Key Issues Dialogue: Albumin in Clinical Fluid Management

Featuring thought leaders from the medical community in the United States and Europe
Back row, from left to right: Dr. Gary R. Haynes, Dr. Georg Henkel, Dr. Thomas Machnig, Dr. Vicente Arroyo, Dr. Luciano Gattinoni and Dr. Albert Farrugia

Front row, from left to right: Dr. Garrett E. Bergman, Dr. Mauro Bernardi and Dr. Greg S. Martin
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Dialogue participants: Vicente Arroyo, M.D., Garrett E. Bergman, M.D., Mauro Bernardi, M.D., Albert Farrugia, Ph.D., Luciano Gattinoni, M.D., Gary R. Haynes, M.D., Ph.D., Georg Henkel, D.V.M., Greg S. Martin, M.D.

Garrett Bergman: Our focus today is on the current state of knowledge regarding albumin, which over the years has been used for various indications, for which there are varying degrees of scientific support and validation. We will examine its role in treating liver disease and sepsis, and its use in cardiac surgery. To begin, what are the biggest issues right now with albumin?

Mauro Bernardi: I think that it is time to consider the use of albumin from a different standpoint. While it is undisputed that albumin is a very efficient plasma expander, there are many other reasons to use it. I think that future research should focus more on the well-known properties of albumin as a scavenger, antioxidant and transporter of endogenous and exogenous substances.

Albumin Versus Crystalloid

Garrett: In what way is albumin different or better than crystalloid? Normal saline would also be a plasma expander, but they’re different.

Mauro: As far as liver diseases are concerned, we do not have a crystalloid plasma expander that reduces mortality in specific settings as albumin does. Moreover, the transvascular escape rate of albumin is lower compared with saline, which immediately moves to the interstitial fluid from the vascular compartment, not to mention the potential problems we have with synthetic plasma expanders. There are concerns about dextrans and starch and their side effects on coagulation, potentially resulting in bleeding. This is particularly important in patients with severe liver disease and in patients with impaired renal function. These are some of the reasons why albumin is better than other plasma expanders.
VICENTE ARROYO: More research on albumin in hepatology should be done as we do not know the ideal dosage. It may differ from patient to patient. The aim of albumin treatment should be improvement in circulatory function. We are convinced that plasma renin activity or plasma renin concentration is the best marker of circulatory function in cirrhosis.

GARRETT: *If albumin were a drug, we might know more about optimal dosage, distribution and so forth. We’re in a transition period in how we think about albumin.*

GARY HAYNES: There is a need to educate healthcare providers about albumin because its use has changed over time and is still controversial. Even some of the literature for volume resuscitation isn’t up-to-date because we have better ways of assessing intravascular volume. Many older studies indicate dosage to meet some endpoint, such as central venous pressure, which no longer is regarded as the best way to assess intravascular volume. But people still doubt the value of albumin in conditions such as resuscitation. Some have been driven by economics to question the benefits of albumin, leading them to emphasize the use of crystalloids in resuscitation. The effectiveness and role of crystalloid has yet to be demonstrated versus copious evidence that albumin does more than just maintain colloid oncotic pressure.

GREG MARTIN: There are people who doubt albumin’s value in almost every condition. Cost is also an issue. I suspect that cost varies quite a bit between hospitals and universities and between countries, based in part on insurance and reimbursement as well as how albumin is manufactured and distributed.

GARRETT: *To what extent are those differences based on the lack of information?*

GREG: One of the biggest limitations for albumin use probably is lack of education. We base education on what we do know, and guide people in the right direction. Sometimes you can’t be definitive and that’s one of the challenges. Two other things strike me. One is the question of when to use albumin. I wouldn’t advocate using albumin as the only fluid or volume expander. We use it to complement other interventions. So, knowing how much of one versus another to use is important, but we don’t always think about it when we use albumin for a specific disease or condition. So for sepsis, do you use albumin to support circulation at the beginning, or after you’ve used crystalloid and are not getting the desired effect? Timing and volume are dose-related. Another consideration that has come up in the past 10 years is the lack of understanding around the clinical relevance of the biological properties of albumin.

GARRETT: *Greg mentioned access to and availability of albumin. Can someone comment further on that?*

ALBERT FARRUGIA: Albumin is more expensive than many of the alternatives. We’re looking at cost-effectiveness of albumin in a particular situation highlighted by
some recent clinical developments. After the Delaney meta-analysis comparing albumin and hydroxyethyl starch (HES) in sepsis came out, it occurred to me that it would be interesting to test this and to look at cost-effectiveness in sepsis, specifically in the intensive care unit (ICU) environment, against competing therapies or different generations of starches. We’re frustrated about the starch situation because every time a range of starch products exhibits adverse events, the companies modify the molecule. They do not withdraw the previous generation from the market and neither do the regulators. Albumin is a natural molecule and it’s not amenable to the same kind of modification as the synthetic colloids. We are using a cost-effectiveness model comparing starch to albumin in the ICU sepsis environment, and the results are going to be very interesting. We can show, using evidence-based parameters, that albumin will be cost-effective in this environment. The whole concept of drug versus volume expander requires a paradigm shift. Evidence requires randomized clinical trials, of certain sizes, linked to the endpoints.

**Volume and Resuscitation**

**Luciano Gattinoni**: The real issue is determining the amount of albumin required to reach the resuscitation goal. With starch, the trade-off is seen in terms of disordered coagulation and kidney function. With crystalloids, the trade-off is in the tremendous amount of fluid compared with colloids. This can lead to edema or fluid accumulation in the patient with negative consequences. With albumin, there are no such complications. In addition, there is the possibility of a strong physiological effect of nitrous oxide (NO) modulation with albumin. We have cost and benefit considerations, and ultimately the scale tips in favor of the benefit to the patient. Good medicine means good economy, not vice versa. When physicians are pressed to save money, the potential for complications and adverse events increases. Albumin has a solid physiological basis. In the results from some of the current trials, I don’t expect to see a 10 percent difference in mortality. But since there is a greater difference in morbidity, an increase in complications, I don’t doubt the value of albumin.

**Garrett**: It seems we need evidence to be able to practice that way.

**Luciano**: That’s correct. So, based on the available information, what are the complications associated with albumin? Acid-base, volume and oxygen diffusion abnormalities are typical complications with crystalloids. With starch there are the problems we mentioned. Unfortunately, statistics are no longer a tool, but rather, the be-all and end-all, as we saw in the Cochrane Study report. The results of a meta-analysis show albumin is the better option.

