APROCCHSS trial ‘encouraging’ for hydrocortisone plus fludrocortisone in sepsis

Long-awaited results of the APROCCHSS (the activated protein C and corticosteroids for human septic shock) trial on the combined use of hydrocortisone and fludrocortisone for adults with sepsis are ‘encouraging’ and ‘practice changing’, according to the principal investigator, who will introduce the trial later today.

“For decades, clinicians caring for these patients have been desperate for an effective treatment and it is most likely that starting this weekend, they will have a different perspective on how to manage patients with sepsis,” remarked Djillali Annane, (Hôpital Raymond Poincaré, and Dean of the Medical School, University of Versailles, Paris, France), who led the study.

“I think these results will change practice for those clinicians who are not currently using steroids, which is about half of them. Among those who do use steroids, only one out of around 25 are using fludrocortisone in combination with hydrocortisone,” he added, emphasizing the importance of the combination.

The trial aimed to investigate the combination of hydrocortisone and fludrocortisone in adult patients with sepsis and hypothesized that corticosteroids would reduce all-cause mortality at 90 days in adults with septic shock.

No widely accepted management strategy for sepsis

Sepsis is a leading cause of death worldwide and it affects thousands of patients every day, placing a huge burden on health systems globally. "Apart from anti-infective drugs, and the correction of respiratory..." Continued on page 2
Corticosteroids in critical illness

APROCCHSS trial ‘encouraging’

Continued from page 1 and cardiovascular disorders, there is no specific treatment for sepsis.” In 2008, when the study began, the international guidelines suggested that physicians may consider using these drugs [investigation-alpha activated (DAA) or corticosteroids] in the more severe cases of sepsis.

Initially, the trial included the recombinant form of human activated protein C, DAA, but this product was later (2011) withdrawn from market after demonstrating failure to reach adequate efficacy in other, manufacturer-led, trials. At this point the APROCCHSS trial was stopped due to lack of product, but restarted a few months later (2012) without the DAA component. During this time, data were kept blinded, and permission was granted by French regulatory and ethical authorities to continue the trial comparing only corticosteroids and placebo.

Researchers have spent decades looking for an effective treatment, including corticosteroids, which have been available since the 1960s, explained Professor Annane. “However, there is not a single corticosteroid, or a single way or dose to use these drugs effectively. In this trial, we wanted to understand more about how to use corticosteroids in patients with sepsis.”

At the start of the study, it featured a 2x2 factorial design with patients assigned to placebo of hydrocortisone, placebo of fludrocortisone and placebo of activated protein C; hydrocortisone plus fludrocortisone and a placebo of activated protein C; hydrocortisone plus fludrocortisone and placebo of activated protein C; or hydrocortisone plus fludrocortisone plus activated protein C. Once the DAA was no longer available, two arms of the study were terminated leaving one arm comprised of placebo corticosteroids, and one arm comprised of corticosteroids (hydrocortisone and fludrocortisone combined).

Hydrocortisone was administered as 50 mg intravenous bolus every six hours, and a 50 µg tablet of fludrocortisone was given via the nasogastric tube once daily in the morning.

A total of 1,241 adult patients were recruited from 35 centers across France, and patients’ consent was obtained from a closest legal relative, if necessary, and confirmed by the patient upon recovery. Vital data that are publicly available in France were used for mortality data.

Participants had proven septic shock and had failed to improve after six hours of appropriate management, noted Professor Annane, briefly describing the characteristics of patients included. “There is a group of patients that show improvement with anti-infective drugs, and hemodynamic respiratory resuscitation and these patients do not require any other form of treatment. These patients were not our target in this study.”

All-cause mortality at 90-days was the primary endpoint, and follow-up duration was six months. Statistical analysis was planned in the intent-to-treat (ITT) population after all participants completed follow-up according to the initial 2x2 factorial design regardless of later developments.

Although delegates will have to wait for the detailed results to be published first, Professor Annane remarked that the improvement in 90-day survival in the corticosteroid arm versus the placebo “was very encouraging”. “Fifteen years ago, I came to this meeting to present results of a trial that looked at hydrocortisone plus fludrocortisone against placebo in adults with septic shock. The results were positive and led to changes in clinical practice, however, this particular study was criticized for a small sample size and high mortality rate in the placebo arm.”

Explaining the motivations for the recent trial, Professor Annane explained that in the early 2000s, there were many differences in patient management in the ICU. For example, there was no lung protective ventilation, so the question remained, “How effective were these drugs?” He concluded that now, 15 years later and with modern management of ICU patients, this trial has provided some exciting answers.
microbiome that lives on their skin,” he said. “It’s not just that they are sweeter!”

He went on, suggesting that microbes may even play a bigger role in our lives, possibly defining the microbiome in our gut, and even guiding who we mate with.

