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The Final thesis

Infusion Therapy in Sepsis and Septic Shock

Chiara Colaric
S1730729
VI year
1st group

Institute of Clinical Medicine, Clinic of Anaesthesiology and Intensive Care

Supervisor: Prof. (HP) dr. Jūratė Šipylaitė

The Head of Clinic: Prof. (HP) dr. Jūratė Šipylaitė

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Email of student: chiara.colaric@mf.stud.vu.lt

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1. Summary

Sepsis poses a great challenge to healthcare providers with its high frequency and mortality rates, and remains one of the most common causes of emergency admissions to the intensive care unit (ICU) globally. In high income countries it is often associated with older age, comorbidities, and the use of immunosuppressants, while the epidemiology of sepsis in low and middle income countries remains less understood. (1)

In 2017 sepsis has been made a global health priority by the World Health Organisation (WHO) and the World Health Assembly in order to improve the prevention, diagnosis methods, and management of sepsis. (1)

Through improved surveillance, as well as an advanced support for organ failure, the in-hospital mortality rates have fallen from 80% to 20-30% in the span of decades. However, there is still a need for further research in order to better identify patient populations and personalize treatments. (2)

Although the role of intravenous (IV) fluid administration has played a major role in sepsis management in the past decades, the question regarding which fluid and what dosage still remain widely unanswered. An important topic in sepsis management is fluid choice, dose, and administration, hence the wide variety of research and clinical trials. (3) Below we will discover which fluids are best suited for the management of sepsis and which ones are no longer recommended.

Early diagnosis and prompt intervention are crucial in the survival of sepsis, hence the need for awareness and knowledge about the treatment and infusion methods. The in-hospital mortality rates have decreased over past years through better surveillance, early treatment of underlying infection, and timely detection of the disease. (4)

2. Keywords:

Fluid resuscitation, infusion therapy, sepsis, septic shock, crystalloids, colloids, albumin

3. Introduction

Sepsis, which is a dysregulated systemic response to severe forms of infection, manifests with hypovolemia and vasodilatation among many other symptoms. It is also one of the most common conditions in patients that are admitted to the intensive care unit. (5) One of the treatments for sepsis is fluid resuscitation which aims to restore the intravascular volume, cardiac output, and oxygen delivery. The volume and choice of resuscitation fluids is of great importance when talking about the treatment of sepsis and septic shock. (6)

Colloids and crystalloids are used for fluid resuscitation in critically ill patients; the difference between those is important when choosing the appropriate fluids for treatment. Crystalloids are classified by tonicity into three types: isotonic crystalloid solutions, hypertonic crystalloid solutions, and hypotonic crystalloid solutions. They contain small molecules, are easy to use, and are cheap, however they might increase the incidence of oedema. Colloids contain larger molecules, provide a faster volume expansion into the intravascular space, however they are more costly and may trigger allergic reactions, blood clotting disorders, as well as kidney failure. (7)

In the treatment of sepsis, antibiotic therapy together with fluid administration to restore hemodynamics is the first line therapy. The way in which hemodynamics are restored is by administering intravenous fluid boluses using crystalloid solutions rather than colloid solutions. (8)

4. Sepsis

When the human body is exposed to a severe infection, a complex and dysregulated inflammatory response could result. This type of improper response to an infection is called Sepsis, which is a life-threatening condition that requires urgent treatment to prevent the progression to septic shock and acute organ failure, most often resulting in death. It is one of the most common causes of death among patients in the Intensive care unit, and particularly difficult to diagnose in such a setting due to multiple comorbidities and underlying diseases. Without prompt and aggressive treatment, patients frequently progress to septic shock, as well as multiple organ failure. (9)

4.1 Aetiology

The infection leading to sepsis is most commonly caused by bacteria, typically originating from the respiratory, genitourinary, or gastrointestinal systems, as well as the skin or soft tissues. While the most common source of sepsis are bacteria, any infective organism can cause sepsis, including fungi, parasites and viruses. Since the aetiology of sepsis is so wide, the range of presentations of sepsis is extremely wide and varies between geographical locations. (10)

