Review Article

Rational Fluid Therapy for Sepsis and Septic Shock; What Do Recent Studies Tell Us?

Asghar Rastegar MD•[1]

Abstract

Sepsis and septic shock persist as major healthcare challenge, with high morbidity and mortality. Fluid management is a large part of the treatment in patients with these disorders. Fluid therapy has been an important component of the care of patients for the past century. However, recently well-designed studies have been published focusing on the impact of the type and amount of fluids on important clinical outcomes. This review summarizes all the relevant recent studies and attempts to develop a rational approach to the initial fluid management of patients with suspected sepsis.

Keywords: Balanced solutions, fluid management, sepsis, septic shock

Cite this article as: Rastegar A. Rational fluid therapy in sepsis and septic shock; what do the recent studies tell us? *Arch Iran Med.* 2015; **18(5):** 308 – 313.

Introduction

Sepsis and septic shock are major public healthcare challenge that affect 750, 000 patients in the US and millions worldwide. The mortality from sepsis has dramatically decreased from 80% to 20% over the last decades.[1] Septic shock is seen in patients with medical and/or surgical morbidities, therefore doctors of these patients should be knowledgeable about recent developments in this area. Over the past two decades, several well-designed trials have been published assessing the optimum types and amount of fluid to be administered to these patients. Using these findings, the Surviving Sepsis Campaign (SSC), has developed guidelines for management of patients with severe sepsis and septic shock. The latest version published in 2012, represents the consensus of 68 international experts from 30 international organizations.[2] This article will review the present state of fluid management in sepsis and septic shock, beginning with a brief history of intravenous therapy and followed by a detailed discussion of the type and amount of fluid to be used in resuscitation of these patients.

Brief history of intravenous fluids

The first attempt to treat a patient with intravenous fluid occurred during the cholera epidemic in England. After studying the blood of patients with severe cholera, William B. O'Shaughnessy noted that blood had lost a significant portion of its water and "neutral saline ingredients". Therefore, he recommended that to treat these patients, one must "restore specific gravity of blood and replace deficient saline matter" in their blood. His assistant Thomas Latta, building on this finding, used intravenous fluid made of salt and water to treat 15 patients with "malignant cholera" and amazingly five of them survived. Although Latta developed four types of fluid, (one of which with Na 134, Cl 118 and HCO3- 16 mEq/L is very close to modern physiologic fluids), his findings were ignored by the medical community for half of the century.[3,5] In a meantime Dutch physiological chemist Hartog Jacob Hamburger, noted that human red blood cells were isotonic with 0.9% saline solution, heralding the era of "physiological saline". Sidney Ringer in 1880's discovered that to sustain excised beating heart of a frog, the fluid must contain other minerals specially calcium and potassium. Ringer's solution was later modified by an American pediatrician, who added lactate as a base to Ringer's solution and created the first "balanced" solution. Physiological saline and Ringer's Lactate now form the basis for development of many other solutions now used in clinical medicines.[3–5]

These solutions however do not contain a major component of plasma, i.e. albumin, which is critical to generate oncotic pressure and decrease transudation of fluid from the vascular to the interstitial space. During WWII, plasma components were successfully fractionated using new developed techniques; therefore human albumin became available. In 1942, due to limited supply and high price of albumin, synthetic material possessing oncotic properties, including dextran, hetstarch and gelatin with different molecular weights were developed as a substitute for albumin.[3]

Table 1 shows a summary of the key characteristics of the most commonly used fluid in clinical medicines. Fluid resuscitation is now an important component of our therapeutic armamentarium and daily millions of liters of fluid are used across the world. However, the type and amount of fluid that should be used in critically ill patients has been evaluated in recent studies . In this review we will summarize these recent studies and develop a set of recommendation based on their findings.

