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Hospital Medicine

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ABSTRACT & COMMENTARY

Initial Choice of Fluid for Sepsis Resuscitation May Affect Mortality

By Samuel Nadler, MD, PhD

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Dr. Nadler reports no financial relationships relevant to this field of study.

SYNOPSIS: The use of balanced salt solutions rather than isotonic saline or colloids may improve in-hospital mortality in patients admitted with septic shock.

SOURCE: Raghunathan K, et al. Association between initial fluid choice and subsequent in-hospital mortality during the resuscitation of adults with septic shock. *Anesthesiology* 2015;123:1385-1393.

Appropriate fluid resuscitation is a foundation of appropriate sepsis care. Which fluid type is best remains unclear. There are studies comparing crystalloids and colloids, starch solutions, albumin, etc. In practice, however, combinations of these options are often employed. Previously, Raghunathan et al demonstrated a superiority of balanced salt solutions when compared with isotonic saline.[1] This study examined the effects of combinations of crystalloid and colloids on in-hospital mortality from sepsis.

This retrospective cohort study between January 2006 and December 2010 evaluated 60,734 patients admitted with sepsis who had received at least 2 L of volume resuscitation, required vasopressors, had not undergone any major surgical procedure, and remained in the ICU for at least 2 days. Four categories of exposures were defined: isotonic saline alone (Sal); isotonic saline and balanced salt solutions (Sal + Bal); isotonic saline and colloids (Sal + Col); and all three (Sal + Bal + Col). The primary outcome was in-hospital mortality with secondary analyses looking at length

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[ALERT]

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of stay and cost per day among survivors. As there were significant differences in baseline characteristics in each group, risk adjustments for 27 known comorbidities were used, including inverse probability weighting, propensity score matching, and hierarchical logistic regression methods.

In the study cohort, most patients (n = 44,347) received Sal, while 3651 patients received Sal + Bal, 11,038 received Sal + Col, and 1698 received Sal + Bal + Col. Using various risk adjustment methods, patients in the Sal + Bal cohort had the lowest absolute mortality (17.64-18.83%) as compared with Sal (20.19-21.35%), Sal + Col (24.16-29.94%), or Sal + Bal + Col (19.23-25.15%). In pairwise comparisons, Sal + Bal was associated with the lowest mortality whether Col were used (relative risk [RR], 0.84; 95% confidence interval [CI], 0.76-0.92; $P < 0.001$) or not (RR, 0.76; 95% CI, 0.70-0.89; $P < 0.001$). Conversely, administration of Col was not associated with an increased risk when Bal were used but did have an increased mortality rate when in combination with Sal (RR, 1.14; 95% CI, 1.08-1.19; $P < 0.001$). This effect persisted when the Col were restricted to albumin and hetastarch was excluded in the analysis. Additional sensitivity analysis demonstrated that the difference in mortality with Col administration could be due to an unidentified confounder but that the difference in mortality between Sal and Sal + Bal was robust. Secondary outcomes such as hospital length of stay and costs per day were comparable in the Sal vs Sal + Bal group, but were higher in the cohorts receiving colloids (Sal + Col and Sal + Bal + Col).

■ COMMENTARY

This study extends the conclusions of a previous analysis of similar data with respect to the choice of fluid for sepsis resuscitation. The baseline differences encountered included a lower rate of congestive heart failure in the Sal + Bal and Sal + Bal + Col cohorts and a higher rate of liver disease in the Sal + Col cohort. With inverse probability weighting and propensity score matching adjustments, these differences can be eliminated but other confounders may still bias results.

When evaluating the outcomes in these cohorts at day 2, there are a few striking results. The Col-containing groups had the highest rates of mechanical ventilation, vasopressor use, bicarbonate infusions, total parenteral nutrition, and diuretic needs. Also telling is that the rate of tracheostomy at day 2 in the Sal + Bal+ Col group was 7.07% as compared with 3.12%, 4.74%, and 3.86% in the Sal, Sal + Bal, and Sal + Col groups, respectively, implying that clinicians saw this cohort as having the greatest likelihood of prolonged mechanical ventilation early in the course of the hospital stay.