Indeed, this ‘big role’ is even clearer when considering that while there are around 30-trillion human cells in our bodies, there are more than 38-trillion microbial cells. Similarly, 20,000 human genes are matched with 2-20-million microbial genes. “So we are 99% bacterial,” emphasized Professor Wischmeyer.

As he underlined, we are now finally able to answer the big questions about our microbes (and thus ourselves) by harnessing technology to identify them. For instance, the Human Microbiome Project, which, as Professor Wischmeyer described, has spent $173-million characterizing the bacterial makeup of 250 people.

“They took the terabytes of this data and they mapped them out,” he said, adding that it is important to note that the microbes that live in different parts of your body can be very different from each other. “The microbes that live in your stool are very different, luckily perhaps, than the ones that live in your mouth.”

He continued: “But where do our microbes come from? They come from birth of course. Until recently, all of us were born by vaginal delivery, and thus for the first two years of life, we have all reflected (in our stools and everywhere else) our mother’s vaginal secretions. But now with the advent of C-sections, babies born that way will resemble their mother’s skin for the first two years.”

Commenting on what impact this may have for the babies themselves, Professor Wischmeyer noted that babies born by C-section are known to have babies born that way will resemble their mother’s skin for the first two years. “When we lose gut barrier function, we lose our microbes in our bodies.

Diving into the reciprocal relationship that microbes have in critical illness, Professor Wischmeyer positioned that vasopressors, sedatives, opiates, mechanical ventilation and of course antibiotics could all have destructive effects on the ‘good’ microbes in our bodies.

To combat this, probiotic and symbiotic therapies could be therapeutically powerful, he reasoned, turning to data from his own meta-analysis of 30 RCTs (2972 patients), showing that probiotics and symbiotics could cause a significant reduction in infections and VAP, with the sickest patients benefiting the most.

“And we know that stool transplants are very successful at curing C. difficile,” he added.

Focused on effective strategies and trials that could lead to clinical treatments and clear benefits for the ICU patient, Professor Wischmeyer described the ICU Microbiome Project, which set out to use a microbiome ‘bar-code’ to predict factors such as risk of mortality, infection, antibiotic use and so on. The first publication came in 2016, looking at 115 ICU patients across four centers in the US and Canada. Results were compared against the American Gut project – featuring 1,242 healthy individuals.

“Our hypothesis in the ICU was this: a healthy gut is a diverse gut,” said Professor Wischmeyer, “and loss of diversity will be associated with a poor outcome.”

Commenting on the results, he reported that critical illness led to a clear shift to ‘proteobacteria’ (pathogens), away from normal healthy gut flora. What’s more, they found that in the ICU, the fecal, oral and skin microbiome all begin to look the same. “When we lose gut barrier function, we lose diversity,” he said.

In terms of some specific bacterial depletions they found in the study, Professor Wischmeyer highlighted faecalibacterium prausnitzii – a vital ‘bug’ in our gut to combat inflammatory bowel disease – noting its “massive depletion”. And on the other side of the coin, staphylococcus aureus and proteus OTU (enterobacteriaceae) were also enriched in ICU patients.

“We saw a great crash in diversity, with as much as 95% of the human fecal screen being made up of one organism,” he said, noting that healthy patients would be expected to have a maximum of 25% overall makeup from the most-abundant organism.

Summarizing the main results for the audience, he said: “We found some associations of ICU death and klebsiella appearance on the skin, and some other bacteria as well. Bacteremia seemed associated with oral mycoplasma overdose … and ARDS also showed some specific organisms appearing in our stools, or in our mouths.

“The role of antibiotics: The question the reviewers gave us was ‘Is it the surgery/critical illness causing the problem, or is it the antibiotics causing the problem?’ We created an Antibiotic Pressure Score, using a published Lancet score, and we found that oral samples do appear to associate with the pressure of antibiotics, but the fecal [microbiome] does not … so dysbiosis of the fecal microbiome in the ICU is due to more than antibiotic use.”

He continued, reiterating that diversity played a role as well, with longer-staying ICU patients having less diversity. “So again the magnitude of ‘change’ in diversity seemed associated with mortality, but we still have a great deal of data to analyze.”

Concluding, he said. “Perhaps we can change the microbial world that we live in, by giving back. Perhaps stool transplants, perhaps ‘poop’ pills, perhaps probiotics to ‘re-sod the lawn’ for our patients, thus giving back the 100-trillion friends that they need, restoring balance to their gut.”

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Could the liver be the master switch in the HPA stress response?

In a session that frames the impact of corticosteroids in critical illness, held this morning in the 100 Hall, Greet Van den Berghe (KU Leuven University, Leuven, Belgium) will take to the stage to introduce her work examining the hypothalamic-pituitary-adrenal (HPA)-axis stress response, with particular focus on the intricacies of plasma cortisol concentrations, arguing that the liver could be a potential driving force in the adrenal insufficiency seen in patients in the ICU.

