Edward Siew: Are Balanced IV Solutions the Solution?

Speaker 1:	00:00	Let's move on to our first speaker, who is Edward Siew from Nashville and the title is Are Balanced IV Solutions the Solution? The solution is this, a title of a country Western song from Nashville.
Speaker 2:	00:12	Alright, well before beginning I'd like to thank the organizers and Ravi for the opportunity to be at this wonderful meeting. My goal for the next 15 minutes or really just briefly review the evolution of this topic and discuss some of the findings of the recently published isotonic solutions in a major adverse renal events trial or SMART study. This is my disclosure slide
Speaker 2:	00:35	And so as many of us know, the history of iv aqueous solution really stemmed out of response to Pestilent , isn't in conflict beginning in the early 19 hundreds when Latta and others found that injecting salts of high oxyginated constitution could restore vitality and organ function in patients suffering from cholera. These early efforts were subsequently refined by brilliant physiologists, including the addition of electrolytes, the identification of the ideal concentration to avoid RBC lysis, and eventually the addition of buffered solutions. Subsequently, the advent of blood fractionation made widely available, the human albumin solutions, and that was followed by the development of semisynthetic colloids. However, with the publication of the safete and chest trials, which I won't be talking about, it's fair to say that attitude starts iv solutions it changed from something seen as benign and almost essential to perhaps a more measured perspective, where we weigh the risks and benefits as we would for any other medication. And so attention has once again shifted back towards the optimal composition of crystalloid solutions.
Speaker 2:	01:38	A question for which there's wide variations in practice patterns, particularly the question of whether balanced solutions may be potentially beneficial or less harmful, but what do we mean by balanced? The literature doesn't really actually provide specific guidelines outside of saying that approximating the constituents of plasma water, but as you can see, many of the most commonly used IV solutions don't really exactly fit that bill, in the case of isotonic saline while balanced in terms of chloride content and sodium content, the chloride content is relatively high compared to plasma water, and the pH is a little

bit lower. In contrast while balanced solutions tend to have more physiologic levels of chloride, they'd also do contain electrolytes, significant amounts of buffer solutions, and in some cases are mildly hypotonic and it's precisely these differences that have led people to raise reasonable concerns about the potential hazards of using these solutions, particularly when infused in large amounts in the case of isotonic saline.

Speaker 2: 02:47

Those concerns have revolved around the development of metabolic acidosis, which is plausible regardless of whether or not you believe it's a dilution of your serum bicarbonate or reduction in your strong ion difference. There are concerns about the potential effects of hyperchloremia on inflammation and potentially renal hemodynamics. In contrast, balanced solutions may predispose to the development of metabolic alkalosis. they are in the case of LR mildly hypotonic and do contain electrolytes. And it's clear from experimental studies that these differences can be induced through infusion, of these solutions. But the overarching question is, do these differences ultimately translate to differences in clinical outcome when given to sick patients? This is a question that's been attempted to be addressed in multiple observational studies, which is very challenging to do. As you can imagine, this is a table using some of the more robust and larger studies, many using sort of advanced matching techniques to try to control for confounding by indication.

Speaker 2: 03:51

And what you can see is that several have suggested an association between isotonic saline and an increased risk for mortality and AKI and while definitive conclusions are difficult to draw from these types of studies, the relative consistency and the biologic plausibility have compelled this question to move on to clinical trials to being answered. And so, you know, some colleagues attempted to extend upon this work by, using open label study testing the hypothesis that chloride liberal strategy would increase the risk of AKI compared to a chloride restrictive strategy in critically ill patients. They used to pre post design, and this was conducted with a single center, where they bundled several crystalloid and colloid solutions that were chloride liberal and made them available to providers for a six month period, Followed by a six month wash out in the ensuing six months that chloride liberal bundle was substituted with a chloride restrictive bundle that included solutions like Hartmann's and Plasma-lyte

