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Sepsis in Critical Care

Professor Djillali Annane is Professor of Medicine and Dean of the Medical School at the University of Versailles, Paris. He is the director of the general intensive care unit at Raymond Poincaré, Assistance Publique Hôpitaux de Paris (APHP). The unit is the largest ICU at the University Hospital of Paris, and has 36 beds, half of them high intensity beds, and half step-down units. Prof. Annane is also Director of the Laboratory Neuroendocrine Response to Sepsis, University of Versailles and Director of the Centre for Clinical Research and Technological Innovation, INSERM, Paris.

Your Team Recently Reported on the Recombinant Human Activated Protein C for Adults with Septic Shock. Why was the Trial Suspended?

Our main research area is sepsis: understanding the mechanism and investigating treatments. In 2007 we started a national multicentre randomised trial that was fully independent from the pharmaceutical industry, to evaluate the benefit- to-risk ratio of activated protein C in patients with septic shock. This was a double-blind randomised trial that was funded by the French Ministry of Health. We used commercialised activated protein C, which the pharmacists at the hospital masked for the purpose of the trial. In October 2011 when Eli Lilly and Company decided to withdraw Xigris ® from the market and the drug was no longer available, Lilly declined to provide us with the treatment and its placebo. Hence, there was no way to continue the trial, and it was terminated after 411 patients were included.

What Were the Findings Before that Point?

First, we have investigated a population with severe septic shock. The observed mortality at 90 days in placebo-treated patients was about 45%, which is almost twice as high as the mortality observed in the PROWESS-SHOCK trial. We enrolled septic shock patients in whom physicians would be happy to have an adjuvant therapy to improve the chance of survival.

The second important finding is the lack of evidence of any benefit on survival or on any other outcome from activated protein C. Taking this finding together with the findings from the PROWESS-SHOCK, ADDRESS, and RESOLVE trials, one may conclude that activated protein C failed to prove any benefit in children and adults with sepsis, regardless of disease severity.

Does this Resolve the Question, or are there Still Unanswered Questions?

As far as activated protein C for sepsis is concerned, I do not believe there are still unanswered issues. Definitely the drug was investigated in children and adults, and in adults it was investigated in a broad range of disease severity, and, in these different cases with different baseline risk of death, activated protein C repeatedly did not show any benefit on any outcome, including survival, need and duration of vasopressor therapy, mechanical ventilation or renal replacement therapy, or length of stay in the ICU or at hospital.

Recently a Number of Big Fluid Trials have been Conducted. Where do We Stand Today with Fluid Resuscitation in Critically Ill Patients and What Future Studies are Required in this Area?

First, I think the important take home message is that fluid therapy is by far the commonest treatment in the intensive care unit, and there are thousands of patients being treated daily with one or more types of fluid. Basically there are two families of fluid - crystalloids and colloids. Crystalloids offer the theoretical advantages of being cheaper, less allergic, and less toxic than colloids. Colloids have the theoretical advantage of faster recovery, of haemodynamic stability. What did we learn from Crystalloid Versus Hydroxyethyl Starch Trials (CHEST) and Hydroxyethyl Starch 130/0.42 versus Ringer's Acetate in Severe Sepsis (6S) trials? First, and this is important to interpret these data, these trials compared one molecule with another – CHEST compared Voluven® to normal saline, and 6S compared Tetraspan 6%® to Ringer acetate (Sterofundin ISO®). It is important to bear in mind that these trials did not compare all crystalloids with all colloids. Hence, they can only answer that there was no evidence that most recent starch solutions are superior to normal saline or Ringer's Acetate. These findings do not mean that there are no differences between the two families of fluids, crystalloids and colloids. However, consistent findings within these trials included an increased risk of renal injury with starches. Thus, in practice one should refrain from using these starch solutions as a first line treatment, and one should prefer normal saline or Ringer's Acetate. This is basically the recommendation in the update of the Surviving Sepsis Campaign guidelines.