Professor Van den Berghe spoke to ISICEM News to introduce her work, and offer a glimpse of some of the key points she will be addressing later this morning.

What are the dangers of prolonged hyper/hypo-cortisolemia in the critically ill?

The hormone cortisol is an essential component of the ‘fight or flight’ response to illness and trauma. Neuronal networks signal the hypothalamus to release corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary to secrete adrenocorticotropic hormone (ACTH), which drives cortisol synthesis and secretion from the adrenal cortex. Cortisol can exert feedback inhibition at the pituitary and the hypothalamic level to regulate its cortisol synthesis and secretion from the adrenal cortex. Cortisol can exert feedback inhibition at the pituitary and the hypothalamic level to regulate its own release.

Cortisol brings about vital endocrine and metabolic effects such as fostering energy provision, dampening inflammation and ensuring hemodynamic homeostasis via fluid retention and sensitization to catecholamines. Hence, an increased cortisol availability during the stress of critical illness is essential for survival. When levels of circulating cortisol are too low, it can result in hypoglycemia, hypotension, shock and death. Too-high levels can also exert negative effects such as hypercatabolism, hyperglycemia, muscle weakness, delirium and immune suppression, which predispose to morbidity that could hamper recovery.

**“Low rather than high plasma ACTH concentrations have been reported in critically ill patients in the presence of elevated cortisol, suggesting ACTH-independent regulators.”**

Greet Van den Berghe

Is recognition of adrenal dysfunction difficult? Surely it is hard to assess history, with lab tests falling short?

Yes, recognition during critical illness is indeed difficult. Low, or insufficiently high, plasma cortisol concentrations could point to a failing stress response that contributes to poor outcome. Because plasma cortisol in such patients is still higher than in healthy individuals, this condition has been labeled ‘relative adrenal insufficiency’.

Currently, experts advise to diagnose adrenal failure by a subnormal cortisol response to a short ACTH (Synacthen) stimulation test, irrespective of the baseline plasma cortisol. However, we have shown that a low cortisol response to Synacthen may also reflect the negative feedback inhibition exerted by high circulating cortisol that is not broken down. Hence, there is ongoing controversy on how to diagnose adrenal failure during critical illness, and consequently, there is also no consensus on treatment of this condition. Other issues are the assays used in clinical practice for measuring plasma cortisol, that are in fact quite inaccurate.

‘Traditional’ thinking was that hypercortisolemia is caused by elevated ACTH. But in fact ACTH is actually lower than normal in critical illness?

Indeed, traditionally, hypercortisolemia during critical illness has been attributed to increased ACTH release. However, low rather than high plasma ACTH concentrations have been reported in critically ill patients in the presence of elevated cortisol, suggesting ACTH-independent regulators. We have recently documented that cortisol production during critical illness is in fact only modestly increased as compared with normal health, with hypercortisolemia to a much larger extent brought about via reduced cortisol breakdown.

With time, a low ACTH can cause adrenal atrophy, so this response may be beneficial for the acute stress response (it is highly economic to elevate cortisol levels via a lack of breakdown rather than constant production, which costs a lot of energy) but in the long-term this may cause adrenal failure.

A more likely explanation that you have proposed is a suppressed cortisol clearance, and a ‘feedback inhibition’? Can you comment more on this? What’s behind the reduced cortisol breakdown in critical illness?

The reduced cortisol breakdown is due to suppressed expression/activity of cortisol-metabolizing enzymes in liver and the kidney. One possible reason for this may be elevated levels of bile acids, that have shown to be able to suppress expression and activity of the cortisol metabolizing enzymes in liver. The liver plays a key role in metabolism and in the stress response. And bile acids are produced in the liver.

Circulating levels of bile acids typically rise in response to critical illness. We have shown that elevated bile acids are indeed linked with the suppressed expression and activity of the cortisol metabolizing enzymes in the liver. However, more research is needed to investigate such a causal role.

What does this mean for treatment? Could ‘traditional’ hydrocortisone administration be pitched too high?

The ‘stress doses’ of hydrocortisone that are typically given to patients in the ICU are 200 mg/day, which equals 6- to 10-fold the normal substitution dose of hydrocortisone. As the breakdown of cortisol is suppressed, such doses will increase circulating cortisol in critically ill patients to much higher levels than would be the case when one injects these doses during normal health, and this holds risks of harm as explained above.

Similarly, is it fair to say that we need more studies to understand/identify which patients have an insufficient HPA-axis response? Absolutely correct. We need more research to understand/identify these patients, and how they should be treated.

What’s an important wrap-up message here?