Sepsis can result from a stay in a hospital or any health care facility, or it can originate from community locations. The most common site of infection that leads to sepsis are the lungs, followed by the abdomen with an incidence of 64% and 20%, respectively. (11)

An almost equal prevalence in gram-positive and gram-negative infections among patients with sepsis has been reported by the Sepsis Occurrence in Acutely Ill Patients (SOAP) study, however, gram-positive bacterial infections might now be more common. (12)

The most frequently identified organisms are *Staphylococcus aureus*, *Pseudomonas* species, and *Escherichia coli*. The risk factors for sepsis include age, immunosuppression, recent treatment with antibiotics or corticosteroids, invasive medical devices, and admission to the intensive care unit. (13)

4.2 History

Originally, in 1989 and subsequently in 1992, sepsis was defined as the "maladaptive systemic manifestation of an infection". In the 1992 consensus it was proposed that severe sepsis be defined as "sepsis complicated by acute organ dysfunction" and septic shock as "sepsis associated with hyperlactatemia or hypotension refractory to fluid resuscitation". (14)

As time passed, the need for a new definition was imminent due to the limitations of the previous criteria. The new criteria for sepsis addressed the previous limitations and focused

more on systemizing organ dysfunction rather than on identifying inflammatory markers, hence sepsis is no longer being considered as only an inflammatory disorder. (15)

The previous classification has been simplified by removing the term “severe sepsis” and changing the terms sepsis, severe sepsis, and septic shock to infection, sepsis, and septic shock. Other than changing the terms, the definition of sepsis itself has been changed to and currently defined as “the presence of an infection combined with an acute change in SOFA score of 2 points or more”. (16)

4.3 Criteria

The Sequential Organ Failure Assessment Score, also known as the SOFA Score, is a scoring system used to assess the performance of various organ systems in the human body, which are the respiratory, coagulatory, cardiovascular, renal, liver, and neurologic. After the data on these organ systems is obtained, a score is assigned. The likelihood of mortality increases with the SOFA score, meaning that the higher the score, the higher is the risk of death. (17)

The intent of the SOFA score is to act as a research tool in which groups of patients can be categorized based on their risk of death. When used in sepsis cases and applied to group of patients, the SOFA score is fairly accurate. However, the SOFA itself has limitations and can not provide information on a singular patient regarding survival, as it focuses on populations rather than individual patients. (17)

4.4 Symptoms

Sepsis patients present with a wide variety of signs and symptoms depending on the severity and progression of the disease. General features include fever, tachycardia, tachypnea, and generalized edema. Features of organ dysfunction may include an altered mental status, hypotension, jaundice, oliguria, symptoms of acute respiratory distress syndrome (ARDS), etc. (18)

Sepsis manifests with a spectrum of severity, beginning with a milder form during which there is a light derangement in vital signs such as increased temperature and respiratory rate, it can then develop to a more severe form which manifests with hypotension that is responsive to intravenous fluids and organ dysfunction. In its worst case, sepsis develops to a point where the hypotension becomes resistant to intravenous fluids with an elevation of serum lactate, also known as septic shock. (19)

4.5 Diagnosis

Early detection of sepsis is critical in preventing the potentially fatal outcome of this condition, as well as in initiating life-saving treatment which includes intravenous antibiotic administration and fluid resuscitation, as well as oxygen therapy. (20)

A single method for diagnosing sepsis has not yet been established, hence the use of a combination of tests and clinical signs such as the presence of an infection, hypotension, tachycardia, and increased respiratory rate. (20)

Laboratory studies used for diagnosis include at least two sets of serum lactate and blood cultures. In addition, a CBC, CRP, procalcitonin, BMP, and electrolytes will be evaluated, as well as liver chemistry, synthetic function test, coagulation panel, and D-dimer. (21)

In order to establish and identify the source of infection, a blood culture must be performed. A blood culture test is needed in order to identify what type of bacteria or fungi are responsible for the infection in the blood. It is required to take more than one blood culture from different veins, and the results take up to several days. (22)

Imaging is used if the site of infection is not readily found. Commonly used imaging tests include chest and abdominal x-ray, ultrasound, CT scan and echocardiography. (20)