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ALBERT: I agree that the first Cochrane meta-analysis was poor. I also agree with you about not being able to demonstrate a 10 percent difference in mortality in a single trial because you’d have to have a huge number of subjects. Hence, we need to rely on statistically based meta-analyses, and they are telling us that the difference could be even greater than 10 percent.

GEORG HENKEL: Regarding the point you made about good medicine and good economics, isn’t pharmacy cost and side effects that are disparate across our societies and insurance systems part of the issue? As Albert suggests, if we don’t have patient outcome evidence, it would be a good idea to show evidence of relative differences in terms of cost.

LUCIANO: From an American point of view, the problem is one of choice.

ALBERT: The cost of drugs in the Western healthcare system is generally between 10 and 20 percent of overall costs. But if we input the types of analyses being used by healthcare technology assessment agencies to cut costs, the fact that albumin has minimal adverse reactions, while the alternative, starch, has renal problems, bleeding problems and so on, makes cost assessment an entirely different matter.

GARRETT: First of all, do no harm.

GARY: A central problem in the US is that we don’t know the cost of treating a disease. When it comes to albumin, we’ve selected unsatisfactory endpoints in the past. When you do meta-analyses, it all rolls out to a global outcome, such as whether the patient lives or dies. But if you pick better clinically important endpoints, such as the length of time the patient is on a ventilator in the ICU or their length of stay, you will have a more convincing argument. Much of the literature favors what’s least expensive without looking at these outcomes. Much of the resuscitation literature presents a grossly oversimplified view of the problem.

Inadequate Comparator Studies Can Yield Misleading Results

GARRETT: If you have poor studies to start with, you’re going to have poor results of the meta-analysis.

MAURO: This was the case with the 1998 Cochrane Report. It should never have been published. Many of these studies weren’t even done with albumin. They were done with precursor intermediates. More recent studies support our position on albumin, including the meta-analysis of Delaney and the two meta-analyses that were published in 2009 in relation to the renal effects on HES.

LUCIANO: At that point were the Boldt data already discredited?

MAURO: No. But since you mention Professor Boldt, I’ll tell you an interesting thing about those meta-analyses. When you take the studies of Dr. Boldt out of the
Delaney\(^2\), Cranhren\(^4\) or Zakarinski\(^5\) meta-analyses for HES effects on renal function, it has an amazing effect on the odds ratio. Delaney already reports an 18 percent improvement in mortality rate with albumin across the whole meta-analysis, but when you extract the Boldt studies, the improvement in mortality rate goes up to 26 percent. And when you remove the Boldt studies, including the retracted studies from those meta-analyses on renal complications, HES looks very bad.

**GREG:** When someone chooses a drug in the US, the cost comes out of the budget of the pharmacy, where cost isn’t reflected in their perception of the patient’s care. So pharmacies tend to be very isolated and try to reduce their budget. In the US, this is often done by restricting formularies—you can use only certain drugs for certain conditions and under certain circumstances—and they don’t see the full picture. What Luciano posed is true, that if you did say the drugs were equal in cost, whether it’s zero dollars or $100, people would choose albumin. So, yes, cost is a factor but it also helps you understand how people can and do believe that albumin has a potential beneficial effect.

**GARRETT:** Do physicians actually make use decisions based on perceived economic differences, or do they focus only on patient need?

**GREG:** I think they do occasionally make use decisions based on perceived economic differences. People sometimes rationalize, at least in critical care, that it’s a good use of my dollars to do everything I can to try and save this patient’s life. In another situation, they may not be as aggressive if a patient who is 95 was brought to the ICU from a nursing home and is terminal or close to terminal. I don’t think that’s common, but I do think it occurs.

**GARY:** Hospital administrators put a price tag on every treatment modality, educating their physician staffs so that they sometimes probably do make a choice based on cost.

**MAURO:** We recognize how hospital administration decisions can affect albumin usage. But the other issue is misuse. We saw this several years ago in our hospital. The consumption of albumin was progressively increasing along with costs.

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etc. After implementation of these guidelines, albumin consumption and the relative costs dropped by 13 percent and remained constant over six or seven years.

**Garrett:** Did they also look at the outcomes?

**Mauro:** Unfortunately not.

**Garrett:** My thought was that sometimes it might be acceptable to increase the costs if the outcomes improve.

**Mauro:** I agree. But in following definitive guidelines, people are in a position to say whether there are potential misuses and positive results.

**Albumin in Liver Disease**

**Garrett:** Let's move onto the topical areas that are the focus of this Dialogue—liver disease, sepsis, and surgery or cardiac surgery. There are certain procedures or areas around liver disease where there's good evidence that albumin can be beneficial. Let's begin there.

**Vicente:** We do not have many doubts about the benefit of using albumin in patients with liver disease. The hepatology community has performed many studies on this topic, so we know the indications and mechanisms of action of albumin in cirrhosis. The first clear indication for albumin use in cirrhosis is paracentesis. Following therapeutic paracentesis, patients frequently develop a circulatory dysfunction 24 to 48 hours after the mobilization of the ascitic fluid. It is characterized by arterial vasodilation, and a decrease in arterial pressure and an increase in cardiac output. There's also a marked increase in plasma rennin activity and plasma noradrenaline concentration. If you give albumin after paracentesis, these rarely occur.

Circulatory dysfunction induced by paracentesis is clinically important for several reasons. There are studies demonstrating that it is associated with impairment of renal function and dilutional hyponatremia in approximately 10 to 20 percent of patients. On the other hand, patients who develop circulatory dysfunction do not live as long as patients with a similar degree of liver impairment and who do not develop circulatory dysfunction. Mauro's recently published meta-analysis\(^4\) shows that preventing paracentesis-induced circulatory dysfunction with albumin is associated with the probability of longer survival.

**Garrett:** Just to clarify, people with cirrhosis who have severe ascites probably need more than one episode of paracentesis.

**Vicente:** This is usually the rule. Ascites is due to renal sodium retention and with paracentesis, the only feature you produce is the removal of the ascites fluid and nothing else. Normally, cirrhotic patients with tense ascites are treated by paracentesis. Once the ascitic fluid has been removed, diuretics are given to prevent re-accumulation.