In this Respect, can You Please give Us a Short Overview of the Most Significant Findings of the CRYSTAL Study?*

I would like to highlight that these findings are as yet unpublished. We presented the main findings at the 2013 ISICEM meeting in Brussels. This pragmatic trial compared a strategy based on crystalloids only to a strategy based on colloids only for the whole ICU stay. This multinational study was conducted in France, Belgium, North Africa and Canada, and included close to 3,000 patients. The trial was designed to show the superiority of crystalloids over colloids based on a systematic review of the information available at this time. Unexpectedly, at 90 days, a strategy based on crystalloids was associated with more deaths than a strategy based on colloids. These data have not yet been published in a peer-reviewed journal, and should be taken with caution until publication.

Do RCTs Such as these Provide Clear Evidence for the Intensivist? Are They Still the Gold Standard?

I think that RCTs are of course still the gold standard. Nevertheless, in the very near future an increased interest in data derived from big ICU databases, regulatory agencies such as FDA and the European Medicines Agency (EMEA), the NHS, the Ministry of Health in France, and many other public or private institutions, are giving more and more attention to and credit to big databases, as a potential new tool for investigating treatment effects.

This Interview will Form Part of Our Edition on Organ Donation. What do You Think Poses the Biggest Challenge for the Intensivist When it Comes to Organ Donation?

Organ donation is really important, given that organs are still missing for transplant recipients. Many people are still dying while waiting for an organ to be available. The ICU is a location where people die, where brain dead patients are admitted, and therefore is a location where potential organ donors could be found. However, the management of organ donors cannot be done in all ICUs. I think that the management of these patients should be limited to a few ICUs with trained staff. In different regions of a country, there should be one or two ICUs that are responsible for dealing with organ donors. Indeed, undoubtedly the way these patients are managed is very important for the quality of organs to be transplanted and subsequently a key factor for successful transplantation. In addition, this organisation in a country may also shorten the time from identification of an organ donor and the time an organ is transplanted to a recipient. It may help improve the efficiency of organ donation.

What do You See as ‘Hot Topics’ in Intensive Care Medicine Currently?

Firstly, we are entering a new era in the way we are doing clinical research in the ICU. In the past few years we already have shifted from moderately sized RCTs to large RCTs, and this will continue in the future. Networks that have been developed in several countries are increasingly interacting together in such a way that in a couple of years most ICU trials will be conducted through internationally linked, national networks. This will definitely present a big jump in clinical research in the ICU, allowing fast conduct of large, mostly academic-driven RCTs.

The second hot topic is the emergence in ICU practice of molecular biology. That will progressively shift patients’ management from ICU based treatments to personalised ICU patient- based treatments. This will be true for sepsis, ARDS, trauma, haemorrhage and for a number of critical illnesses.

What Research are You Working on Now?

We are continuing trying to understand the mechanisms of sepsis and to develop treatments for sepsis. Currently we are working on the modulation of the adrenergic system as a therapeutic approach to sepsis. Briefly, we think that while septic patients require alpha agonists like norepinephrine for a haemodynamic purpose, and may require beta 2-agonists for metabolic purpose, they also may require beta 1-antagonists for immune purpose. We are looking at ways to fine tune the adrenergic system during sepsis. We are doing a set of experiments in small and large animals, and, in 2013, we may start a phase II trial in patients with sepsis in collaboration with 5 to 6 ICUs across France. If these phase II trials are up to expectation, we will move to a phase III trial in 2014.

What do You See as the Most Significant Breakthroughs in Intensive Care Medicine Recently?

That’s a tough question! If one looks at recent published RCTs done in the ICU one will see that most of them resulted in negative trials, and sometimes even the experimental treatment harmed patients. For example, the 6S trial found higher mortality rates with a starch solution in patients with septic shock.

A very recent trial showed a dramatic improvement in survival in ARDS patients by using the prone position. I think that this is likely one of the most important advances that will change practices.

Intensive care is a young specialty. Intensivists and trialists in intensive care are still learning how to do clinical trials. I believe we will see more positive trials, while getting better knowledge both in the understanding of diseases and in the methodology of clinical trials. We will include molecular tools to select the patients and to monitor treatments. We will have more skilled investigator sites relying on strong, internationally linked clinical networks.

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