Type of fluid

Saline vs. balanced fluids

The "normal" or "physiologic" saline, with sodium and chloride concentration of 154 mEq/L and without any other normal

Authors' affiliations: [1]Section of Nephrology, Department of Medicine, Yale School of Medicine, New Haven, USA.
•Corresponding author and reprints: Asghar Rastegar MD, Section of Nephrology, Department of Medicine, Yale School of Medicine, 1074 LMP, 333 Cedar St., New Haven CT. 06520, USA. Tel: 203-737-2078 Fax: 203-785-3070, E-mail: Asghar.rastegar@yale.edu.
Accepted for publication: 14 January 2015

Table 1. Selected characteristics of commonly used IV fluids.

Solution (Abbreviation)	pH	Ingredients in 1L	Osmolality (mOsm/L)
5% dextrose in water (D5W)	5.0	Dextrose 50 Gm	252
0.9% sodium chloride (NSS)	5.7	NaCl 9 Gm Na 154 mEq Cl 154 mEq	308
Lactated Ringer's (LR)	6.6	Na 130 mEq K 4 mEq Ca 3 mEq Cl 109 mEq Lactate 28 mEq	273
0.45% sodium chloride (1/2NSS)	5.6	Na 77 mEq Cl 77 mEq	154
5% dextrose in normal saline (D5NSS)	4.4	Dextrose 50 Gm Na 154 mEq Cl 154 mEq	560
5% dextrose in 0.45% sodium chloride (D51/2NSS)	4.4	Dextrose 50Gm Na 77 mEq Cl 77 mEq	406
3% saline	5	Na 513 mEq Cl 513 mEq	1026
5% saline	5.8	Na 855 mEq Cl 855 mEq	1710
10% dextrose in water (D10W)	4.3	Dextrose 100 Gm	505
5% Dextrose in lactated ringer (D5LR)	4.9	Dextrose 50 Gm Na 130 mEq K 4 mEq Ca 3 mEq Cl 109 mEq Lactate 28 mEq	525
Albumin 4% (Iso-oncotic albumin)	6.7–7.3	Human albumin 40 Gm Na 140 mEq Cl 128 mEq Octanoate 6.4 mmol	260
Albumin 20% (Hyperoncotic albumin)	6.7–7.3	Human albumin 200 Gm Na 48-100 mEq Ctanoate 32 mmol	130

constituents of human plasma has been the preferred solution for resuscitation worldwide. It is well known that internists prefer to use normal saline for resuscitation. However, surgeons prefer more balanced fluids, such as Ringer's Lactate (RL) which has 28 mEq/L of a bicarbonate substitute such as lactate, physiological concentration of potassium and calcium as well as lower chloride content (109 vs 154 mEq/L)**.** Until now, no controlled study has compared chloride-liberal (Cl-L) and chloride-restrictive (Cl-R) solutions. Recently, the result of a single center, prospective, open label, sequential period pilot study of Cl-L vs. Cl-R has been published. This study enrolled 1644 patients, admitted consecutively to all adult ICU's in New Zealand and Australia.[6] In the first six months the patients were treated with standard IV fluids, including Cl-L solutions such as 0.9% saline, 4% succinylated gelatin solution (chloride concentration: 120 mmol/L) and 4% albumin in sodium chloride (chloride concentration: 128 mmol/L), based on clinician preferences. In the second 6-months, patients were treated with balanced solutions including lactated crystalloid solutions (chloride concentration: 109 mmol/L), balanced buffered solutions (chloride concentration: 98 mmol/L), and 20% albumin solution (chloride concentration: 19 mmol/L). The study allowed exceptions for specific indications, if approved by the attending clinicians. These two groups were well matched and the median follow up was 11 days. During the intervention phase, the use of Cl-L fluid and 4% gelatin solution decreased from 2411 L to 52 L and 538 L to 0 L respectively. While the use of lactated crystalloid solution increased from 469 L to 3205 L. The mean serum creatinine concentration increased by 14.8 μmol/L during the Cl-R phase compared with 22.6 μmol/ during the control period ($P = 0.03$; adjusted $P = 0.07$), and the rate of significant renal injury decreased from 14% in Cl-L to 8.4% in Cl-R period ($P < 0.001$). These differences remained statistically significant after adjustment for all other important variables. However, the ICU or hospital mortality, the median ICU length of stay, and ESRD were similar. This finding is supported by two retrospective observational studies using large administrative databases. In the first study infusion of normal saline on the day of open abdominal surgery resulted in significantly greater postoperative complications, including use of dialysis, compared with those receiving balanced solution as Plasma-Lyte.[7] In the second study using propensity-matched cohorts, acute postoperative hyperchloremia was associated with significant increase in mortality.[8] In animal studies, Wilcox and colleague observed that high chloride solutions have negative impact on renal blood flow and GFR.[9] Recently this effect was studied in human subjects.[10] Infusion of 2L of 0.9% saline (no Plasma-Lyte), resulted in a significant reduction in mean renal artery flow velocity ($P = 0.045$) and 11.7% decline in renal cortical tissue perfusion ($P = 0.008$) from the baseline (Figure 1). The result of the