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of ascitic fluid. In 90 percent of patients you can prevent early accumulation of ascites. However, in many patients the response to diuretics decreases either due to the natural course of the disease or to treatments that decrease the natriuretic potency of diuretics, such as non-steroidal anti-inflammatory drugs, so patients develop new episodes of ascites. The European Association for the Study of the Liver and the American Association for the Study of Liver Diseases agree that the treatment of choice for a patient with tense ascites is paracentesis with albumin followed by diuretics. Refractory ascites is the ascites that does not respond to diuretics. Patients with refractory ascites accumulate ascitic fluid very rapidly and need to be treated with paracentesis every two weeks.

**Albumin as a Drug and Dosing Issues**

**GARRETT:** *Have there been studies using other volume expanders?*

**VICENTE:** Yes, but polygeline, dextran 40 and dextran 70 are not as effective as albumin in patients with cirrhosis. The prevalence of circulatory dysfunction in cirrhotics treated with paracentesis and albumin is approximately 10 percent. In patients treated with synthetic plasma expanders, circulatory dysfunction occurs in 35 percent, and in patients not receiving any plasma expander it is 70 percent. Because the concentration with albumin in ascitic fluid is approximately eight grams per liter of ascitic fluid, the replacement albumin dose given to patients treated by paracentesis is eight grams per liter of ascitic fluid removed.

Due to the effectiveness of albumin in preventing paracentesis-induced circulatory dysfunction (PCD), it was not surprising to presume that albumin could also be effective in preventing circulatory dysfunction induced by infections in cirrhosis. This was the rationale of our study exploring the potential benefit of albumin in the prevention of circulatory dysfunction in cirrhotic patients with spontaneous bacterial peritonitis (SBP). Prevention of circulatory dysfunction in patients with SBP was also considered an important issue because there was evidence that these patients do not die as a consequence of liver failure or bacterial infection. Rather, they die as a consequence of impaired circulatory function with severe vasoconstriction and reduced organ perfusion. In the brain, it may contribute to encephalopathy. The homeostatic activation of the sympathetic nervous system causes intestinal hypomotility, resultant bacterial overgrowth and migration of bacteria and bacterial products from the intestinal lumen to the systemic circulation. This causes bacterial infections and/or systemic inflammatory response syndrome. Vasoconstriction in the hepatic circulation leads to hepatic hypoperfusion and impairment of hepatic function. Finally, renal vasoconstriction causes hepatorenal syndrome.

**GARRETT:** *There are many variables we would have to control.*

**VICENTE:** Yes, but parameters estimating the degree of renal impairment are excellent markers of circulatory dysfunction. Diuretic requirements estimate the degree of sodium retention. The presence of dilutional hyponatremia correlates with the degree of impairment in free water excretion. Finally, serum creatinine estimates glomerular filtration rate. These parameters correlate with the degree of impairment in circulatory function and are excellent predictors of mortality.

**Decline in Hospital Mortality Rate**

**VICENTE:** Of course, every important therapeutic measure should be based on randomized comparative studies. However, the complexity of the studies depends on the mortality rates at various time points. For example, because early mortality associated with circulatory dysfunction induced by paracentesis is low, we would need a trial of a large number of patients, followed up on a long-term basis, to demonstrate an effect on survival. For this reason, the beneficial effect of albumin in patients treated by paracentesis is based on meta-analyses or on studies assessing prevalence of renal complications in patients developing circulatory dysfunction. However in SBP, which is associated with high early mortality rate, we were able to demonstrate the beneficial effect of albumin on survival in a randomized controlled trial with only 100 patients. In this study albumin reduced hospital mortality rate by 60 percent.

**LUCIANO:** It seems to me albumin has nothing to do with volume. After paracentesis you decreased intra-abdominal pressure, but you also decreased the amount of albumin circulating in the body. Let’s consider whether the albumin works as an oxygen scavenger and NO modulator. The immediate effect is positive because the obstruction has been relieved. Then you focus on the basic disease. There is less control of NO production and circulatory failure occurs, which has nothing to do with volume. This is where albumin functions as a drug.

**VICENTE:** You are correct. Albumin is not only a plasma expander. Several years ago we performed a study on the effect of albumin in systemic hemodynamics in patients with SBP. We measured cardiopulmonary pressures, cardiac output and peripheral vascular disease at the time of infection diagnosis. Then patients were randomized in two groups. One group received starch and the other received albumin at 1.5 grams per kilogram body weight at infection diagnosis and 1 gram per kilogram body weight.

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three days later. Resolution of the infection occurred in approximately 95 percent in both groups. In patients receiving albumin, no significant change in effective blood volume, as estimated by the plasma renin activity, was observed. In contrast, in patients receiving starch, a significant increase in renin occurred, indicating impaired circulatory function. In patients receiving albumin, a significant increase in systemic vascular resistance was also observed, suggesting that an albumin-induced arterial vasoconstriction was probably the mechanism preventing the circulatory dysfunction associated with SBP. This effect is clearly unrelated to the plasma volume expansion effect of albumin.

LUCIANO: Using albumin to treat liver disease illustrates why it should be considered a drug.

VICENTE: Yes, albumin has many biological effects other than those related to oncotic pressure. The albumin molecule is a transporter of catabolic substances from the site of production to the site of excretion, and of metabolic substances from the site of synthesis or absorption to the different organs in the body. Furthermore, albumin binds reactive oxygen species and has powerful antioxidant activity. Recent studies in cirrhosis have shown the molecular structure of circulating albumin is greatly modified by accumulating endogenous substances saturating albumin-binding sites, as a consequence of the liver failure. Many of the functions of albumin (binding capacity, transport function, antioxidant activity) are significantly impaired in cirrhosis.

We are now exploring plasma exchange with albumin in cirrhosis patients with hepatorenal syndrome and severe liver failure. The investigation is to assess whether the substitution of the altered albumin with an exogenous non-altered molecule improves some of the problems associated with liver failure. A recent randomized controlled trial done in Denmark has also explored this hypothesis in patients with fulminant hepatic failure. They used fresh frozen plasma instead of albumin and they found a 30 percent reduction in mortality in the group of patients treated by total plasma exchange.