["This effect persisted when the Col were restricted to albumin and hetastarch was excluded in the analysis."]

While this is a retrospective analysis, some confidence can be gained that Bal seem to improve patient outcomes, regardless of Col co-administration. Looking at mortality at the hospital level, with an increasing proportion of balanced salt solution use, there is decreasing mortality. In general, one would not expect clinicians to adjust the proportion of Bal vs Sal based on perceptions of severity of illness. But this may belie that hospital-level interventions and protocols may have an effect on sepsis mortality.

Overall, this study adds to the evidence that Bal improve patient outcomes with sepsis. There has yet to be shown a significant risk or cost associated with their use, and lactated ringers is as prevalent in most ICUs as isotonic saline. It may be time to start using Bal routinely as part of sepsis resuscitation. ■

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ABSTRACT & COMMENTARY

Bedside Ultrasound: Is It a Reliable Tool for Guiding Resuscitation in Patients with Undifferentiated Hypotension?

By Kathryn Radigan, MD

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Dr. Radigan reports no financial relationships relevant to this field of study.

SYNOPSIS: The use of bedside ultrasound for patients with undifferentiated hypotension in the emergency department substantially changed the plan of care and reduced physician diagnostic uncertainty.

SOURCE: Shokoohi H, et al. Bedside ultrasound reduces diagnostic uncertainty and guides resuscitation in patients with undifferentiated hypotension. *Crit Care Med* 2015;43:2562-2569.

The use of bedside ultrasound has expanded tremendously over the last few decades. As it is readily available and relatively inexpensive, ultrasound provides the opportunity to examine hypotensive, critically ill patients, potentially leading to a faster, more accurate diagnosis.

Shokoohi et al used bedside ultrasound in an emergency department (ED) to help determine the etiology of undifferentiated hypotension. In this prospective, observational trial conducted at a single, academic, tertiary care hospital within a 32-month period, 118 patients with a systolic blood pressure < 90 mmHg after initial fluid resuscitation without an obvious source of hypotension were examined with an ultrasound using a standardized hypotension protocol. Although the duration of ultrasound exam was not recorded, a formally trained attending physician with extensive experience in emergency and critical care ultrasound performed the ultrasound protocol and included a focused cardiac scan to assess cardiac contractility, right ventricle size, and the presence of pericardial effusion/tamponade. It also included an inferior vena cava, abdominal, and transthoracic scan. Primary outcome measures included change in treating physician's diagnostic certainty before and after ultrasound and concordance of post-ultrasound ED diagnosis with chart review final diagnosis. Secondary outcomes were changes in treatment plan, use of resources, and changes in disposition after performing ultrasound protocol.

Results of the study revealed a 28% decrease in mean aggregate complexity of diagnostic uncertainty before and after ultrasound protocol (1.85-1.34; -0.51; 95% confidence interval, -0.41 to -0.62) along with a significant increase in the proportion of patients with a definitive diagnosis from 0.8% to 12.7%. There was exceptional concordance with the blinded consensus final diagnosis (Cohen kappa = 0.80). Furthermore, 24.6% of patients experienced a significant change in the use of IV fluids, vasoactive agents, and blood products, and there were significant changes in plans for further diagnostic imaging (30.5%) and ED disposition (11.9%). Early use of bedside ultrasound for critically ill patients with undifferentiated hypotension had a clinically significant effect on physicians' differential diagnosis with subsequent changes in patients' ED management.

■ COMMENTARY

Performance of bedside ultrasound has become an invaluable tool for immediate assessment of the critically ill patient, especially for evaluation of goal-directed therapy in the setting of a hemodynamically unstable patient. Shokoohi et al were able to show that early use of bedside ultrasound by a formally trained, experienced attending physician resulted in a statistically significant reduction in physicians' diagnostic uncertainty, with the leading diagnoses after ultrasound highly concordant with the final diagnosis. It also guided management decisions with significant changes in resuscitation efforts, diagnostic imaging, and ED disposition. Additionally, echo in the critically ill patient is known to be portable, quick, easy to use, and cost-effective.[1] It can also be used serially in patients to assess response to interventions in "real-time."