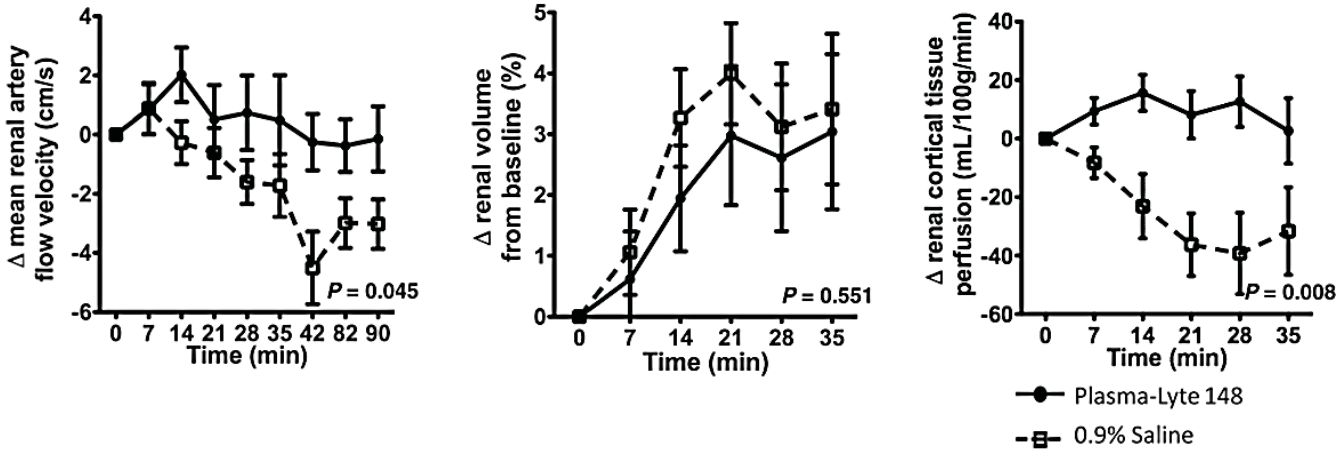

Figure 1. Changes in renal artery blood flow velocity, renal volume, and renal cortical tissue perfusion after infusion of 2 L of 0.9% saline and Plasma-Lyte 148 over 1 hour. All values are mean (SEM). The *P*-values are for the test of 0.9% saline versus Plasma-Lyte 148 using the analysis of variances and a repeated measures model.[10]

above-mentioned study by Yunos, et al. is intriguing. However, as pointed out in the accompanying editorial, several interventions occurred during the second period including: lower sodium intake, more buffer administration, and higher use of hyperoncotic albumin, making it difficult to decipher which component led to the observed effect. In addition the design of the study is open to observational bias.[11]