MAURO: In the debate about the use of albumin after paracentesis, a major issue was the focus that is placed on a laboratory event, a 50 percent increase in plasma renin activity six days after paracentesis. I think that a meta-analysis that we recently performed addresses these issues. Albumin reduced the odds of post-paracentesis circulatory dysfunction (PPCD) by 61 percent, versus alternative treatments, either plasma expanders or vasoconstrictors. What is relatively new is the finding that it reduced hyponatremia by 42 percent. Moreover, for the first time, we were also able to show that albumin reduced mortality by 36 percent. This is statistically significant.

All guidelines say we should give albumin after paracentesis. The European guidelines recommend we give eight grams of albumin per liter of ascites fluid removed after large-volume paracentesis. The American guidelines suggest six to eight grams per liter
for large-volume paracentesis be considered. The European guideline also says that with paracentesis of less than five liters, it should be taken into account that the incidence of PPCD is lower. Nevertheless, albumin is preferable to other plasma expanders given the concern about the use of dextran or starch. The American guidelines say that albumin infusion may not be necessary following paracentesis of less than five liters. So, there is a different attitude toward albumin administration to prevent PPCD, and differing degrees of willingness to use albumin between Europe and the US.

GARRETT: You would think they read the same journals and see the same data.

MAURO: We should also discuss the non-oncotic properties of albumin. When ischemia-modified albumin was measured in patients with cirrhosis, there was a definite increase in concentration. Thus, by administering albumin to patients with advanced cirrhosis, we are treating patients unable to increase their albumin production under critically ill conditions and whose circulating albumin may have already lost its function. In fact, its ligands are likely occupied by endotoxin, cytokines, etc., circulating levels of which are strikingly elevated. We have recently started with experiments trying to modify albumin ex vivo. We are using a rat model of cirrhosis and endotoxemia to learn what happens when albumin that has been completely reduced at the cis-34 residue is administered. This is a first attempt to use modified albumin as a drug. If the result will be positive, we will try to translate this knowledge into clinical practice.

GARRETT: This sounds like drug development or optimization. You mentioned the guidelines for large-volume paracentesis. What about the guidelines for albumin use with SBP or hepatorenal syndrome?

VICENTE: In Europe we treat hepatorenal syndrome by the administration of terlipressin, an analog of vasopressin with a preferential vasoconstrictor effect on the splanchnic circulation, and intravenous albumin. Terlipressin improves circulatory and renal function by reducing the severe splanchnic arterial vasodilatation present in cirrhosis. The mechanism by which albumin contributes to improved circulatory function is probably multi-factorial including plasma volume expansion, arterial vasoconstriction and an increase in cardiac contractility. Using the two products together is important since the use of either alone reverses only 10 percent of hepatorenal syndrome cases, whereas the combination can reverse 60 percent of cases of hepatorenal syndrome. Terlipressin is not yet approved for clinical use in the US.

MAURO: The first line of treatment (in Europe) is terlipressin plus albumin.

GARY: Based on your experience in Europe, can less albumin be given or is there a dose response relationship?

VICENTE: There are few trials assessing whether albumin is effective using doses lower than those currently accepted, i.e., eight per liter of ascitic fluid removed in
paracentesis and 1.5 grams per kilogram body weight at infection diagnosis, and 1 gram per kilogram body weight three days later in patients with SBP. We really do not know whether doses should differ from patient to patient according to the degree of impairment in circulatory function.

**Luciano:** Do you think that the possible mechanisms of albumin in preventing circulatory dysfunction and of albumin plus terlipressin are completely different?

**Vicente:** Probably not. Type 1-HRS is frequently precipitated by bacterial infections or transudation of bacterial products from the intestinal lumen to the systemic circulation leading to a generalized inflammatory reaction and release of endogenous vasodilators. Therefore, it is likely that the various beneficial effects of albumin in preventing circulatory dysfunction and hepatorenal syndrome in SBP, and in treating Type 1 hepatorenal syndrome are related to a common pathogenetic pathway.

**Albumin in Sepsis**

**Garrett:** We touched on albumin in sepsis when we talked about SBP. What are the similarities and differences between the pathophysiology as it pertains to albumin in SBP, and in chronic liver disease versus sepsis.

**Greg:** From a basic perspective, two or three things stand out. Both conditions are marked by something infectious and both are generally marked by an activation of the inflammatory system. I think both of those contribute to an abnormality in permeability, which is a hallmark of sepsis. An abnormal permeability of the endothelium and often the epithelium leads to abnormalities of fluid balance and fluid handling and a need for fluid administration. Those are the major similarities from a high-level perspective. I’m sure there are a lot of mechanistic similarities as well, but those are the major ones from the larger, more clinical perspective.

**Luciano:** I think compartmentalization makes a difference. Sepsis is a completely diffuse, overall inflammatory state. With spontaneous peritonitis it seems that the compartmentalization construct still works better. The intensity property is the same and the capacity property is completely different. We have the usual things— inflammatory response, permeability and so forth—probably at different intervals. We should be careful how we refer to sepsis because it is a big umbrella that covers a number of areas.

**Greg:** It’s an important distinction to make because sepsis is such a large catchment of conditions. If patients are infected and hospitalized with SBP, they almost certainly have sepsis. But we often think just in terms of people who have severe sepsis or septic shock. That’s where I think Luciano is differentiating the compartmentalization—that SBP could cause severe sepsis if organ dysfunction occurs, or it could cause septic shock if the patient has vasodilatory shock.
VICENTE: If you don’t treat patients very early, you may only have a 50 percent success rate.

GARY: One approach to this question is to consider it in terms of the patient with end stage liver disease, the cirrhotic patient versus the septic or the peritonitis patient, because I think you’re right, there’s much overlap there. There’s also hemodynamic similarity: low blood pressure, low systemic vascular resistance and relative intravascular volume depletion. We always question cardiac contractility in sepsis or bacterial peritonitis. In liver disease it’s less clear. There are some patients who have preserved cardiac function and some who do not, and it’s difficult for us to assess the status of these patients preoperatively. We perform a transplant and find everything goes well with the surgery. Some of them do well afterwards but others struggle. Vascular resistance starts to increase when you don’t have that cirrhotic liver any more. Only then do we find their left ventricle can’t push against this new, higher vascular resistance. It’s difficult to sort out which patients have reversible contractility defects.