Speaker 2: 04:49

The primary outcome in this study with stage two or three AKI and as you can see from this, a Kaplan- Meier curve, patients initially signed to the chloirde liberal arm, experienced AKI at a

much higher rate than that in the chloride restrictive arm with an adjusted hazard ratio .52, interestingly, there is no difference in mortality despite these differences in moderate to severe AKI and some of the limitations of this study included that it was single center, the unclear effect that the pre post design may have had an altering a provider behavior and the bundled nature of the intervention. The ANZICS group followed this up with a pilot study called the SPLIT study, which tested the hypothesis that routine use of plasmalyte 1:48 might decrease the risk of AKI compared to saline. This was, this a cluster randomized double blind study where 1 of 4 ICUs were randomized to alternating 7 week blocks of study fluid.

Speaker 2: 05:48 They enrolled about a little over 2000 patients. Most of these were postsurgical on many cardiac surgery patients, and as you can see, the median amount of study fluid given was about 2 liters in each arm. The investigators were able to capture the amount of fluid given before and you can see in each arm about meeting of 1 liter of plasma was given in both. The primary outcome in this study was stage two or three AKI, and the investigators saw no difference in the rate of AKI between the two arms. In terms of secondary outcomes, there was a one percent difference in observed mortality favoring the plasma-lyte arm. but the P value did not reach statistical significance. And so at about the same time, there are two pragmatic studies launched at Vanderbilt University, designed to compare the effectiveness of balanced crystalloids and isotonic saline on patient outcomes in a real world setting.

Speaker 2: 06:48 This included the SMART study that was involved, 5 ICU's at Vanderbilt, and a companion study called the SALT-ED study, that involved patients in the emergency room that was subsequently admitted to the non ICU floor. Because of the nature of this session and time limitations, I'm going to focus primarily on the SMART study, where the intervention was balanced solutions in the form of LR or plasma-lyte A versus isotonic saline. The design was an unblinded cluster randomized multiple crossover study, and the primary endpoint was major adverse kidney events defined as death, dialysis, or doubling of baseline serum creatinine at hospital discharge or 30 days, whichever came first. And in the SALT-ED study, the primary outcome was length of stay. This is a graphical depiction of the design in SMART. And so again, ICU's we're randomizing to one month alternating blocks of study fluid beginning at the first of every month and ending on that last day of every month.

Speaker 2: 07:48 Based on preliminary data, in terms of where most of the patients were admitted from, some ICUs were randomized

together, for example, the neuro and cardiac ICU at our institution, the majority of patients tend to come from the operating room, whereas a medical trauma and surgical, most tend to come from the emergency room. And, the reason for this was to try to better coordinate, pre ICU crystalloid delivery with other points of the hospital in people being admitted to these units. This is a snapshot of the Computer Order Entry System, in this case during a month for balanced solutions. And what you can see is that providers that at all times had a choice between lactated ringers, plasmalyte or ordering off protocol solution, including normal saline. The study enrolled 15,800 patients, about 8,000 in each arm. Patients groups were well balanced in terms of a demographic and comorbidities, about a half came through the ED. A third were from the medical ICU., 15 percent had sepsis, a quarter, were on vasopressors and a third were on mechanical ventilation. In terms of kidney disease burden, we estimated that about 17 to 18 percent of patients had evidence of chronic kidney disease, before admission, about 5 percent had prior renal replacement therapy, and the baseline serum creatinine was .89 in both arms, about 8 percent had evidence of AKI at the time of ICU admission.

Speaker 2: 09:20

This is a table showing the distribution of IV fluids and the 24 hours prior to ICU admission as you can see overall more saline was delivered to the saline arm compared to the balanced arm. And conversely, more balanced solutions were delivered to patients and balanced arm than the saline arm. That pattern held in general across different ICUs with the exception of the cardiac ICU in which, predominantly balanced crystalloid was given in both arms. This is a figure showing the mean cumulative volume of crystalloid between ICU admission in hospital discharge as a cumulative volume on the y axis and time on the x axis. And as you can see about 2 liters on average of study fluid we're given in both arms with most of that happening within the first couple of days, compared to a less than 500 ccs of off protocol fluid.