Saline vs. albumin

Albumin has been used frequently as a volume expander in critically ill patients. Due to the high cost and the general availability of this solution, many centers have limited the use of albumin for patients who would clearly benefit from it. Several recent studies have focused on its use in critically ill patients. The SAFE study, a randomized, double blind controlled trial involving 6997 patients, evaluated the 28-day mortality in patients who received 4% albumin or saline, in addition to other fluids and blood products given at the discretion of the treating clinicians.[12] During the three study days, the patient in the albumin group received less total fluid compared to saline group. However the 28-day mortality (20.9% in albumin and 21.1% in saline group) as well as, ICU and hospital mean lengths of stay, number of days on mechanical ventilation and on renal replacement therapy was similar. Although, the findings did not reach the significant level, the patients with head trauma did worse and those with sepsis did better on albumin. In post hoc analysis of the data collected within 24 months, 71 of 214 patients in the albumin group (33.2%) had died, as compared with 42 of 206 in the saline group (20.4%) (RR 1.63; 95% confidence interval [CI], 1.17 to 2.26; P = 0.003).[13] A systemic review also supports the finding that albumin infusion improved survival for patients with sepsis.[14]

In a recent study, a multicenter, open-label, randomized, controlled trial involving 1818 patients with sepsis was carried out in 100 ICU's in Italy.[15] These patients were randomized to receive 20% albumin or crystalloid infusion. Patients in the albumin group received 300 mL of 20% albumin solution daily for 28 days or ICU discharge, whichever came first. The goal was to maintain a serum albumin level of 30 g per liter or more. Albumin group, who received less total fluid, had a higher BP and lower heart rate, as well as shorter time on vasopressor or inotropic agents (*P* = 0.007). The death rate at 28 and 90 days were 31.8% and 41.1% compared to 32.0% and 43.6% in albumin vs crystalloid group respectively (*P* = NS). A post hoc analysis of 1121 patients with septic shock (not those with sepsis *without* shock) showed significantly lower mortality at 90 days in the albumin than in the crystalloid group [RR with septic shock, 0.87; 95% CI, 0.77 to 0.99].

Crystalloid vs. hetstarch

Hydroxyethyl starch (HES) is used extensively in certain countries around the world and is a polymeric glucose derived from maize or potato starch by hydrolysis and hydroxyethlylation. HES is characterized by mean molecular weight (MW) of 70, 000 to 670,000 Daltons, variable degree of substitution reflecting the average number of hydroxyethyl groups per unit of glucose, with concentration of 6% (iso-oncotic) or 10% (hyper-oncotic) and C2/C6 ratio reflecting hydroxyethylation site at C2 and C6 atoms of glucose. The most commonly used HES, identified as 130/0.4/6%/9:1, has a molecular weight of 130,000, with 0.4 degree of substitution, a concentration of 6% and C2/C6 substitution of 9:1.[16] The major concern in using HES is its potential nephrotoxicity due to osmotic damage to proximal tubules. This concern was first raised in 2001 among a small number of patients with sepsis treated with HES compared to gelatin.[17] Below we review in some detail three recent RCT studies and two meta analysis dealing with this issue.

CHEST study includes 7,000 patients admitted to ICU's in Australia and New Zealand, randomized to receive 6% HES 130/0.6 in 0.9% saline or 0.9% saline alone, for all fluid resuscitations.[18] The primary outcome was death within 90 days and secondary outcome included acute kidney injury and the need for renal-replacement therapy (RRT). During the first four days, the HES group received significantly less study (526 ± 425 mL vs. 616 ± 488 mL), and non-study (921 ± 1069 mL vs. 982 ± 1161 mL) fluid than the saline group. Most of the fluid was administered in the first 24 hours. The 90-day mortality was similar (18% in HES group vs 17% in saline group). Although the incidence of AKI was similar, the HES group required RRT more often than the saline group (7% vs 5.8% RR 1.21; 95% CI, 1.00 to 1.45; *P* =

0.04).[18] In 6S study, 798 patients with severe sepsis, cared for in 26 ICU's in Scandinavia, were enrolled in a multicenter, double blind, randomized trial comparing 6% HES 130/0.42 or Ringer's acetate for resuscitations.[19] The primary outcome, death or end-stage kidney failure at 90 day was reached in 51% of patients on HES and 43% on Ringer's acetate ($P < 0.03$). In addition, RRT was used in 22% of patients on HES and 16% on Ringer's acetate ($P < 0.04$). The difference in mortality noted in 6S study, is primarily related to the difference in study population. This study focused on patients with severe sepsis, while in the CHEST study only 28% had sepsis. In addition, this study compared HES with Ringer acetate, rather than saline.