GREG: While it’s a completely tangential topic, the fact that albumin has been shown to alter myocardyocyte contractility is an interesting related subject. In sepsis you see the same cardiomyopathies and we generally consider them fully reversible. But they’re not always.

Fluid Resuscitation: Timing and Choice

GARRETT: Is there convincing evidence that the choice of resuscitation fluid can impact the outcome of sepsis?

GREG: There’s convincing evidence that the timing of fluid makes a difference. In trauma it’s obviously the golden hour, or in stroke or myocardial infarction it’s the golden hours. I think we now realize that’s true in sepsis as well. Time correlates to organ dysfunction and can increase mortality, so there clearly is a time for fluid resuscitation that’s important. The goals of fluid resuscitation are also relevant. Goal-directed therapy is hopefully specific to a sepsis-related outcome, as reflected in the Surviving Sepsis Campaign guidelines, with central venous pressure being one, but also central venous oxygen saturation and other targets of oxygen delivery and consumption. A remaining question is whether the type of fluid makes a difference. In addition to the data summarized here, there are data from different studies yet to be considered, such as the SAFE Study10, which strongly suggests the type of fluid makes a difference, as well as Luciano’s ALBIOS Study11 and the PRECISE Study12.

**LUCIANO:** These studies taken together make sense because the population is the same. We have to remember the difference in mortality. For example, in the use of streptokinase in myocardial infarction, the absolute improvement in mortality was only around one percent. In patients requiring intensive care, there is not usually one disease. The statistician said we would never get a p value of 0.05 because a 10 percent difference in mortality would be huge. So, demonstrating a two to three percent difference would be a great success.

**MAURO:** I think that these huge studies, apart from their absolute result, should be used to identify patient populations that might benefit more from a specific approach.

**ALBERT:** What about the issue of how fluids are administered in terms of timing? I’m thinking about the fluid resuscitation study by Kathryn Maitland\(^1\). I don’t know if you can classify the patient population as close to being septic. But it is a bit counter to the previous studies, as they gave a large bolus infusion of either albumin or crystalloid. How might that influence things?

**Maitland Study**

**GREG:** As you said, the Maitland Study involved bolus infusion, which is not the way we’d normally monitor and decide how much fluid to give. The patient population is also significantly different. Whether it really is all the same pathophysiology is hard to know. The thing that stands out is that the SAFE Study was well done; they did early resuscitation, starting in the pre-hospital setting, to get fluid administered early. One major factor that prevents the study from being definitive is that the fluid was not given to patients only with septic shock, but also to patients later determined to have had only sepsis or severe sepsis.

**GEOG:** It’s a mixture.

**GREG:** Yes. I’ve always thought that the greatest effect with sepsis resuscitation would probably be in those patients who present in shock and need fluid resuscitation. They’re treated following the Surviving Sepsis Campaign guidelines or the early goal-directed therapy algorithms. I think that’s partially the signal you see from the SAFE Study. There were quite a few patients in the study, but the analysis was diluted by all the patients who weren’t really in shock. The general concept of early fluid resuscitation is still important. I think it would be unfair to take the Maitland Study and extrapolate those findings, to think early fluid resuscitation might actually have an adverse effect in sepsis, when you have so much other evidence that says early targeted fluid resuscitation and other things are beneficial.

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**GARRETT:** Are these recommendations codified in any kind of guidelines?

**GREG:** There are the Surviving Sepsis Campaign Guidelines that were launched nine years ago by a worldwide committee. The express goal was to help people recognize sepsis and reduce mortality, realizing that there wasn’t any one intervention but rather a bunch of things that might help, even to some extent just providing better supportive care. Early goal-directed therapy, timely antibiotic administration and tight glucose control were all codified into one set of guidelines.

**LUCIANO:** Before commencing a large trial, it’s important to conduct more physiological studies to better understand what you want to accomplish.

**GARRETT:** These studies are important, but it’s also important to know whether we’re making a difference.

**LUCIANO:** My view is that you first have to understand the mechanism. Outcome is a consequence of this. Apply the mechanism and you usually have a better outcome and treatment. Any time two groups participate in a one-to-one comparison study, the control group shows decreased mortality.

**GEORG:** It’s a higher level of science to do a trial with a very good hypothesis. But in sepsis there are hundreds of hypotheses; you have so many mediator systems that are complementary. If you consider all the drugs that can and have been used with totally different rationales in clinical trials in sepsis with totally different effects, it would be difficult to say which would then be the most proven hypothesis.

**LUCIANO:** Again, this is the reason we still need a lot of physiological studies.

**GEORG:** Agreed. The Surviving Sepsis Campaign Guidelines on fluid resuscitation say the data are contradictory and nothing can be recommended. Therefore, we just say some form of fluid needs to be given. My question is whether the data that has come from Simon Finfer and others in the past six years is enough to make a change?

**LUCIANO:** No, but I’m sure the next time the guidelines are revised we will have the results of this trial and the kind of fluid recommended. I don’t know how many interventions we did in intensive care that were as successful as the Surviving Sepsis Campaign, without any randomized trial. Time is important. You will see this with albumin. We learned that when you start with acidosis, every minute in those first hours counts if your treatment is to make a difference.

**VICENTE:** In the trials that they are going over in sepsis, is time included in the results?

**LUCIANO:** Yes, we did a double randomization where we equalized the number of patients. One-third of subjects were randomized within the first six hours and two-thirds between seven and twenty-four hours.
**KEY ISSUES DIALOGUE: ALBUMIN IN CLINICAL FLUID MANAGEMENT**

**VICENTE:** There are studies trying to show how to prevent the development of septic shock through treatments other than antibiotics. In addition to antibiotics, do you take other measures to prevent the development of septic shock such as giving plasma volume expansion or vasoconstrictors?

**LUCIANO:** We took the classical approach which is to administer antibiotics as early as possible. In this study we gave fluids that target the liver. The only difference is the target in one group of patients was reached only with crystalloids. In the other group it’s crystalloids plus albumin, 60 grams.

**VICENTE:** How did you select 60 grams?

**LUCIANO:** We had a previous study that used 60 grams of albumin.

**GARRETT:** *Does it make a difference if you use the five percent solution or the 25 percent solution?*

**LUCIANO:** In Italy we use 20 percent solution.

**GARRETT:** *Is that because you want to give the protein but not so much fluid?*

**LUCIANO:** We are looking at the target, not the amount of fluid. So we give fluid with the amount of albumin necessary to reach a given hemodynamic target.