4.6 Screening methods

Screening tools for sepsis were designed to promote early detection of sepsis. Most of these tools have a wide variety of diagnostic accuracy and a poor predictive value, although the use of some has shown improvements in care processes. Some of these tools used for sepsis screening are systemic inflammatory response syndrome (SIRS) criteria, quick Sequential Organ Failure Score (qSOFA), or Sequential Organ Failure Assessment (SOFA) criteria. (23)

The qSOFA uses three variables in order to predict death and a prolonged ICU stay in patients with known or presumed sepsis: a Glasgow Coma Score less than 15, a respiratory rate equal to, or greater than 22 breaths per minute, and a systolic blood pressure equal to, or less than 100 mmHg. When any two of these variables are present simultaneously, we consider the patient to be qSOFA positive. (23)

Neither the qSOFA or the SIRS criteria are ideal screening tools for sepsis, and their limitations need to be taken into consideration. However, while there is a variation in their sensitivity and specificity, they play an important part in early detection for a timely intervention. (23)

4.7 Treatment

The management of sepsis and septic shock should be performed as a medical emergency. Timely intervention which includes removal of the source of infection is key to an effective treatment, and an aggressive assessment of an unidentified source through laboratory testing and diagnostic imaging is critical for the initial management of sepsis. (3)

An early initiation of an appropriate antimicrobial therapy, in conjunction with restoration of tissue perfusion via fluid resuscitation are a crucial part of initial sepsis management. The aim of such treatment is to correct the hypovolemia by increasing blood volume, with a consequent increase in venous return and cardiac preload, subsequently increasing CO and ultimately oxygen delivery. Although different types of fluids for the treatment of sepsis have been proposed over the years, crystalloids have repeatedly been recommended over colloids. (24)

In conjunction with fluid resuscitation, obtaining appropriate cultures and immediate administration of empiric broad-spectrum antimicrobials should be performed in the initial phase as well. (25)

4.8 Source Control

Source control includes removal of the infected tissue, drainage of an abscess, and if there is an infected device that is causing the sepsis then it should be removed immediately as well. Source control is considered best practice in the management of sepsis and can be done via percutaneous drainage or open surgery. An inadequate early source control was shown to be associated with an increase in 28-day mortality from 26.7% to 42.9%. (1)

5. Infusion Therapy

In early sepsis, patients tend to often be hypovolemic due to increased insensible losses and decreased oral intake. The process of inflammation during sepsis alters vascular resistance resulting in sepsis induced vasodilation, increases venous capacitance, and causes capillary leakage. All of the above mentioned changes that occur during early sepsis lead to a state known as “relative hypovolemia”. (26)

5.1 Sepsis Resuscitation

One of the most important and common methods in managing critically hypotensive patients is fluid resuscitation. For over 100 years we have been using crystalloids, mineral salts, or other water soluble molecule solutions for fluid resuscitation. In the past decade, several colloids have been developed in order to improve intravascular volume more efficiently. However, efficacy and safety of colloids has been challenging to evaluate in certain patients since there might be an interruption in the integrity of the endothelial glycocalyx layer under inflammatory conditions such as sepsis, surgery, or trauma. (6)

Sepsis disrupts the endothelial glycocalyx layer and causes damage to the microvasculature, which results in an interstitial accumulation of fluid and subsequently edema. Although fluid resuscitation is the gold standard in the initial treatment of sepsis, edema related complications are unfortunately a common consequence of current resuscitation strategies. (27)

The optimal fluid regimen, which includes the type and volume of fluid to be given, is unclear. Over the past decade, there have been numerous randomized controlled trials and meta-analyses to help form an appropriate conclusion to this issue, resulting in no clear consensus or recommendations on a specific therapy. (28)

The most recent recommendation by the Surviving Sepsis Campaign is 30 cc/kg of crystalloid within the first 3 hours for any hypovolemic septic patient, the type of crystalloid to be used is, however, not specified. (29)