Proper training is the main challenge of utilizing ultrasound for the diagnostic assessment and treatment of the ICU patient. The recent International consensus statement on training standards for advanced critical care

echocardiography states that training programs should be rigorous and include competence-based testing.[2] The American College of Emergency Physicians suggests that didactic training, extensive hands-on experience, and expert review, along with formal certification, be included in every case.[3] This is particularly important, as proper training for intensivists requires competence in patients who are the most technically difficult in the most challenging situations. Unfortunately, this particular study did not address proper training, as the ultrasonographers were only described as formally trained attending physicians with "extensive experience" in emergency and critical care ultrasound but without specific reference to the methods of training and/or certification. Fortunately, other recent studies have suggested that training internists and residents with minimal ultrasound skills is feasible and effective.[1,4] Regardless of whether the ultrasonographer is a new resident early in training or a well-seasoned attending, it is most critical for the physician to appreciate when necessary images are not acquired or are insufficient for diagnosis. At that point, the timely acquisition of a formal, comprehensive, confirmatory 2-D echocardiogram is essential, which was only performed in a limited number of patients in this study.

It is also important to highlight that the ultrasonographers within this study were blinded to patient's history and physical exam. It makes one consider the limitations of a trial that would randomize patients to standard care vs bedside echocardiography while blinded to details related to the clinical presentation. However, while these ultrasonographers were blinded to the clinical presentation, there was still a statistically significant change in diagnostic certainty, thus supporting application of ultrasound assessment despite the operator. In our practice, it is important to interpret information in the context of the available clinical presentation with the available hemodynamic information and respiratory data (i.e., central venous pressure, response to fluids, urine output, chest X-ray, venous oxygenation, etc.).

The role of bedside ultrasound in critically ill patients is extremely valuable and continually evolving. As this manuscript supports, bedside ultrasound has become a beneficial modality in the treatment, care, and monitoring of critically ill patients. Establishing optimal bedside echo protocols with the assurance of exceptional training and maintenance of skills remains a critical concern. We should continue to develop high quality and accuracy for echocardiography skills while applying this information to the clinical context of the patient to achieve the optimal benefit for each individual. ■

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ABSTRACT & COMMENTARY

Clinicians Are Skeptical of Early Warning Systems for Sepsis

By Elaine Chen, MD

Assistant Professor, Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, Section of Palliative Medicine, Rush University Medical Center

Dr. Chen reports no financial relationships relevant to this field of study.

SYNOPSIS: While early warning systems for sepsis lead to clinical action, clinicians are skeptical and do not perceive them to be beneficial.

SOURCE: Guidi JL, et al. Clinician perception of the effectiveness of an automated early warning and response system for sepsis in an academic medical center. *Ann Am Thorac Soc* 2015;12:1514-1519.

Severe sepsis is very common, with high morbidity and mortality. Early recognition and intervention improves mortality. However, the diagnosis may often be missed in early sepsis. An academic

health system developed an electronic early warning and response system (EWRS) for sepsis in 2012, monitoring real time vital signs and laboratory data for hospitalized, non-ICU, acute care patients and notifying clinicians when specific criteria were met. This EWRS accurately identified patients at increased risk for deterioration and death, resulting in more timely sepsis care and ICU transfer, and possibly reducing sepsis mortality.[1]

["Successful implementation of new clinical systems includes clinican acceptance."]

All non-ICU medical and surgical inpatients were screened continuously for systemic inflammatory response syndrome (SIRS) criteria as well as criteria suggesting organ dysfunction. Whenever a patient fulfilled four or more criteria, a text page was sent to the covering provider (physician or advanced practice provider) and rapid response coordinator, and the bedside nurse received a pop-up notification in the electronic health record (EHR). Clinicians were instructed to meet at the bedside within 30 minutes to evaluate the patient and make any management changes. A patient could only trigger the alert once during hospitalization.

