressor group compared to the standard care group at 6 hours of care, 37.4 mL/kg versus 88.9 mL/kg ($p<0.0001$).[39] The 24 hour positive fluid balance was also significantly decreased in the early vasopressor group compared to the standard care group, 4.8 mL/kg versus 9.6 mL/kg ($p<0.0001$).[39] They also found a decrease in the time patients spent on a ventilator, 1 day for early vasopressor versus 4 days in the standard care group ($p<0.0001$).[39] Length of stay in the pediatric intensive care unit was also decreased, 4 days for the early group compared to 6 days in the standard group ($p<0.002$).[39] There was no change in mortality between the early vasopressor group and the standard care group, 11.1% in the early group and 9.8% in the standard group ($p=1$).[39] This was a small study that used historical patients as a control.[39] It shows that mortality is not increased with this change in treatment and that there might be significant benefits with this treatment modification.[39]

A feasibility trial for the conservative versus liberal approach to fluid therapy of septic shock in intensive care (CLASSIC) trial looks at restricting fluids after the initial 30ml/kg bolus given.[40] In the fluid restriction group, patients are given boluses of 250-500 mL for many reasons. The reasons to give crystalloid fluid were; if their lactate level was above 4 mmol/L, if MAP remains below 50 mmHg despite norepinephrine, if there was mottling above the knee, or oliguria was present in the first 2 hours of randomization.[40] The standard of care group was given fluid boluses as long as there was a hemodynamic improvement after the bolus.[40] This feasibility study randomized 151 and patients showed no increase in mortality, 33% in the fluid restricted group and 41% in the standard care group ($p=0.32$).[40] Adverse reactions also had no change, specifically cardiac ischemia 4% versus 12% ($p=0.11$), and acute kidney injury 37% versus 54%($p=0.03$) in the restricted and standard care groups respectively.[3,12] There was also no change in

the amount of renal replacement therapy needed in the restricted group, 92%, versus the standard care group, 92% (p=0.7).[40] The need for ventilator support was also unchanged, 79% in the restricted versus 72% in the standard care (p=0.48).[40] These small studies demonstrates that decreased fluids and earlier use of vasopressors are not detrimental to the patients and may provide some benefit.[38-40] Further, larger scale studies are needed to verify that this treatment change is safe, beneficial, and to more accurately evaluate how effective it is before it can be considered as a new standard of care or replace old guidelines.

Early administration of vasopressors has been shown to decrease morbidity and mortality when given in the correct circumstance. Too early is detrimental and too late has unfavorable outcomes as well. Along with timing the administration of vasopressors is the administration of crystalloid fluids, not enough fluid is hazardous and too much can have deleterious effects. Finding the right balance of fluid administration and timing of vasopressors, all while trying to limit the time that a patient is in a hypoperfused state is difficult but imperative to helping them survive.

Discussion

Sepsis continues to have a high mortality rate despite numerous changes and improvements to care. The standardizing of sepsis care by the Surviving Sepsis Campaign has helped to decrease mortality but many of their early care guidelines are weak recommendations with weak evidential support. It is unfortunate that these guidelines are not definitive because these early treatments are essential to help stabilize patients and regain perfusion to their tissues.[3] It seems logical that the quickest way to return perfusion would be the best treatment for patients in septic shock. However, defining this treatment can be difficult as there are many factors at

play in how a patient will respond to a given treatment. A recent retrospective analysis by Seymour et al found that there are four phenotypes of patients, alpha, beta, gamma and delta.[41] These phenotypes are based on how they respond to vasopressors and which organ systems have been effected.[41] Mortality rates change based on these phenotypes, with alpha having the best mortality and delta the worst.[41] Patients are complex beings with complex and sometimes unknown medical histories that need to be considered by health care providers when considering how to move forward with treatment.

A patient's past medical history plays a significant role in the severity and progression of sepsis [2,41] as well as deciding which vasopressor they should receive.[10,11,20-25] For example, the evaluated studies looking at vasopressin did not include patients with a history of severe congestive heart failure due to the adverse reactions of vasopressin in patients with heart failure.[20-25] Congestive heart failure patients are also the patients that a provider is most concerned about giving massive amounts of fluids to due to the risk of pulmonary edema. These circumstances limit who can receive which therapy, which plays a contributing factor to the weakness of the current guidelines and recommendations.