When talking about fluid resuscitation we need to first focus on the initial resuscitation. The resuscitation of a patient with severe sepsis or sepsis induced hypoperfusion, such as hypotension or lactic acidosis, should begin as soon as soon as the condition is recognized and should not be postponed until ICU admission. During the first 6 hours of resuscitation, the goals of initial resuscitation of sepsis induced hypoperfusion should include all of the following: central venous pressure of 8-12 mmHg, mean arterial pressure ≥ 65 mmHg, urine output ≥ 0.5 ml/kg/hr, and a central venous or mixed venous oxygen saturation ≥ 70 %. (30)

5.2 Optimal Fluid Management after Resuscitation

Little attention has been dedicated to the optimal fluid management after the first 6 to 12 hours of sepsis. Although the optimal fluid strategy for each phase of the treatment remains largely undefined, there is a broad agreement that fluid management may differ during different phases of sepsis. Monitoring the patient's cardiac output, pulse pressure and stroke volume variation, as well as the interior vena cava diameter and stroke volume assessment by echocardiography are all recommended procedures to help guide fluid administration. However, many dynamic measures cannot be used for patients who are breathing spontaneously or receiving low tidal volume ventilation. (27)

5.3 Fluid Choice

Since the invention of IV fluids, there have been ongoing debates as to which fluid is best suitable for critically ill patients suffering from infection. The ideal fluid for sepsis resuscitation would increase intravascular volume without causing edema, be similar to plasma in terms of chemical composition, and in a cost-effective manner improve patient outcomes. Unfortunately, to this day no such fluid exists. The available IV fluids on the market are categorized as crystalloid or colloid. (2)

5.4 Crystalloids

Crystalloid fluids are a subset of intravenous solutions created for the use in clinical settings. They are composed of water-soluble electrolytes that include sodium and chloride, lacking proteins and insoluble molecules. Isotonic crystalloid solutions contain the same amount of electrolytes as the plasma, while hypertonic and hypotonic crystalloids contain more and less, respectively. Most crystalloid solutions that are commercially available are isotonic to human plasma and do not exert an osmotic effect in vivo. (31)

Crystalloid solutions are the first choice for fluid resuscitation with patients that suffer from hypovolemia, haemorrhage, sepsis, and dehydration. Their function is to expand intravascular volume without causing significant fluid shifts between intracellular, intravascular, and interstitial spaces or disturbing the ion concentration. (25)

The most frequently used crystalloid solution is Normal Saline (0.9% NaCl solution), other commercially available crystalloids are lactated Ringer's/Hartman's solution, acetate buffered solution, acetate and lactate buffered solution, acetate and gluconate buffered solution, 0.45% NaCl (hypotonic) solution, 3% (hypertonic) solution, 5% Dextrose in water, and 10% Dextrose in water. (24)

Normal saline

Normal saline, or 0.9% sodium chloride is the most commonly used intravenous fluid worldwide. Due to its strong ion difference of zero, as opposed to plasma which has a strong ion difference of about 24 meq/L, normal saline is considered “unbalanced”.

Resuscitation with normal saline has been shown to cause a hyperchloremic metabolic acidosis which appears to alter renal blood flow and alter renal function, it is also associated with increased inflammatory markers. As a result of these findings, the use of normal saline in the treatment of severely septic patients is undergoing investigation. Instead, the use of “balanced” crystalloids might be a safer alternative. (30)

Balanced Crystalloids

Two similar and closely related solutions known as Lactated Ringer’s and Hartmann’s solution are an example of balanced crystalloids. Lactated Ringer’s solution is used in the United States, whereas Hartmann’s solution is used in Europe.

Another balanced crystalloid is Plasma-lyte, which is a relatively new crystalloid that was designed as a physiologic fluid. These fluids have an electrolyte content which more closely resembles that of plasma, as well as a much lower chloride concentration than normal saline. The difference between these solutions is that lactated Ringer’s and Hartmann’s solution both contain calcium ion, whereas Plasma-lyte does not, allowing Plasma-lyte to be given concurrently with blood products while lactated Ringer’s and Hartmann’s solution carry the risk of potentially causing a blood clot in the transfusion line.