The most recent RCT includes 2857 patients in 57 ICU's in France, Belgium, North Africa, and Canada, compared the effect of colloids (gelatin, dextran, HES, or 4 & 20% albumin) or crystalloids (isotonic or hypertonic saline or Ringer's Lactate) on mortality. The 28-day mortality of 25.4% in colloid vs. 27% in the crystalloid group were similar, however the 90-day mortality was lower in HES than crystalloid group (30.7 vs 34.2% respectively ($P < 0.03$). However, there was no difference in the rate of renal replacement therapy (11.0 vs. 12.5%). The subgroup analysis showed 28 and 90 day mortality was similar in HES vs. saline and HES vs. Ringer's.[20] This study has been criticized for the lack of baseline match between the two groups, use of multiple colloids solutions and low recruitment from each site, raising question about its internal validity and generalizability.

Two meta-analyses are relevant to our discussion here. In 2013, a meta-analysis focusing on HES 130/0.38 – 0.45 studies in patients with sepsis includes 9 trials with 3456 patients. Risk ratio (RR) for AKI (1.18 CI 0.99 to 1.40) and renal replacement therapy (RRT) (1.36, CI 1.08 to 1.72) was higher in HES group.[21] However, the mortality rate was similar. A second meta-analysis with data from 14 studies with 18,916 patients with sepsis was published recently. This analysis focused on the effect of different resuscitative fluids on mortality in adult patients with sepsis or septic shock.[22] To weight the quality of the data and define the level of confidence in their recommendations, authors used 4-node (crystalloids vs. albumin vs. HES vs. gelatin), and 6-node (crystalloids vs. albumin vs. HES vs. gelatin, with crystalloids divided into balanced or unbalanced and HES divided into low or high molecular weight) network meta-analyses (NMA) methods, as well as GRADEII methodology.[23] The 4-node analysis suggests a greater mortality with starches than with crystalloids (all data given as odd ratio and credibility ratio,[8] which is the Baysian analogue of 95% confidence band followed by the level of confidence in the data) (OR, 1.13 [95% CrI, 0.99 to 1.30]; high confidence) and lower mortality with albumin than with crystalloids (OR, 0.83 [CrI, 0.65 to 1.04]; moderate confidence) and starches (OR, 0.73 [CrI, 0.56 to 0.95]; moderate confidence), and balanced crystalloids superior to saline (OR, 0.78 [CrI, 0.58 to 1.05]; low confidence) moderate confidence). It is important to note that almost all confidence intervals cross the unity line and the level of confidence are mostly low to moderate.[22]

It is surprising that although intravenous fluid has been used routinely for more than a century, we have just begun to carefully evaluate the relative effectiveness of different fluids available for resuscitation. Although the above data is helpful in providing general recommendations regarding the use of selected solutions, as pointed out recently, we still have a long way to go before we can develop patient-specific fluid recommendations.[24] However, these data provide enough evidence to recommend avoiding the use of hetstarchs as volume expanders, and limiting the use of albumin in patients with septic shock. Further data needs to be achieved to recommend more balanced solution for resuscitation.