Another factor that appears to affect vasopressor therapy is how severe the septic shock is at the initiation of the vasopressor treatment. Use of the combination of vasopressin and norepinephrine was more effective when the patient was in a state of less severe septic shock.[10,11,21-23,26] Patients being treated with vasopressors later required higher doses and had higher associated mortality. Higher doses are also associated with a higher frequency of more severe adverse reactions.[9,12-14]

Where the initial infection is located is another major contributing factor when determining treatment. Many of the studies noted or cited the initial source of the infection, with pneumonia and intra abdominal being the most common, but, unfortunately, none investigated this further.[9,15,16,24,32-34] It is not listed which sources of infection tend to be more serious, or if there is any major differences caused by the source sites.[9,15,16,24,32-34] The studies do not explain if certain sources have a higher mortality or are less likely to respond to or need higher doses of vasopressors.[9,15,16,24,32-34] This may be due to the smaller size of these studies or the retrospective nature of the larger studies.[9,15,16,24,32-34] According to UpToDate, mortality is affected by the location of the infection site and the type of microbe causing the initalinfection.[2] In both animal trials that were evaluated, the studies had placed their subjects into septic shock using fecal implantation into the peritoneal cavity.[29,30] How transferable to other sources of infection are these evaluations? There is data that shows race effects norepinephrine dosing,[16] and the type and site of infection affect the mortality of patients.[2] Do the different sites and types of infection affect how a patient will respond to treatments? These are areas that need to be further studied as this appears to be a multifactorial disease process.

Even before determining which therapy is best for a patient, health care providers must achieve their initial goal: obtaining a MAP greater than 65 mmHg. Furthermore, attaining this goal as early as possible is crucial. Establishing tissue perfusion early is associated with decreased mortality and use of vasopressors to achieve this is shown to be fairly consistent and beneficial.[35-40] The timeline for starting vasopressors is currently being debated. Waechter et al found that too early can be detrimental, but too late can be just as detrimental. One aspect found to be detrimental with early administration of vasopressors is that there is a lack of crystalloid

bolus given.[37] There is a consensus that starting with a fluid bolus before administering vasopressors is an appropriate step. The Surviving Sepsis Campaign guidelines for the Hour-1 Bundle include a bolus of 30 mL/kg rapid infusion for the treatment of hypotension or a lactate greater than 4 mmol/L.[5] The administration of vasopressors shows to have a beneficial effect after administration of at least 1,000 mL of the initial 30 mL/kg bolus.[36-39] Getting the first liter of fluid in and starting vasopressors is also most beneficial if done between hour 1 and hour 6 after the onset of shock, with some research pointing to between hour 1 and 2 as being the most beneficial.[35-37] Quick recognition of the signs of septic shock allows for a fast initiation of fluid boluses and earlier administration of vasopressors, currently norepinephrine, to combat the hypoperfused state.

Norepinephrine as a monotherapy is the current standard of care, though at higher doses it is associated with increased frequency of adverse effects, increased severity of adverse effects, and higher mortality.[9,12-14,37] Compared to other monotherapy vasopressors, norepinephrine has similar if not better rates of mortality, especially compared to dopamine, vasopressin, terlipressin and epinephrine.[10,32,34] Since monotherapy does not always work or isn't beneficial to particular patients there needs to be other safe and effective alternative options. Patients who are in septic shock that are unresponsive to both fluid boluses and norepinephrine are considered to be in a more severe state of shock.[2-4] The unresponsiveness could be due to a late presentation, a delay in care, or a rapidly progressing disease process.[2-4] Early detection and appropriate treatment is a key to decreasing mortality.[3,5] This becomes apparent when looking at adding vasopressin to norepinephrine in the treatment of septic shock.[20-25]