**GARRETT:** *But it has oncotic pressure so the fluid gets brought into the vascular space anyway?*

**LUCIANO:** It is difficult to say because with the effects of permeability, it is unclear where the fluids go.

**SAFE Study**

**GREG:** The SAFE Study used an iso-oncotic solution, so I don’t think you would always use 20 percent or always use 5 percent. For fluid resuscitation, I tend to use more of an iso-oncotic fluid to avoid dehydrating the intra-cellular space. I’m trying to expand the plasma volume. So that’s why you might use crystalloids with albumin. For instance, in our acute respiratory distress syndrome studies¹⁴,¹⁵ (ARDS), we used the hyper-oncotic 20 or 25 percent albumin in general because our goal was to try to mobilize fluid out of the interstitial space.

**LUCIANO:** This will be a new hyper-oncotic fluid, because it should be 12 liters of five percent albumin. We give less, so it’s about 10 to 15 percent real concentration. But I expect we will see a different concentration at the end of the study.

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**GREG:** The ongoing studies are complementary?

**LUCIANO:** Yes, and we’re very curious to see the oxygen radicals and the other functions of albumin that we can test. Even if we only test in one-third of the patients, it would be fantastic.

**GREG:** One difference that stands out between five percent albumin and 20 or 25 percent albumin is the free radical scavenging and the anti-oxidant effects. Maybe the hyper-oncotic albumin really is necessary, which wasn’t the case in the SAFE Study. You question how much is biological and drug effect, versus how much is plasma volume expansion.

**ALBERT:** In relation to the crystalloid component, apart from comparing to a crystalloid arm, you’re also delivering albumin suspended in a crystalloid solution. It’s been suggested to us that we should be suspending five percent albumin in balanced salt rather than in normal saline. Do you have any comments about that?

**GREG:** My guess would be that the albumin outweighs the small amount of crystalloid that you’re getting in addition to that. That doesn’t mean that the albumin effect might not be even better if you used a balanced salt solution. I think there is a growing body of evidence that normal saline has adverse effects. If that’s true, then mixing albumin in something that doesn’t have those adverse effects might be beneficial.

**GARY:** Why was hetastarch mixed in saline in the first place? It could have been put in a balanced salt solution. Saline has been around for a long time as a resuscitation fluid, but the amount of sodium chloride in every albumin bottle isn’t that much, and it is similar to the extra-cellular fluid composition. Giving a certain amount of sodium chloride can cause acidosis. But it’s not likely with such small amounts. I think they’re just sticking with a position that they’ve had to defend over the years because of some weak studies that go back to the use of dextran.

**LUCIANO:** What do you mean by a balanced solution?

**GARY:** There’s calcium and other electrolytes in addition to sodium chloride.

**LUCIANO:** We studied the problem in three papers in vitro, ex vivo and now in animal liver and the rules are clear. If a solution with a strong ion difference is used, after the lactate has been metabolized it is greater than the baseline bicarbonate that you start with, and you go towards alkalosis. If it’s lower, you go to acidosis. With a value for bicarb of 29, you go to alkalosis if you started out with a normal pH. With saline this works in vitro, ex vivo and in animals. We have a big chloride load in animals, but it is not the chloride that gives acidosis. The protons come from the carbon dioxide partial pressure that results if you give distilled water. With the same amount, you get exactly the same degree of acidosis. It’s not the charge of chloride.
However, when you give chloride and sodium, you have far more fluid retention in animals, very likely because of osmolarity which is greater than in Ringer’s lactate solution. The rule governing acid base equilibrium is clear. But to give a lot of sodium chloride in patients with sepsis and possibly with kidney problems is not advisable. For the single patient it is far better to give Ringer’s lactate, which is more balanced.

### Albumin in Cardiac Surgery

**Garrett:** *Our last topic today is cardiac surgery, specifically, the use of albumin to prime the pump when you use bypass.*

**Luciano:** How much is the priming volume now in cardiac surgery for an adult with model lungs?

**Gary:** The priming volume varies. It’s about 1,500 mL in most instances.

**Greg:** There are published data comparing albumin versus starches, and there is less bleeding with albumin. The large analysis of Medicare patients suggests a lower mortality for those who received albumin as part of the pump priming than those who did not. This is another condition that’s been difficult to study because the mortality is so low, particularly in the modern era when we’re seeing more off-pump bypass procedures. Mortality is under one percent for pump bypass surgeries in large-volume centers. So the ability to achieve differences in mortality is difficult. Whether you can achieve an intermediate outcome such as time on the ventilator and so forth is another consideration.

**Luciano:** Blood loss and coagulation disturbances are other outcomes.

**Greg:** I haven’t seen a lot of conflicting data that says that albumin is inferior with regard to blood loss. In general it’s superior to starches, but whether it’s superior to crystalloids may be more debatable.

**George:** Regarding starches, it’s similar to what we discussed earlier about how much benefit you need to show so that the higher cost is accepted. And this might be different in the various health economic systems.

**Greg:** Part of the cost equation has to include transfusion and other interventions. These cardiac surgical patients are on a pathway where they have their surgery, they go to the recovery unit, they go to the ICU and in general they’re extubated in the recovery unit. If they fall off that pathway, that’s a huge issue. And if they actually bleed and require transfusion, then that’s an issue, too. Blood is not inexpensive.

**Garrett:** *What’s commonly used and what percentage of different fluid is used to prime the pump?*

**Gary:** There are a couple variables. One is the cardiopulmonary bypass circuit. There are a number of manufacturers and they have different coatings on the internal...
surfaces. They’re also heparinized to decrease thrombocytopeny associated with cardiopulmonary bypass. But there are a number of pump prime solutions that are used. Colloid has been relied on for years as a way of preventing the sudden drop in colloid oncotic pressure when the primed pump is connected to the patient, diluting the patient’s entire blood volume. There is no standard. This emerged as an issue in the 1980s when we became more cost-conscious and were looking for an alternative to a colloid. A number of small studies showed a favorable outcome using hetastarch as opposed to albumin. But the results weren’t reliable. One variable, when you get into these kinds of surgery studies, is variation in surgery, surgeons and surgical technique.