Successful implementation of new clinical systems includes clinician acceptance. The authors hypothesized that clinicians would perceive the EWRS as useful and effective. They tested their hypothesis by surveying clinicians immediately after receiving the EWRS alert to evaluate their perception of the value of the alert. A 16-item questionnaire examined the utility of implementation of the EWRS. The rapid response coordinator distributed paper surveys within 2 hours of an EWRS alert for 6 weeks. Subjects included providers and bedside nurses in a single academic medical center. Anonymously completed surveys were returned to a designated envelope.

The EWRS generated 247 alerts; 494 surveys were distributed, and 232 were returned (127 from providers and 105 from nurses) for an overall response rate of 47%. Both providers and nurses reported that patients were medically stable both before and after the alert in approximately 80% of cases and did not commonly perceive the presence of a new critical illness. Sepsis was the suspected trigger in one-third of cases and volume depletion in one-fifth. In one-third of cases, clinicians perceived the values to be erroneous at baseline or inconsequential.

Management changed in approximately half of patients, most commonly by way of closer monitoring, basic diagnostic testing, or therapies such as intravenous fluids and antibiotics. Less than half of providers or nurses found the alert helpful and less than one-third thought it improved patient care. Nurses thought more favorably about the EWRS than providers.

Overall, clinicians were lukewarm in their support of the EWRS. The authors noted that users received no formal education regarding the importance of early sepsis recognition and treatment. The authors suggested that the alert may have resulted in behavioral modifications that improved clinical outcomes, but that clinicians may not have appreciated that the tool was a catalyst to better patient care. Alternatively, the alert may have caused pressure to order tests or escalate care in patients who did not truly require it. That most patients were perceived to be stable both before and after the alert may be a sign of low signal-to-noise ratio, which has a risk of leading to alert fatigue. Further investigation can focus on acceptability, resource allocation, and system improvement.

■ COMMENTARY

Previously, the article by Umscheid et al described with great enthusiasm some potential benefits of the EWRS.[1] In contrast, this article tempers that enthusiasm, with only moderate clinician support. While clinicians are often initially skeptical of any changes that disrupt their usual work flow, the benefits may be borne out over a longer time period before clinicians recognize them. Thus, I would be hesitant to discount the results of lukewarm clinician support to a potentially beneficial early warning system.

However, as three clinicians were required to evaluate and communicate about each alert, this alert is highly personnel-intensive. EHRs have the potential to (and do) provide alerts at many points of contact. I have watched clinicians ignore myriad alerts in order to proceed with their work. Additionally, I would be hesitant to warmly welcome a system that identifies stable patients 80%of the time because it has the potential to overburden busy clinicians with low-yield clinical data. While I am optimistic about the EWRS and its potential to improve outcomes in sepsis, this system needs some improvements prior to widespread adoption. ■

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1. Umscheid JA, et al. Development, implementation, and impact of an automated early warning and response system for sepsis. *J Hosp Med* 2015;10:26-31.

ABSTRACT & COMMENTARY

Spironolactone for Resistant Hypertension

By Michael Crawford, MD, Editor

Dr. Crawford reports no financial relationships relevant to this field of study.

SYNOPSIS: A randomized, double-blind, placebo-controlled study in resistant hypertension patients on three drugs, including a diuretic, showed that the addition of spironolactone was superior to doxazosin and bisoprolol for lowering blood pressure and it was well tolerated.

SOURCES: Williams B, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): A randomised, double-blind, crossover trial. *Lancet* 2015;386:2059-2068.

Sternlicht H, Bakris GL. Spironolactone for resistant hypertension-hard to resist? *Lancet* 2015;386:2032-2034.