Amount of fluid

The goal of fluid management in patients with sepsis is to give adequate amount of fluid to normalize patient's circulatory state in a timely manner. In 2002, Rivers and colleagues published the first RCT evaluating the impact of rapid normalization of circulatory state on the mortality in 263 patients presenting with 2/4 systemic inflammatory response (SRI) criteria.[25] Patients were randomly assigned to early goal directed therapy (EGDT) or standard treatment and managed in the emergency department for the first 6 hours. Patient assigned to EGDT arm, received a 500 mL bolus of crystalloid every 30 minutes to achieve a central venous pressure of 8 to 12 mm Hg and MAP 65 mm Hg. If the BP goal was not achieved, vasopressors were given to maintain a MAP of at least 65 mm Hg. Vasodilators were given if SBP was > 90 mm Hg until it was 90 mm Hg or below. If the central venous oxygen saturation was less than 70%, red blood cells were transfused to achieve a hematocrit of at least 30%. After the central venous pressure, mean arterial pressure and hematocrit were optimized, if the central venous oxygen saturation was less than 70%, dobutamine was administered. The standard arm had similar MAP, CVP and urine output goals but did not follow the remainder of the above protocol. The amount of fluid infused in the first six hours was significantly greater in EGDT compared to the standard group (5 vs. 3.5L). The EGDT group received more transfusion (64.1% vs. 18.6%) and inotropes (0.8 vs. 13.7%), ($P < 0.001$). However, during the first 72 hours after the start of treatment, the two groups received the same amount of fluid and inotropes. The primary endpoints of in-hospital and 28-day mortality were significantly higher in standard than EGDT (46.5% vs. 30.5% and 49.2% vs. 33.3% respectively). The findings of this study, supported by several single center studies in the US and a large multicenter study in China, has become the national international standard for care and rated as a grade (1C) recommendation by Surviving Sepsis Campaign.[2] This effect is however limited to studies where the therapy was initiated early upon arrival in the emergency department.[26]

The study by Rivers, et al. involved several specific interventions. Therefore, it was difficult to know which maneuver played a critical role in improving reported mortality. According to an intervention, the measurement of central venous oxygen saturation ($ScvO_2$) is invasive in nature and requires specialized equipment, which is not available in many centers worldwide. In their study, Jones and colleagues evaluated non-inferiority of lactate clearance defined as $(\text{lactate}_{\text{initial}} - \text{lactate}_{\text{delayed}}) / \text{lactate}_{\text{initial}}) \times 100$ compared with $ScvO_2$ in 300 patients, using Rivers, et al. protocol.[27] Central venous catheter was placed in experimental arm and control, but the result was not recorded. Treatment in the experimental arm was guided by lactate clearance with the goal of 10% reduction after a minimum of 2 hours. There was no difference in treatment provided to each group in the first 6 hours in the emergency department or in the first 72 hours in the inpatient units. In the intent-to-treat analysis, the in-hospital mortality rate was 17% (25 of 150) in the lactate clearance group compared with 23% (34 of 150) in the ScvO2 group (P = NS). In conclusion, this study supports the concept that $ScvO_2$ measurement, which is an invasive procedure,

can be replaced by measurement of lactate clearance. However, it should be noted that these patients had significantly lower mortality and were not as critically ill as those studied by Rivers, et al.[26]