Be careful with using so-called ‘stress doses’ of hydrocortisone – or therapeutic doses of steroids for other reasons for that matter – as these doses may be far too high! Clinicians should take into account the several-fold longer half-lives of these steroids during critical illness. Doses that are fine outside of the ICU may be too high during critical illness. Finally, we should do more research to understand/identify which patients have an insufficient HPA-axis response and how this should be treated. The prolonged critically ill patient may be particularly at risk of adrenal atrophy.
Improving pediatric care in East Africa

Kathryn Maitland is a professor of pediatric tropical infectious diseases (Imperial College London, UK) who has spent the last 17 years based in Kenya leading a research group focused on emergency care-based research.

This morning, as part of the ‘International Perspectives’ session, Professor Maitland will discuss some of her latest work, illustrating the importance of addressing system-wide issues in patient management as a means of improving high-quality evidence generation in the resource-limited setting. Professor Maitland spoke to ISICEM News ahead of the session to explain how these investigations came into being, and what her current research involves.

Describing what led her to initiating the FEAST (Fluid Expansion As Supportive Therapy) trial, the landmark study of the effects of early fluid resuscitation in children with severe infection, Professor Maitland began: “We had conducted early safety study incorporating physiological responses in children, in particular, severe malaria, which demonstrated an expected positive correction of shock. We needed to study this because at the time most children were not getting fluid resuscitation, including children with suspected sepsis. For severe malaria there weren’t any recommendations for children with shock. As severe malaria and sepsis cannot be differentiated at the point of admission (emergency room) we therefore went on to do a pragmatic Phase II trial including both children with severe malaria and sepsis...that is, ‘the undifferentiated critically ill patient’, where you have to make a decision urgently.”

The results, she said, surprised all involved, with significantly increased 48-hour mortality in critically ill children with impaired perfusion found consistently across all study centers and subgroups.

FEAST, explained Professor Maitland, gave her and colleagues confidence in conducting other emergency care trials where the World Health Organization (WHO) recommendations are based on low quality of evidence.

Indeed, the ongoing TRACT (Transfusion and treatment of severe anemia in African children) trial examines the WHO recommendation of restrictive transfusion guidelines in Africa, intended to protect the limited supply of blood relative to demand.

“You have to make a decision urgently.”

The problem is that this recommendation has never been tested,” noted Professor Maitland. “Doctors don’t believe them and they just go ahead and transfuse; blood is diverted away to someone who might not benefit from it, from those who might need it who arrive critically ill with profound anemia and die within hours of coming in the door.”

TRACT’s recruitment of its 4,000-strong cohort is expected to complete in a couple of months’ time, with patients being followed up for 180 days.

“What we have realized from the literature is that transfusion might affect immediate outcome, but there may also be downstream adverse effects,” said Professor Maitland of the study’s rationale.

“And the blood that we are transfusing won’t have had the same storage conditions as it would in Europe. It is not as rigorous. It is also whole blood, and therefore not leukocyte-reduced. That might have downstream effects. We do know that mortality in the six months following hospital admission is higher than that of children in hospital. So there is a downstream mortality. Also, there are a huge number of children...”

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Improving pediatric care in East Africa

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that relapse and get readmitted."

The TRACT trial tests two hypotheses: first, that a liberal rather than a conservative blood transfusion policy will decrease mortality (cumulative to four weeks) in children admitted to hospital with severe anemia (hemoglobin (Hb)<6g/dl); second, that a supplementary multi-vitamin mineral treatment, or cotrimoxazole prophylaxis, or both, for three months post-discharge will reduce rates of readmission, severe anemia relapse, re-transfusion or death (cumulative to six months) compared to current recommendations (iron and folate). Findings from TRACT are expected to emerge in 2018.1

A few weeks ago, Professor Maitland’s team also initiated the COAST (randomized controlled trial of high flow AIRVO2) versus low flow oxygen (usual delivery) versus control (no immediate oxygen) in African children with putative severe pneumonia) trial, which explores ways of identifying which children would benefit from oxygen delivery, and which form of delivery would be the most beneficial. In a similar vein to TRACT, the cost of oxygen treatment renders supply erratic in some regions of Africa. “Decisions about giving oxygen are relatively random,” suggested Professor Maitland.

“If you follow WHO guidelines, which have very non-specific definitions for pneumonia, potentially anywhere between one-third and two-thirds of patients could be on oxygen. We have done a pilot study, and have used FEAST and other studies to inform the design.”

The background to all of this work, stressed Professor Maitland, describes a lack of ICU care in general in all but the wealthiest cities on the continent. “For the burden of pneumonia, this is never going to be sufficient.”

The difficulty with which funding was generated to carry out the FEAST trial highlights the relatively neglected nature of this research area, where lack of precedence may reduce the chance of funding allocation. “A lot of people had said, this is a trial you cannot do. of course, that was like a red rag to a bull for me! “We have tried to put a really strong case that, actually in many children’s final illness, many will access life from pneumococcal disease; yet, actually working out who needs fluids, oxygen or blood transfusion, and how much to give, could be really cost effective. Changing the arguments, and being persuasive, is important.”