Resistant hypertension is common, and the choice of additional drug therapy in this condition is not clear. Investigators tested three drug classes as additional therapy beyond the recommended angiotensin-converting-enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB), calcium blocker plus diuretic. An alpha-blocker to further reduce peripheral resistance (doxazosin), a beta-blocker to reduce renin (bisoprolol), and additional diuresis with spironolactone were tested in a randomized, double-blind, placebo-controlled, crossover trial. The study included patients on maximally tolerated doses of the recommended three classes of drugs who had a clinical blood pressure (BP) of > 140 mmHg systolic or > 135 for diabetics and average home BP measures > 130 over 4 days (18 measurements). After 1 month of single-blind placebo, patients were rotated through four regimens for 6 weeks at the lower dose and 6 weeks at the higher dose: spironolactone 25-50 mg/day, doxazosin 4-8 mg/day, bisoprolol 5-10 mg/day, and placebo. The primary endpoint was the average of three home systolic BP twice a day for 4 days (24 measurements). Plasma renin was measured at baseline, and serum electrolytes were measured at each visit. Researchers screened 436 patients 18-79 years of age, randomized 335 patients (mean age 61 years), and placed 314 patients in the intention-to-treat analysis. Two hundred thirty patients completed the entire protocol. The average decrease in systolic BP on spironolactone was significantly greater than on placebo (-8.7 mmHg, $P < 0.0001$) and the response to doxazosin (-4.0 mmHg, $P < 0.0001$) and bisoprolol (-4.5 mmHg, $P < 0.0001$). Spironolactone's superiority persisted across all measured renin levels except the very highest, where it was equally as efficacious the other two drugs. Adverse events were not different with the three drugs, and only six patients on spironolactone had a potassium > 6.0 mmol/L on one occasion only (maximum 6.5). The authors concluded that spironolactone was the most efficacious fourth drug for patients with drug-resistant hypertension.

■ COMMENTARY

Resistant hypertension is defined as levels above the patients target on maximally tolerated doses of three drugs, one of which is a diuretic, and afflicts about 10% of treated hypertensives. Current guidelines suggest adding a fourth drug, but do not specify which one. It has been suggested that resistant hypertension is a result of non-compliance, not necessarily with drug therapy but rather lifestyle modifications such as reduced salt intake, alcohol consumption, and weight loss. The most important of these is probably salt intake. In this study, 24-hour urine-sodium excretion on placebo was 8 g. Thus, the concept of additional diuresis has arisen. Some believe that switching to a longer-acting diuretic, such as chlorthalidone or indapamide, works, but this has not been systematically studied. Another concept is that those treated with long-term ACEI/ARB develop aldosterone escape, leading to salt and water retention. Therefore, previous observational studies suggest aldosterone antagonists may be efficacious in resistant hypertension. This study tested this hypothesis and compared spironolactone to two other classes of agents: beta-blocker and alpha-blocker.

In this population of predominantly white subjects, spironolactone was remarkably effective. It was twice as effective as bisoprolol and doxazosin. Also, about 60% achieved target BP (< 135 systolic) on spironolactone vs about 40% on the other two drugs. Although bisoprolol and doxazosin were better than placebo, only spironolactone showed a dose response relationship, suggesting that higher doses, if tolerated, would produce better results. The authors suggested that the use of spironolactone in resistant hypertension may reduce the fuel for non-pharmacologic approaches such as renal denervation. Also, the study raises the question as to whether the earlier use of spironolactone would be beneficial. In the past, combination pills with hydrochloro-

thiazide and spironolactone were popular to reduce the incidence of hypokalemia. Perhaps these agents should receive another look in light of these data.

This study has several strengths. The authors used average home BP, which is always lower, as their endpoint measure. There was a big placebo effect noted in clinic BP (-10 mmHg) but not with average home BP. The population was relatively large for this type of study and several biochemical measures were taken, which will be reported later.

There are also weaknesses. The trial was of short duration and has no outcome data. The patients were predominantly white and had glomerular filtration rates (GFR) > 45.