In sepsis literature, there is lacking data in comparing balanced crystalloids to normal saline, however an animal study which investigated normal saline versus Plasma-lyte resuscitation in a rat model of sepsis found reduced short-term mortality as well as decreased acute kidney injury in the Plasma-lyte group. (32)

Hypertonic saline

Hypertonic saline is a solution of sodium chloride (NaCl) in water with a higher sodium concentration than normal blood serum. There was an increased interest in the use of hypertonic saline for sepsis resuscitation in the 1990's and early 2000's. The proposed benefits included reduced endothelial cell edema leading to improved microcirculatory flow, increased myocardial contractility, and decreased neutrophil infiltration and inflammatory damage in the lungs. It was postulated that "small volume" resuscitation with hypertonic saline would achieve hemodynamic normalization by recruitment of fluid from the intracellular space, thereby limiting interstitial edema. Small clinical trials were performed in patients who were already hemodynamically stable revealed improved hemodynamics such as increased cardiac output after resuscitation with hypertonic saline versus normal saline. (33)

As time passed, the use of hypertonic saline in the management of sepsis has subsided as it has shown to worsen coagulation parameters in vitro. In addition, hemorrhagic trauma patients that have received hypertonic solutions during pre-hospital resuscitation were found to have increased coagulopathy compared to those who have received resuscitation with normal saline. (34)

5.5 Colloids

Colloid solutions contain high molecular weight molecules also known as macromolecules that are suspended in a crystalloid carrier solution. Unlike crystalloids, colloids are substances that can not as easily diffuse through membranes, thus being confined to the intravascular space. The insoluble molecules in colloids include starch, bovine protein also known as gelatine, and human protein also known as albumin. (35)

The use of colloids is for plasma volume expansion. The particles in colloid solutions are too large to pass through a semipermeable membrane such as capillary membranes, making it possible for colloid solutions to stay in intravascular spaces for longer periods of time that crystalloids. They are typically used to maintain circulating fluid volume after blood loss from trauma or surgery. (36)

Albumin

Albumin accounts for 50-60% of the protein content in plasma by mass, making it the most abundant plasma protein. Around 40% of the body's albumin is located in the intravascular space, and it is the primary determinant of the oncotic pressure of plasma. (37)

Human albumin has been administered to patients in order to provide adequate oncotic pressure and intravascular volume for decades. However, a Cochrane Review from 1998 suggested that the administration of albumin may be potentially harmful in critically ill patients that were resuscitated with albumin compared to crystalloid solutions. Subsequent trials reported contradictory findings. (38)

For clarification purposes, a large multinational randomized controlled trial known as the Saline versus Albumin Fluid Evaluation (SAFE) study was conducted. In the SAFE study, 4% albumin solution was compared with normal saline as fluid replacement in 7000 randomized critically ill patients, with results which indicated that albumin administration was safe and that there was no difference in 28 day outcomes between the two groups. Subsequently, a predefined subgroup analysis of septic patients showed that there was a modest mortality benefit which favoured 4% albumin after adjustment for baseline covariates that those receiving normal saline. (39)

Between 1982 and 2012, Patel et al completed a meta-analysis that included 16 clinical trials investigating the use of albumin as a resuscitative fluid in septic patients. A mixture of randomized trials was included which compared albumin to a number of different fluids including normal saline, lactated Ringer's, and hydroxyethyl starch (HES) solutions. No statistical difference in mortality in septic, severely septic, or septic shock patients that were resuscitated with albumin compared to the other fluids was found. (40)

Hydroxyethyl starch

Hydroxyethyl starch, also known as HES, is a semi-synthetic colloid solution which is a non-ionic starch derivative from chemically modified plant starch. Different types of HES solutions have varying pharmacokinetics due to differences in molecular weight, degree of hydroxyethyl substitution of the starch molecule, and the concentration of the solution. Hydroxyethyl starches used to be the most commonly used colloids worldwide, however their use has subsided after several randomized clinical trials and systematic reviews revealed potential harm, including an increased risk of bleeding, acute kidney injury, and mortality.
The most recent type of HES, known as HES 130/0.38-0.45 or tetrastarch, was put on the market in 1999. Since then, it has been discovered that HES 130/0.38-0.45 also poses a risk of serious adverse events in patients with sepsis as a result of three large trials that were published in 2012. (41)