**Advantages of Albumin**

**GARRETT:** *Are there good data to demonstrate the advantages of albumin?*

**GARY:** There are a couple of very good references showing a beneficial effect from adding albumin to the pump prime, such as a smaller decrease in platelet counts and less platelet injury. Now if you extend some of these experimental models out for many hours, it doesn’t have any clinical relevance, but certainly in zero to three or four hours of cardiopulmonary bypass, there’s clear evidence that albumin is beneficial. Now albumin is the only thing that’s recommended. Hetastarch should no longer be used, but I’ll bet there are hospitals in the US that still use it for pump priming.

**GARRETT:** *Has it ever been demonstrated that when albumin is used, fewer units of platelets are used?*

**GARY:** There are several articles that demonstrate less bleeding afterwards. The approach has been to consider what’s done intra-operatively and measure post-operative bleeding or post-operative outcome. As Greg mentioned, if a patient bleeds a lot and has to be taken back to the operating room for surgical exploration, it’s very expensive and increases the risk to the patient. Often with surgical re-exploration, there’s no surgical sign of bleeding. But chest tube output can be measured. It’s one of the better indicators, because trying to estimate blood loss during such a case is pointless. Again, a decrease has been demonstrated in blood loss, in the need for re-operation and in the use of blood products.

**GARRETT:** *Has this information been effectively disseminated, and is there an educational opportunity?*

**GEORG:** There’s always the discussion of the importance of the molecular weight of starches in terms of side-effects. There have been many small studies, but overall I suppose that’s a matter of debate.

**GREG:** This is one area where there is reasonable evidence to suggest that albumin has less bleeding risk, and to some extent is less expensive in the long run, because of the bleeding and transfusion costs. I’m not sure whether there are any guidelines
about pump priming and peri-operative fluid management in these patients. Does the American Society of Anesthesiology deal with this, or does a cardiac society deal with it?

**GARY:** There are resuscitation guidelines, but there is variation in practice. Fluid administration is titrated to the individual needs of the patient based on physiologic targets such as cardiac output, blood pressure, and left- and right-sided heart filling pressures.

**GREG:** Hopefully the Surviving Sepsis Campaign Guidelines might slowly move people towards a standard that’s less variable.

**GARY:** Guidelines in that area could be very useful. As for fluid administration, it’s variable because of many different patient factors. But in general, fluid is given post-bypass to optimize cardiac output and, of course, you can have a combination of bleeding problems. Again, it would be hard to get guidelines because there is little standardization.

**Variations in Albumin**

**LUCIANO:** No one knows the exact physical and chemical characteristics of the albumin that is administered. After the preparation of albumin, what is left? Is this kind of data available?

**ALBERT:** All the albumin preparations that are used in trials are not necessarily the same. People don’t measure these things because they are not linked and this is a question of indication.

**GEORG:** There are common denominators. There is a pharmacopeia for albumin, which is different in Europe than in the US, and to get your lot released by the regulators you have to comply with certain standards. Parameters are simply release criteria. There is, of course, the situation where certain parameters you mentioned are not measured because they are not part of the pharmacopeia. This relates to the fact that in Europe the main indication is volume replacement and many other indications are seen as sub-indications of volume replacement. We heard today that independent of the level or volume, albumin has additional properties and the fact that you are doing these studies is expanding the frontiers.

**LUCIANO:** Going back to the matter of balanced solution, the net charge of albumin for each millimole of albumin is 22 millimoles of negative charges. But what if there were 50 instead of 22 millimoles of negative charge? At the outset, the pK should be around 6.8. If it’s 6.6 or 7.0, it dramatically changes the complexion of the effect. The tier group, which is fundamental for scavengers, is still present or has destroyed the mask. Independent of the regulatory approval and oversight system, if you want to position albumin as a drug it’s important to be fully informed on the subject.
**GEORG:** If I compare that to molecular weight distribution of molecules of the starches, I think here we have the main difference. Albumin has one molecular weight. If you look at starches, you have 50 percent with molecular weight of 130,000, and you have a whole spread of molecular weight particles.

**Albumin Versus Crystalloid**

**LUCIANO:** Starch is dead. You’re really making a comparison with crystalloid. It’s a question of the market and so on, but from the medical point of view, to use starch is wrong. It’s not good medicine. That means it’s also bad economics.

**GEORG:** You’re saying that as an intensivist. But there are many people in the area of anesthesia, at least in Europe, who have a different perspective.

**GARY:** I didn’t appreciate that there were variations in how albumin is produced. One thing to keep in mind is that there are other factors. For instance, if the patient is acidotic or alkalotic it’s going to affect the physicochemical properties of these molecules, and they affect all the physicochemical properties of everything else. So you really need clinical studies that are tightly controlled, especially to look for these small differences in outcome. It’s particularly interesting to consider patients who go through cardiac surgery may receive a number of different drugs before they get to the operating room. When they arrive we induce general anesthesia with other drugs, give them industrial size doses of heparin, induce profound hypothermia and then try to look at some outcome study. A lot of this literature has focused on the effect of the cardiopulmonary bypass pump, the plastic circuit itself, and two or three hours worth of perfusion. When you remove that from the equation by studying patients who had cardiac bypass graft performed off-pump, we find that albumin achieves a better outcome. We have fewer physiologic derangements in those kinds of surgical procedures than we do in the on-pump procedures.

**GARRETT:** Are there any closing thoughts on albumin?

**MAURO:** There are so many aspects of cirrhosis and sepsis that have common features. The fact that we can discuss our respective problems and find so many common points of interest is unusual. It does not happen often that hepatologists and intensivists have the opportunity to sit down and exchange ideas and experiences. Even in patients with cirrhosis and no proven infection, possibly many of the hemodynamic and humoral features are actually due to bacterial by-products. We should talk to each other more often and share results.

**GARY:** An issue that we considered today is the correct amount of albumin to give. Because we follow these goal-directives, by aiming for a certain central venous pressure or cardiac output, how do you determine the correct amount? If you’re giving albumin for its oncotic properties, how do you measure that, especially in a fast-paced environment like an intensive care unit or operating room?
**Greg:** It’s a subtle difference over starches in the sense that you can actually measure albumin. Most hospitals don’t even have the ability to measure colloid osmotic pressure anymore in the US.