A systems approach in such studies is important, too, explained Professor Maitland. Involving community members improves trust, buy-in, and adherence. “Certainly, some of the feedback that we got around our communications strategies was that people used to be frightened to come into the hospital, but all of a sudden things have changed with the FEAST team putting triage in place. At the end of the day, with a systems-based approach you are able to see benefits of the delivery of a really high-quality trial, and better overall standard for the hospital – which we did and communities appreciated this.”

“FEAST also gave funders confidence that this could be done. Ironically, the same issue came up with the review of the transfusion trial – the reviewers considered that there was a very slim chance the team would be able to run this trial, with the blood transfusion services disjointed from the hospital labs that process and allocate the blood. But once again we took a systems approach, involving those in the transfusion services in the trial.”

“Yes, we have had massive challenges, but in just over two and a half years we have recruited nearly 4,000 patients. No one was confident that we would be able to do that. And we have found out the most extraordinary things, because we are so rigorous about recording absolutely everything, including the pack details, and re-cross-matching the whole thing – there were lots of systematic errors, which we were able to feed back.”

Professor Maitland speaks during ‘International Perspectives’, taking place this morning in 400 Hall from 10.50.

References

“In just over two and a half years we have nearly recruited 4,000 patients … And we have found out the most extraordinary things, because we are so rigorous about recording absolutely everything.”

Kathryn Maitland
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Manager: V De Vlaeminck
Email: vvenisc@intensive.org
Dept of Intensive Care, Erasme University Hospital
Route de Lennik, 808, 1070 Brussels, Belgium
Phone: 32 2 555 32 15/3631
Email: sympicus@intensive.org

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Alcohol and critical illness

Exploring the burden of alcohol in critical illness

“A alcohol use disorders are responsible for 3.3 million deaths/year worldwide.”
Craig M Coopersmith

“A like any other major co-morbidity (cancer, diabetes, COPD), [alcohol use disorder] is associated with significant challenges and worse outcomes.”
Craig M Coopersmith

plenary lecture that focused on the detrimental – and some-what overlooked – effects of alcohol in critical illness was presented yesterday by Craig M Coopersmith, Professor of Surgery and Director of Surgical/Transplant ICU at Emory University and Emory University Hospital, Atlanta, Georgia, USA. Framing the overall burden of alcohol use disorders in healthcare, he stressed that around 20-40% of patients admitted to the hospital will have alcohol use disorders, peak- ing at around a third when looking at the ICU specifically. “Alcohol use disorders are responsible for 3.3 million deaths/year worldwide (5.9% of all global deaths),” he told ISICEM News ahead of his lecture. “On average, every person in the world aged 15 years or older drinks 6.2 liters of pure alcohol a year. However, since less than half drink alcohol at all (38.3%), those that drink consume on average 17 liters of pure alcohol annually.”

The sweeping reach of alcohol-related harm stretches far, but looking at ICU-centric illnesses specifically, Professor Coopersmith began with ARDS, noting that alcohol use disorders are an independent risk factor. Evidentially, he relayed a study of 351 patients in the medical/surgical ICU, versus 22% with alcohol in critical illness, versus 22% without alcohol history. “In patients with septic shock, the risk of ARDS is 70% in patients with alcohol abuse – more than double of those without alcohol abuse,” he said.

Professor Coopersmith went on to note that alcoholics also have independent risk factors for development of both typical and atypical pneumo- nias. Furthermore, alcohol alters the oropharyngeal flora to be colonized by more gram-negative organisms, and inebriation blunts upper airway reflexes and renders people more sus- ceptible to aspiration. What’s more, alcohol increases epithelial permeability and protein leak, impairing fluid clearance through alterations in tight junction proteins.

Alcohol also has a profound effect on delirium, as Professor Coopersmith described. “Delirium is more common in the ICU in patients with alcohol use compared to those without. With- drawal syndromes, including delirium tremens [DTs], occur in 20% of alcoholics who stop drinking acutely, and DTs have a mortality of 5-15%.”

What’s more, he noted that alcohol is associated with greater morbid- ity and resource utilization in the ICU, with no clear treatment protocol. While fixed doses of benzodiazepines are often used, they can cause exces- sive sedation, and respiratory depres- sion delirium. However, improved outcomes outside of the ICU can be had by harnessing symptom-triggered dosing which, as Professor Cooper- smith described, are most commonly administered using Clinical Institute Withdrawal Assessment for Alcohol (CIWA) guidelines. “But they cannot be performed in up to 45% of hospitalized patients,” he said, adding that some data have pointed towards a symptom triggered benzodiazepine protocol using SAS and CIA as being better than fixed doses. He also mentioned dexmedetomidine as being an effective adjunct for decreasing delirium, and better than benzodiazepines alone.