Plasma

After erythrocytes, leukocytes, and platelets are removes from the blood, what is left is called plasma. Plasma is a protein rich fluid and could even be thought of as a "super-colloid".
Although plasma is unstudied in the setting of sepsis, it has the potential of being an ideal resuscitative fluid which in the setting of sepsis would achieve euvolemia without causing oedema. What is known to date about plasma based resuscitation mostly comes from studies that were performed in the setting of trauma and haemorrhagic shock. Using plasma as the primary volume expander instead of crystalloid or colloid fluids in damage control resuscitation principles has been associated with decreased mortality, decreased oedema-mediated complications, as well as a decreased incidence of inflammatory-mediated complications such as venous thromboembolism, acute respiratory distress syndrome (ARDS), and multiple organ failure. (42)

The effects on the endothelial glycocalyx (EGL) have been shown to be similar between trauma and sepsis, meaning that both produce similar changes and have similar effects on the EGL itself. Serum levels of EGL components such as the protein syndecan-1 are elevated in both trauma and septic patients compared to healthy individuals, and increasing levels of

serum EGL components correlate with an increase in morbidity and mortality in trauma as well as sepsis. (43)

Plasma resuscitation has been shown to repair the EGL and reduce pulmonary endothelial permeability in animal models of haemorrhagic shock, and more recently it has been shown to reduce gut injury and inflammation in an animal model as well.
Although the results in animal models look promising, there is currently no definitive data in human subjects to show that plasma reduces endothelial injury in trauma or in sepsis. (42)

5.6 Crystalloids vs. colloids

Sepsis causes a disruption of the endothelial glycocalyx layer and damage of the microvasculature, which results in interstitial accumulation of fluid and edema. Fluid resuscitation is the foundation in the initial treatment of sepsis, however, the optimal fluid regimen, as well as the fluid type and volume, is unclear. (44)

The ideal fluid for resuscitation is one which restores intravascular volume while minimizing the occurrence of edema, unfortunately edema is a common consequence of current resuscitation strategies. (45)

The most recent guidelines by the Surviving Sepsis Campaign recommend 30 cc/kg of crystalloid within the first three hours for hypovolemic septic patients, without any specification on the type of crystalloid to be used. Crystalloids are recommended as first-line therapy, the safest choice being balanced crystalloids since there is increasing evidence associating normal saline with increased mortality and kidney injury. (36)

5.7 Early Goal-Directed Therapy (EGDT)

In 2001, a landmark study by Rivers et al. compared the usual care to a more protocolized approach to sepsis resuscitation with the use of IV fluids, vasopressors, and blood transfusion. During the trial, 263 patients suffering from sepsis and hypoperfusion were randomized to either the standard therapy or EGDT which utilizes continuous monitoring of central venous

pressure, mean arterial pressure, as well as central venous oxygen saturation to guide the use of intravenous fluids, vasoactive drugs, and red cell transfusions in order to optimize tissue oxygen delivery. The in-hospital mortality was 16% lower with EGDT than with the usual care. (46)

The remarkable improvement in mortality that was reported during this trial led to the incorporation of goal-directed fluid resuscitation into the recommendation for early sepsis management in the Surviving Sepsis Campaign (SSC) Guidelines, which was established in 2002 and published in 2004. The first guidelines that were published in 2004 highlighted the importance and need for aggressive fluid resuscitation. It was subsequently felt that fluid resuscitation could be with either crystalloids or colloids, which resulted in a surge of research into the ideal fluid for sepsis. (47)

6. Vasopressors

Vasopressors are medications used to create vasoconstriction for the treatment of hypotension and hemodynamic instability associated with shock, they are commonly used to restore and maintain blood pressure in patients with sepsis. Vasopressors are an integral part of supportive care in sepsis by maintaining adequate organ perfusion and interrupting the progression of organ dysfunction. Although the appropriate timing of initiation of vasopressors is unclear, restoring circulatory volume early is necessary to ensure adequate perfusion of distal organs. Currently there is an increasing amount of evidence to guide us as to when exactly vasopressors should be initiated in a patient's resuscitation in order to improve perfusion. (48)