Speaker 2: 10:16

This figure shows the plasma values of chloride and bicarbonate in both arms. And what you can see is that patients admitted to the saline arm or assigned to the saline arm, tended to have higher chloride concentrations in that and the balanced arm with about a third of them having a chloride, a value at some point greater than 100, 10 millimoles per liter compared to a 25 percent in the balanced arm. Conversely, patients in the saline arm also tended to have lower bicarbonate levels with 42 percent of them having at least one bicarbonate level less than 20 versus 35 percent in the balanced arm. This is a slide that shows the incidence of the primary composite outcome of

		major adverse kidney events, percentage of patients is shown here on the y axis. and a group assignment on the x axis. 14.3 percent of patients in the balanced arm experienced death, new renal replacement therapy or persistent kidney dysfunction compared to 15.4 percent in the saline arm. that difference reached statistical significance with a P value of 0.4,
Speaker 2:	11:22	To break this down in a little bit more detail. The majority of outcomes experienced - the biggest difference was in a 30 day or in-hospital mortality. In 11.1 percent of patients in the saline arm and 10.3 percent in the balanced arm, the P value of .06, 2.9 percent of patients experienced renal replacement therapy versus 2.5 percent in the balanced arm. And there were essentially no differences in the persistent kidney dysfunction outcome between the two arms. In terms of secondary outcomes, more patients experienced a stage two or greater AKI after ICU admission, then the balanced arm which did not reach statistical significance. And there were essentially no differences in other secondary outcomes with the exception of minimal differences in renal replacement three days. This is a figure that shows the incidence of MAKE30 by volume of study fluid received, incidence of MAKE30 on the y axis, and total volume is on the x axis and a as you can see, there was no separation between patient that did not get fluid and some gradual separation of about 1 and a half liters or so to about 3 and a half
Speaker 2:	12:33	In terms of a prespecified subgroup analysis, the, benefit or the ???? effect of balanced crystalloid seemed to be more evident in patients admitted to the medical and neuro ICUs in patients with sepsis and in patients without traumatic brain injury. The point estimate for categories of kidney function, including normal, prevalent AKI CKD, were all similar to that of the primary parent study, as well as saying potentially some benefit in those receiving previous renal replacement therapy. The strength of this study was its sample size which allowed for the detection of small but important differences. It's pragmatic approach being embedded within a clinical care allowed for a large sample size, and the early receipt of fluid. Limitations of this study included that it was a single center, it was unblinded, and so the decision to start renal replacement therapy was based on clinical care and the treating clinicians, the data as a whole were censored at discharge, and, in the balanced arm, there were two fluids available and there was roughly a similar uses between LR and plasma-Lyte.
Speaker 2:	13:56	Lastly, this was a single center, one single finding. I will say that this is not the last that you will hear about this. There are two

		large ongoing studies, one in Brazil called the BASIC study in one by the ANZICS group called the PLUS study, but although it was a single finding, and we didn't get a chance to really talk about the SALT-ED study, which was the companion study Non-critically ill ED patients, which the primary outcome in this study was negative and that was length of stay, but in terms of the incidence of make, the findings were consistent, in this study as seen in the, SMART study.
Speaker 2:	14:34	And so in summary, iv solutions are among the most common intervention in the critically ill, emerging clinical trials are informing us that not all of them are the same. Neither of them is perfect and each of them has their potential physiologic derangements in the case of isotonic saline that's hyperchloremia. More acidosis possibly effects on renal blood flow. Balance fluids may have more propensity for alkalosis, contain electrolytes, and in some cases are mildly hypotonic. The risk of MAKE30 is modestly higher among patients receiving isotonic saline compared to balanced solutions in critically ill patients and improving understanding of potential mediators have this effect, the effect of dose, heterogeneity of treatment effect and important sub groups are needed. With that, I'd like to thank the Vanderbilt Critical Care Pragmatic Trials group, particularly at the leads of the study, Matt, Semler, Wesley Self and Todd Rice, really it took an army of effort to make this happen and we recognize our mentorship Doctor Arthur P wheeler. Thank you.