In general, vasopressin as monotherapy has no effect on mortality compared to norepinephrine monotherapy.[10,18-26] Used alone there is no effect, but vasopressin used in combination therapy with norepinephrine and administered in early shock has shown a decrease in mortality compared to norepinephrine montherapy.[10,19,21,22,24,26] This specific subgroup benefits from the early recognition of sepsis and the quick establishment of treatment. This subgroup of the early presentation of septic shock does not fall into the current Sepsis 3.0 definition, specifically because the definition dictates patients need to have a lactate of less than or equal to 2 mmol/L.[21] Vasopressin may contribute another benefit with treating septic shock. There is suspicion and some i*n vitro* data to support that norepinephrine may inhibit the body's immune response in fighting off an infection and that vasopressin does not have the same effect.[42] The addition of vasopressin to norepinephrine has shown to be beneficial unless patients cannot receive vasopressin due to abnormal cardiac function, such as severe congestive heart failure. Patients in septic shock with preexisting cardiac problems do have other options for a combination therapy. This subgroup of patients could receive norepinephrine and dobutamine as a dual therapy to achieve tissue reperfusion. [10,11] Looking at different combinations and how it affects subpopulations of patients is important to determine the best option for each patient and providing stronger, clearer guidelines moving forward.

Terlipressin, with its long acting and selective V1 agonist, seems like it would be a great choice in treating the hypotension associated with septic shock but for the general population of patients it appears to have no added benefits over norepinephrine.[31,32,34] Terlipressin monotherapy may have a place in a subset of patients as shown in certain studies. For patients with a previous medical history of liver cirrhosis, a low dose infusion was as effective at obtaining and

maintaining the MAP goal and also had the added benefit of less severe effects on variceal bleeding.[31] Combination therapy of terlipressin and norepinephrine shows some promise with improving mortality, and achieving tissue perfusion quicker and maintaining it longer compared to norepinephrine alone.[33] The problem with terlipressin is that high dose bolus administrations are associated with higher incidence of severe adverse reactions, specifically digital ischemia and severe diarrhea.[32] Another problem with terlipressin is that it is currently not approved for use in the United States.

Conclusion

Early identification of sepsis, septic shock, and even the pre-shock stage allows for expedited therapy. These patients are very ill and can decompensate very rapidly if they are not treated quickly and appropriately. The initial fluid bolus recommended by the Surviving Sepsis Campaign may not be supported by high quality evidence, but the evidence is there, although not strong, for the recommendation to remain in place. There is currently a randomized clinical trial in process, Crystalloid Liberal Or Vasopressors Early Resuscitation in Sepsis (CLOVERS), looking at giving patients only 1 L of crystalloid fluid before starting vasopressors compared to the current practice of up to 3 L before initiating vasopressors.[43] Even though it is considered weak evidence, giving a fluid bolus initially before starting vasopressors appears effective and helps to decrease mortality.

Along with early recognition and early treatment comes the use of combination vasopressor therapy versus norepinephrine monotherapy. Monotherapy with norepinephrine is very effective at treating the hypoperfusion state. That being said, vasopressin and terlipressin as initial monotherapy appears to be just as effective and may be a better option in certain patient

subgroups. Unfortunately, terlipressin is not currently approved to be used on human patients in the United States.

For patients who are unresponsive to monotherapy, it is important to start combination therapy early to limit the total dose of norepinephrine. Combination therapy should be based on the patient, their current situation, and their medical history. Patients who do not yet meet the criteria for septic shock based on the sepsis 3.0 criteria, i.e. lactate less than 2 mmol/L, could benefit from combination therapy with low dose vasopressin and norepinephrine to achieve tissue perfusion after receiving an initial fluid bolus. The effectiveness of early use of combination vasopressin therapy is based on secondary evaluation of randomized control trials. Even though the data from these secondary evaluations is promising, further confirmation through randomized control trials should be performed to verify this treatment's effectiveness versus the current standard of care for this patient set.

For the best benefit in patients suffering from septic shock, the most important takeaway is early recognition of their deterioration followed by early fluids and vasopressors as soon as an initial fluid bolus is onboard. This treatment algorithm, using crystalloid fluid boluses and early norepinephrine in combination with other vasopressors like vasopressin, terlipressin, or dobutamine, is currently the most effective way known to counteract the hypoperfused state caused by septic shock.

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