6.2 Norepinephrine

Norepinephrine (NE) is recommended as the first line vasopressor in the management of septic shock patients. The vasoconstrictive action of NE is excreted through the stimulation of α1-adrenergic receptors, while having little influence on the heart rate. A series of validated reasons has supported the growing consensus for the need of early Norepinephrine administration in septic patients over the years. The reason for this is that prolonged

hypotension is one of the main determinants of mortality, thus reversing hypotension or even limiting its duration improves patient outcome. (49)

Another reason that supports early NE administration is the fact that the stimulation of α1-receptors on the venous side triggers venous constriction and, as a result, increases the amount of stressed blood volume which leads to an enhanced venous return and improved cardiac preload. Under such conditions, fluid administration should be more efficient as it would be done in a more pressurized venous system, which would act on the stressed volume and ultimately end up reducing the amount of fluid given. (50)

Lastly, in the initial phases of septic shock, cardiac β1-adrenergic receptors are still expressed on cardiac cells which allows cardiac contractility to increase through norepinephrine administration. This effect of NE is also promoted by an accompanying increase in diastolic arterial pressure, which is the perfusion pressure of the left ventricle coronary artery. (51)

The consensus once NE administration is started is that the dosage should be titrated to obtain a mean arterial pressure (MAP) of 65 mmHg. Whether higher values should be targeted is not clear. A study, known as SEPSISPAM, compared 65 mmHg to 85 mmHg as a MAP target, however there were no significant differences in terms of mortality between the two. (51)

However, when a subgroup of patients who had a history of arterial hypertension were analysed, a higher MAP target wa shown to be beneficial on the renal function. As a result, the European Society of Intensive Care Medicine (ESICM) recommended that a MAP value which is greater than 65 mmHg should be the initial blood pressure target in septic shock patients who suffer from arterial hypertension. The use of a second vasopressor is advised when elevated doses of NE are required for refractory hypotension. (50)

6.3 Other vasoactive agents

Vasopressin

To reduce the amount of adrenergic tone and increase vasoconstriction through a different receptor stimulation, the 2016 SSC guidelines suggested to add another vasoactive agent called vasopressin to norepinephrine in case of refractory shock. One meta-analysis showed that in the association of vasopressin with NE, the rate of arrhythmic events such as atrial fibrillation was reduced compared to the use of NE by itself. However, no changes regarding mortality were recorded. It is important to point out that vasopressin is not available in all countries. (48)

Epinephrine

In case of concurrent cardiac dysfunction, the use of another second-line vasopressor is recommended by the 2016 SSC; this vasopressor is epinephrine. According to existing literature, however, no superiority was observed in terms of patient survival with the use of epinephrine alone compared to patients treated with a combination of norepinephrine and dobutamine. (52)

Dopamine

The use of dopamine is currently only recommended in case of bradycardia. Although it was recommended by previous guidelines, it should not be used in the management of septic patients as a vasopressor or a renal protective agent. Its use has been shown to be associated with an increased risk of cardiac arrhythmias and mortality, compared to norepinephrine. (49)

7. Conclusion

Sepsis is still a common condition that is associated with a high mortality and long-term morbidity for patients who survive. Despite there still not being an ideal treatment and fluid resuscitation method, sepsis outcomes have drastically improved as a result of major improvements in supportive care, rapid recognition of the disease, and the delivery of effective antibiotics. (30)

The optimal fluid for the initial resuscitation in sepsis remains unclear since it is a complicated condition that resists a one size fits all approach. Balanced crystalloids appear to be superior to normal saline, albumin seems to be equivalent to crystalloids in terms of outcomes, but are considered second-line due to the higher cost. Hydroxyethyl starches have shown to increase mortality and acute kidney injury (AKI) in critically ill septic patients and are no longer indicated for the treatment of sepsis after the EMA and FDA issues warnings in 2013. Clinical data regarding the use of hypertonic saline is very limited, and there is no data regarding the use of plasma in sepsis resuscitation. There are, however, theoretical benefits of resuscitation with plasma in sepsis, which includes repair of the endothelial glycocalyx layer, restoration of microvasculature integrity, and limitation of interstitial edema, which should prompt further investigation. (30)

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