A big topic of discussion is the role of alcohol use disorders in sepsis, as Professor Coopersmith described. “The increased mortality in alcohol/ sepsis appears to dominantly be the result of altered gut integrity and immune defects,” he said. “Although much work needs to be done, altera- tions occur in gut apoptosis, villus length, proliferation and permeability. Furthermore, alterations occur in cytokine production by CD4+ T cells, with delayed kinetics of CD69 on these cells, prolonged expression of CD69 on memory CD4+ T cells and decreased o-glycosylation of CD43 on memory CD4+ T cells.”

Importantly, Professor Coop- ersmith noted that recognition of alcohol use disorder in hospitalized patients only occurs in around 25% of cases. In addition, 75% of ICUs do not have a tool to assess for alcohol use disorder or alcohol withdrawal syndromes.

This under-recognition compounds the types of assessments that the 11 DSM-V substance abuse criteria (for example) attempt to elucidate, focusing as they do on questions regard- ing a person’s alcohol frequency, the ability to stop, interference with jobs, family and hobbies, sickness after consumption, personal harm/risk increases and so on.

“We should be carefully look- ing for alcohol use disorders in our patient,” said Professor Coopersmith. “Like any other major co-morbidity (cancer, diabetes, COPD), it is associated with significant challenges and worse outcomes. Although we cannot modify the behavior of our patients prior to them coming to the ICU, an understanding of their history will help us manage patients with alcohol use disorder more effectively.”

“Looking forward, an improved understanding of the pathophysiology of why patients with alcohol/criti- cal illness do worse will help develop new therapies targeted towards this vulnerable and underappreciated population.”
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Inhaled analgesic for fast pain relief

Getting faster pain relief to injured patients was the theme of a presentation by Frank Coffey (Nottingham, United Kingdom) held yesterday at ISICEM.

“The relief of suffering is paramount for any doctor and the ability to deliver timely analgesia to acutely injured or ill patients a priority for an emergency medicine physician,” said Coffey, who is head of a research team at the Emergency Department (ED) at Nottingham University Hospitals’ NHS trust, a major trauma center, and one of the busiest EDs in the Europe.

The proximity to so many trauma patients has placed him in an excellent position to look at efforts to improve access to appropriate levels of analgesia, which are so often unmet he said. “Pain relief is a major issue in pre-hospital and emergency medicine, and many studies have highlighted the unacceptable delays to analgesia for patients in EDs across the developed world,” he explained.

Today, pain relief options are often limited in these environments said Coffey. Analgesics such as intravenous opioids or nitrous oxide – the most widely used – have their downsides. “The former requires intravenous access, and as a controlled drug has the problems associated with storage and security,” he said. And the latter, nitrous oxide, requires a health worker to administer, can be unwieldy to access and is contraindicated in chest injuries where there is potential of worsening a pneumothorax.

“It’s portability is affected by an attached cylinder. When it is piped into rooms, availability and accessibility are issues in a crowded ED,” said Dr. Coffey.

With such limited options, safe and efficacious alternatives should be welcomed. “There is room in the formulation of pre-hospital and ED settings for a fast-acting analgesic agent, not requiring intravenous access or close supervision,” he said.

That’s why Dr Coffey will be talking about work carried out to evaluate just such an alternative. He has been analyzing the use of methoxyflurane, an inhaled analgesic delivered via the handheld Penthrox device. It has been used extensively in Australia and New Zealand for over 30 years but is only just being considered a viable option in Europe. “There haven’t been any breakthroughs with inhaled analgesia for many years, which makes the migration of Penthrox to Europe very exciting,” he said. “Given the current interest and focus, it seems incredible that this has taken so long.”

A key reason for a delay in introducing this device into Europe, has been the fear of the nephrotoxicity. Methoxyflurane was widely used for anesthesia during the 1960s and early 1970s. However, nephrotoxicity was reported following deep methoxyflurane anesthesia. Subsequent studies established that nephrotoxicity was associated with inorganic fluoride levels and was dose related.

Much smaller doses required for pain relief don’t seem to have the same effect, however, said Coffey. A recent review by Professor Anthony Dayan, a toxicologist in the UK, also concluded that the sub-anesthetic doses used for analgesia in the Penthrox inhaler did not carry a risk of nephrotoxicity, for example. And a wealth of anecdotal evidence plus a number of studies over the last five years have shown benefits of Penthrox in different clinical settings he said.

Coffey’s own work has been to add to the safety profile of methoxyflurane. He was lead researcher on the STOP! Study, a multicenter analysis of the short-term efficacy of methoxyflurane for the treatment of acute pain in patients presenting to an ED with a physical wound or injury, such as fractures, lacerations, burns, dislocations, contusions or injury due to foreign bodies.