**Luciano:** Thirty years ago it was measured.

**Georg:** Why isn’t it measured anymore?

**Greg:** People don’t use it.

**Luciano:** Recently the question came up about the amount of oxygen that is carried by one gram of hemoglobin. The answers were 1.34, 1.32, 1.39. How is this possible? Then try to explain the molecular weight of a unit of hemoglobin. One number doesn’t exist. When the hematologist researches molecular weight, the answer depends on the kind of hemoglobin being examined. There are usually different weights—1.38, 1.39, 1.34, 1.32—it’s impossible to have just one number.

**Gary:** Is part of the answer having a standard source of albumin? There is the potential for a recombinant albumin, which may make some sense, but is not practical.

**Mauro:** It’s more expensive. The problem with recombinant albumin is that the molecule doesn’t assume the final configuration, which is essential for binding. You are able to assemble one amino acid after the other but then the problem is to assess the general shape of the molecule.

**Gary:** It sounds like we’re always going to have this issue of some variation in the product.

**Garrett:** I think regulators allow for the differences in manufacturing from company to company because if they restrict it too much, there are companies that won’t be able to do it. On that note, we’ve come to the end of our time together. I want to thank you all for taking part in our examination of albumin and its use in clinical fluid management. Because of our varied disciplines, we’ve achieved a cross-pollination of ideas and information that is truly unique.

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The views and opinions expressed in this Key Issues Dialogue are those of the participants and do not necessarily reflect the official policy or position of CSL Behring.
About the Participants

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Vicente Arroyo’s main research interest is cardiocirculatory and renal failure, ascites, and acute bacterial infection in cirrhosis. He is the Director of the Esther Koplowitz Biomedical Research Center and Chairman of the Chronic Liver Failure European Consortium.

Vicente has been Director of the Digestive and Metabolic Diseases Department at the Hospital Clinic of Barcelona and Chairman of the Department of Medicine. His published work consists of original articles (274), editorial and review articles (154), books (22) and chapters of books (164), and he has delivered 346 invited lectures.

Vicente is a member of the Spanish, European, American and International Associations for the Study of the Liver.

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Senior Director Medical Affairs NA—CSL Behring

Garrett E. Bergman leads the scientific and medical support to commercial operations for the North American business unit of the company. An academic pediatric hematologist for 15 years, Garrett has since worked in large pharmaceutical companies and small, biotech startups for more than 20 years, heading the Clinical Research & Development, Regulatory Affairs, and Medical Affairs divisions in several companies. He has led the successful development of several plasma-derived biologics and drugs.

**Mauro Bernardi, M.D.**
Professor of Internal Medicine, Department of Clinical Medicine, University of Bologna

Mauro Bernardi is noted for his research in cirrhosis and related complications, hepatocellular carcinoma, chronic viral hepatitis and liver transplantation. He teaches post-graduate courses in internal medicine, gastroenterology and infectious diseases in the University of Bologna medical school, and he is former director of the Department of Internal Medicine, Cardioangiology and Hepatology.

Mauro is a past member of the Scientific Committee of the Italian Association for the Study of the Liver, and of the governing Board of the European Association for the Study of the Liver (EASL). Currently, he is treasurer of EASL and vice-chairman of EASL-Chronic Liver Failure (CLIF) Consortium. He is a member of the editorial boards of *Digestive and Liver Disease* and *Gut*, and a former member of the *Journal of Hepatology* editorial board.

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Gary was previously Chief Resident, Anesthesia and continues to hold the position of Professor of Anesthesia at the Medical University of South Carolina. He has lectured widely on a range of clinical topics. These include various aspects of albumin, such as in perioperative management of cardiac surgical patients, and safety and efficacy as a resuscitative therapy in the ICU.

Gary’s work has been published in Academic Medicine, Southern Medical Journal, American Journal of Anesthesiology, Journal of Gynecologic Surgery and the European Journal of Anesthesiology, among other publications.

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Luciano Gattinoni’s research interests include parenteral nutrition, metabolic therapy, acid-base equilibrium, organization of intensive care units, cost-benefit analysis and prognostic indices. A recipient of the Society of Critical Care Medicine’s Lifetime Achievement Award, he has added to the understanding of lung function, including changes following acute injury and during critical illness.

Luciano is the author or coauthor of more than 200 research articles and reviews, and he has led numerous cooperative investigative trials, some of which have been published in the British Medical Journal, the Journal of the American Medical Association and The New England Journal of Medicine. He is currently editor-in-chief of Minerva Anestesiologica and serves on the editorial and advisory boards of several journals.

Albert is a Fellow of the British Institute of Biomedical Sciences. He has published over 120 papers, invited reviews and book chapters, and he has edited two books. His international appointments have included the WHO Global Blood Safety Collaboration, the European Pharmacopoeia Commission, the US Pharmacopoeia and the Council of Europe Committee Quality Assurance in Blood Transfusion.

Luciano Gattinoni, M.D.
About the Participants

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Georg Henkel has over 20 years of experience at CSL Behring and predecessor companies in marketing and sales of plasma-derived therapies. Georg is based in Marburg, Germany, and he is responsible for the Critical Care Product Portfolio of CSL Behring.

He previously worked in national as well as international functions and been responsible for regional and global launches. Georg also worked as a post-doctoral fellow at Rutgers University.

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Greg Martin specializes in pulmonary and critical care medicine and he conducts clinical research with a particular focus on sepsis and acute lung injury. He directs the research program in Emory’s Center for Critical Care, chairs the Division ICU Standardization Committee, and serves as Director of the Medical and Coronary Intensive Care Units and Chair of the ICU Operations Committee at Grady Memorial Hospital. He also directs the Clinical Core of the Emory Alcohol and Lung Biology Center.

Greg has written extensively about the causes and consequences of severe sepsis and lung injury, including contributions to Medscape/WebMD and Emory’s institutional publication *Sound Science*.

**About CSL Behring**

CSL Behring is a global biotherapeutics leader. Committed to improving the quality of life for people with rare and serious diseases, the company manufactures a range of plasma-derived and recombinant therapies for the treatment of coagulation disorders, primary immune deficiencies, hereditary angioedema and inherited respiratory disease. The company’s products are also used in cardiac surgery, organ transplantation, burn treatment and to prevent hemolytic disease in the newborn. CSL Behring is a subsidiary of CSL Limited. For more information, visit www.csblehring.com.