The study by Rivers has been followed by three multi-institutional studies carried out in the US, UK and Australia, New Zealand for further evaluation regarding the impact of the EGDT protocol. The result of two of these studies was recently published.[28,29] The first study, a multicenter, randomized trial entitled Protocolized Care for Early Septic Shock (ProCESS), carried out at 31 hospitals in the United States. This study involves 1341 patients assigned, in a 1:1:1 ratio, to one of three groups: protocol-based EGDT (PBEGDT), protocol-based standard therapy (PBST), or usual care (UC). Patients randomly assigned to PBEGDT, followed a protocol the similar used by Rivers, et al. PBST also used a team approach with a set of 6-hour resuscitation instructions, a central catheter to measure $ScvO_2$, and packed red-cell transfusion only when the hemoglobin level was less than 7.5 Gm/dL. Protocols for the use of fluid and pressors were similar to EGDT arm. In patients in the UC arm, the bedside providers directed all care, while the study coordinator only collected data. The primary outcome of the study was the rate of in-hospital death from any cause at 60 days. Secondary outcomes included death from any cause at 90 days and 1 year. During the first 6 hours, the amount of fluids administered differed significantly among the groups (2.8 liters in the PBEGDT group, 3.3 liters in the PBST group, and 2.3 liters in the UC group ($P < 0.001$). More patients in the two protocol-based groups received pressors than in the UC group ($P = 0.003$) and Dobutamine, and packed red blood cells were used significantly more often in the PBEGDT group than the other two groups. By 6 hours, more patients in each of the protocol-based groups than in the usual-care group had achieved the target mean arterial pressure of 65 mm Hg or higher ($P = 0.02$). By day 60, the in-hospital mortality rate in EGDT, PBST, and UC were 21%, 18.2% and 18.9% respectively (P = NS). There were also no significant differences in 90-day mortality, and 1-year mortality. Surprisingly the incidence of AKI requiring renal replacement therapy was higher in the PBST group than in the other two groups (6.0% in the PBST group vs. 3.1% in the PBEGDT group and 2.8% in the UC group, $P = 0.04$). The second study was conducted in 51 centers mostly in Australia and New Zealand and randomly assigned 1600 patients to EGDT or usual care. In the first 6 hours the EGDT group received more fluid (1964 ± 1415 mL vs. 1713 ± 1401 mL), were more likely to receive pressors (66.6% vs. 57.8%), red blood cell transfusion (13.6% vs. 7.0%) and dobutamine (15.4% vs. 2.6%), ($P < 0.001$). However, the 90 days death rate of 18.6 vs 18.8 was similar. The difference in findings between these two studies and the study by Rivers, et al. is partly due to bias documented in single center compared with multi-centered studies. In addition, in a study by Rivers, patients with higher fluid/pressors requirements have higher mortality. Finally, over the past two decades significant progress has been made in caring for critically ill patients blurring the difference between protocol-based and standard care. It is also important to note that none of these studies have shown a worse outcome in patients treated with specific protocol. As a matter of a fact, in many settings a well designed protocol could improve outcome by limiting variation in care and allowing adjustment based on the actual effectiveness of the protocol in the real world.

Among patients with sepsis, extreme caution should be exercised in patients with acute respiratory distress syndrome (ARDS), who are treating with rapid administration of fluid. In a study of 1000 patients with ARDS, all intubated and on positive pressure breathing with PaO2 to FIO2 of < 300 and bilateral infiltrate on chest X-ray, were randomly assigned to liberal or conservative fluid management based on a complex protocol with CVP goals of 10 – 14 in liberal and < 4 in conservative group.[30] The liberal-strategy group received more fluid than the conservative-strategy group with a higher seven-day cumulative fluid balance of 6992 ± 502 mL vs. –136 ± 491 mL respectively ($P < 0.001$). The primary outcome of death at 60 days was similar (25.5 vs. 28.5 conservative vs. liberal group P = NS). However, conservative group had more ventilator-free days and more days out of ICU. In addition more patients on liberal protocol required renal replacement therapy (14% vs. 10% $P < 0.06$), however this did not achieve significance. In a subgroup analysis of 306 patients who also had AKI, odd ratio for mortality at 60 days was 1.61 for each liter increase in daily fluid balance.[31]

Given these recent studies how should we approach emergency department patients with possible sepsis? The first critical step is to quickly identify patients with possible sepsis and begin the treatment as soon as possible. Early treatment of sepsis however requires coordinated approach between care-givers including physicians in emergency department and intensive care unit as well as support by trained nurses, and other support staff. The focus of the above studies was only on aspect of medical care. Although as summarized above, recent well-designed multi-centered studies do not show a benefit from protocol-driven care compared with standard care. It should also be noted that the care must be coordinated and timely. Evidence-based protocol modified to fit local realities, can serve as a template for training of the key staff and collection of relevant data critical to improve clinical outcome. The organization Surviving Sepsis Campaign has recently published a helpful implementation and improvement guideline, which is available in their website available at www.survivingsepsis.org.

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