“It was the first high quality, randomised controlled trial to assess its efficacy and safety,” he said.

Coffey presented the findings of that study at ISICEM, using a sub-analysis that has been carried out on adult patients who were randomised to receive either methoxyflurane or placebo via a Penthrox inhaler.

There were several important findings, including the effects of inhaled methoxyflurane on liver and kidney function. “It adds weight to the safety profile of the drug from other studies and experience in the southern hemisphere,” he said.

Interestingly, he notes that patients were able to administer rapid pain relief to their own requirements. The effects of methoxyflurane also seem to last longer than nitrous oxide so there is less need for continuous inhalation. It can act as a bridging analgesic when there is a delay in intravenous access, said Coffey. “On occasions it may obviate the need for opioid analgesia for conditions such as dislocations or fractures,” he said.

“The pain relief from reduction or splinting allied to Penthrox with or without simple analgesia, may offer sufficient pain relief,” he said.

Of interest in the future, said Dr Coffey, would be to study the effect of this pain reliever in patients with more severe pain. That is because STOP! excluded patients initially presenting with a verbal pain score of greater than seven. “Anecdotal evidence is that it is equally effective in more severe pain,” he said.

Dr Coffey would also like to see a study across the pre-hospital and ED pathway comparing Penthrox with current standard practices, with robust economic analysis, as well as qualitative evidence – such as interviews to support quantitative data. More interest is being shown in this analgesic by other research groups; a pediatric study is currently being planned in the UK, he said.

“Pain relief is a major issue in pre-hospital and emergency medicine, and many studies have highlighted the unacceptable delays to analgesia for patients in EDs across the developed world.”

Frank Coffey
It is very important that we see these as not synonymous.

A 2014 study by Quill et al. identified a variability in withholding and withdrawing life support in ICUs across the US ranging from 12% to 62% (after adjustment for illness severity and other patient- and ICU-related factors). The investigators concluded that although patient factors explain some of the variability in the decisions to forgo life-sustaining therapy, significant effects of ICU culture and practice influence end-of-life decision-making. Similar findings came from a UK study.

A systematic review on the topic by Mark et al. (2015) identified substantial variability in the withdrawal of life-sustaining treatment across world regions and countries, as well as between ICUs within countries and even between physicians within the same ICU.

"There is certainly variability between different countries and regions that has to do with culture and legal issues. But we see almost as much variability within countries and even within single ICUs, which suggests that we don’t have consensus about how to approach these issues. I think it is a call for us to develop consensus in how we think about these issues, as well as how we teach them to our trainees." Dr Curtis cited the work of Nelson et al. (2011) who critically reviewed existing data on models that have been used to structure clinical initiatives to enhance palliative care for critically ill patients in intensive care units and their families. They identified three models: one ‘consultative’, focused on bringing in palliative care specialists into the ICU; a second ‘integrative’, increasing palliative care skills of ICU clinicians; and a third and perhaps most effective model that uses both approaches.

While there is not a lot of data on a mixed model that combines the other two approaches, Dr Curtis described work centered on an integrative model. “We wanted to improve the skills of ICU physicians and nurses. We did this through an intervention that was focused on the hospital in a multifaceted quality improvement-type program. We started with a randomized trial in the same year of before/after pilot in my own hospital and were able to show improved family- and nurse-rated quality of dying and a reduction in length of stay for patients who died in the ICU, showing earlier decisions about withdrawal of life support.”

The intervention included five components: clinician education, local champions, academic detailing, clinician feedback of quality data, and system supports. This study was then extended to include 12 hospitals, but no improvements in quality of dying or changes in ICU length of stay were identified. “One of the lessons from this study is that we were able to make a difference within our own institution, when we really designed the intervention for our institution. When we then tried to go and disseminate that to other hospitals we were not as effective. A lot of these types of quality improvement interventions really need to be developed or at least heavily adapted within an institution and responding to that institution’s culture.

“There are a lot of ways to communicate with families. Having families on rounds, talking to them at the bedside, is one that I really think has made a big difference in our hospital. But there is something different that happens on family conference when families are away from the bedside and have the opportunity to go through some of the issues, and to be supported by clinicians as they think through these issues that they and their loved one is facing.”

Turning to the state of evidence supporting palliative care consultation as a means of improving outcomes, Dr Curtis cited a number of studies that supported proactive approaches in different patient subsets, demonstrating improved quality care and decreased length of stay. A 2016 multicenter randomized study, explained Dr Curtis, provided evidence contradicting the use of palliative care provider-led family meeting in the absence of an ICU physician, but importantly this study did not involve a palliative care consultation that integrated with the ICU team.