There were remarkably few adverse events and they were not different between the three drugs (all < 3%). Hyperkalemia was infrequent and resulted in no serious events. The authors noted that serum sodium decreased 1.2 mmol/L on average, and potassium increased 0.5 mmol/L. Estimated GFR decreased, but no more than you would expect while administering another diuretic. Whether this has long-term consequences is unknown. The authors did not observe gynecomastia, but the length of exposure to spironolactone is probably too short to see this side effect.

The editorial by Sternlicht and Bakris concluded that despite the imperfections in this study, using spironolactone for resistant hypertension is "hard to resist." Future studies should clarify general applicability and whether a more aggressive thiazide diuretic approach would be just as effective. ■

BRIEF REPORT

Delay in Performing Endovascular Reperfusion Results in Worse Disability Outcomes

By Matthew E. Fink, MD

Louis and Gertrude Feil Professor in Clinical Neurology and Chairman, Department of Neurology, Weill Cornell Medical College; Neurologist-in-Chief, New York Presbyterian Hospital

Dr. Fink reports no financial relationships relevant to this field of study.

SOURCE: Sheth SA, et al. Time to endovascular reperfusion and degree of disability in acute stroke. *Ann Neurol* 2015;78:584-593.

In the past year, multiple clinical trials have reported that intra-arterial endovascular reperfusion with mechanical clot extraction, using the SOLITAIRE stent retriever device and others, results in better neurological outcomes than treating patients with intravenous thrombolysis alone with TPA. There is still uncertainty regarding the maximum time window, and how important early intervention is as related to neurological recovery and long-term outcomes. The investigators used the combined databases of the SWIFT (Lancet 2012) and STAR (Stroke 2013) trials to identify patients treated with the SOLITAIRE device who achieved substantial reperfusion. They then ranked the 90-day modified Rankin scale outcomes for "time of onset to recanalization" (OTR) time intervals ranging from 180 min to 480 min.

Analysis of these data showed substantial time-related reductions in disability for the entire range of outcomes. A shorter OTR time was associated with an improved 90-day Rankin Scale outcome in all groups. The mean Rankin scores were 1.4 for the 120-240 min OTR group, 2.40 for the 241-360 min group, and 3.3 for the 361-660 min group ($P < 0.001$). There were no significant differences between the groups in the incidence of intracerebral hemorrhage, mortality, or length of hospitalization. The predicted probability and confidence interval of good neurological outcome (mRS 0-2) at 90 days was a continuous variable inversely related to the time from symptom onset to recanalization. For every 15-min acceleration in the time to reperfusion, 34 per 1000 patients treated will have improved disability outcomes, which translates to 1 out of 100 patients improved, for every 5 minutes of reduced OTR time. ■

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CME QUESTIONS

1. In the retrospective study by Raghunathan and colleagues, which choice of fluid for resuscitation of patients with sepsis was associated with the best risk-adjusted hospital survival?

a. Saline

b. Colloids

c. Saline plus colloids

d. Saline plus balanced salt solutions

e. No differences were seen between groups

2. Based on the study by Shokoohi et al., early use of bedside ultrasound for unstable patients with undifferentiated hypotension led to subsequent statistically significant changes in all of the following ways *except*:

a. An increase in the number of patients with a specific diagnosis

b. A change in the use of IV fluids and vasopressors

c. A change in the use of subsequent imaging

d. A change in ED disposition

e. A decrease in mortality

3. In acute stroke, cerebral reperfusion using mechanical clot extraction results in better neurological outcomes than pharmacological thrombolysis alone. Based on the analysis by Sheth and co-investigators, what can be said about time to recanalization?

a. Within the window of 180 to 480 minutes, the time to recanalization did not affect clinical outcomes.

b. Shorter time to recanalization was associated with better neurological outcome.

c. Shorter time to recanalization was associated with higher risk of subsequent hemorrhage.

d. Shorter time to recanalization was associated with a higher mortality.

e. All of the above

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss pertinent safety, infection control and quality improvement practices;
- explain diagnosis and treatment of acute illness in the hospital setting; and;
- discuss current data on diagnostic and therapeutic modalities for common inpatient problems.

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