Curtis and others carried out a randomized trial in the same year of...
Improving palliative care: parentalism versus autonomy

Continued from page 11 communication facilitators to reduce family distress and intensity of end-of-life care (somewhat falling between the consultative and integrative approaches). “The intervention was what we called a ‘communication facilitator’ – a nurse or a social worker who is not trained to take over this communication for the ICU team, but rather to help the ICU team meet the families’ communication needs. The nurse or social worker was trained to identify individual family members’ communication needs, and provide that information back to the ICU team along with suggestions for how those needs might be met. The facilitators also were trained in mediation, so they were trained to identify and address conflict, including conflict between the ICU team and the family as well as conflict within the family or conflict within the team.”

“We enrolled 268 family members of 168 patients. We looked at family psychological symptoms at 3 and 6 months. We saw a trend towards reduction in depression at 6 months. We saw no change in anxiety and no change in PTSD at 3 months, perhaps a trend toward decreased PTSD at 6 months. We also saw a significant reduction in ICU length of stay and in costs.”

Different communication strategies can exist under the umbrella of palliative care; identifying which strategies are effective, explained Dr Curtis, is therefore of importance. He cited the 2007 Lautrette et al. multicenter randomized controlled study to evaluate the effect of a proactive communication strategy that consisted of an end-of-life family conference conducted in the end-of-life decision-making process when acting as surrogate decision-makers. A normal distribution of preferences – along the scale of family versus physician input and influence – was identified; however, peak preference differed depending on the country or region in question. Hence, a greater preference for shared decision-making was found in some studies, while a greater preference for physician-made decisions with family input was found in others.11,12 Gries et al. (2010) demonstrated how concordance between the decision-makers’ preferred role and their actual role led to reduced PTSD and depressive symptoms, relative to those whose preferred role was not actually met.13 “Although you see a shift in the distribution between different areas and cultures, there will always be a distribution,” argued Dr Curtis. “And it will be important for us to attempt to match the family’s preferred role is in decision-making.”

“We ought to look at this as a spectrum, from paternalism (where the doctor decides) at one end of the spectrum, to autonomy (an ‘informed choice’) at the other end of the spectrum, with shared decision-making in the middle. Our default starting point should often be shared decision-making, but we need to be able to move up and down the spectrum depending on the prognosis, our certainty of the prognosis, and importantly depending on the family’s preferences for the role they play in decision-making. We have some data to suggest that although we see a spectrum, the spectrum tends more to depend on the doctor’s preferences rather than the family’s preferences or the patient’s circumstances.”

References

Futile care versus medical nihilism in liver failure

J ulia Wendon (King’s College London, UK) opened Wednesday morning’s session on the failing liver, delineating the boundary between futile care and medical nihilism. She addressed clinical decision-making questions by exploring data relating to prognostic models and bottom-of-the-bed assessments, as well as examining reasons for and ethics surrounding critical care provision. “The reasons for admission are multiple,” she said. “In fact what we see is that, despite the various precipitants of admission to ITU, you see end-organ dysfunctions of hepatic encephalopathy, cardiovascular failure, renal failure and respiratory failure, and metabolic disorder. “Our aim is to try and treat those patients who have a reversible component, and thus not provide futile care: looking for those who we can reverse, either to recovery or recompensation.”

Dr Wendon reaffirmed the purpose of critical care. “We try and avoid death from specific organ failures, we want to provide time for organ recovery, and clearly we want to provide excellent nursing care, and attentive medical care. The allied health professional inputs are really important. And communication with the family: if there is going to be a poor outcome, let’s at least communicate that early on. Particularly in the cirrhotic population, that balance of running very fast in one direction for a transplant, versus being realistic about what the outcome is going to be, is very pertinent.”

“Critical care does not provide magic. But we are not going to punish liver patients; we are going to offer them a fair and equitable service.”

Dr Wendon cited a 2010 study by Das et al., which investigated prognosis and long-term survival

The falling liver Silver Hall Wednesday 10:25

How to improve palliative care in the ICU Arc Room Tuesday 17:00

“It will be important for us to attempt to match the family’s preferred role in decision-making.”

Jared Randall Curtis

The falling liver Silver Hall Wednesday 10:25

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in a cohort of 138 patients, and identified that mortality increased alongside the number of organ failures as defined by computation of the Sequential Organ Failure Assessment (SOFA) score. The question that must be asked, said Dr Wendon, is whether these organ failures are reversible, and whether the patient can therefore be stabilized. Notably, Das et al. found that 20-40% of patients who had required organ support on admission demonstrated a six-month survival rate of 40%.1

A 2012 UK-based study compared cirrhosis patients against dialysis-dependent chronic renal failure patients, showing that for the same level of severity of illness (as modelled on the Intensive Care National Audit & Research Centre [ICNARC] model) the outcome for cirrhotic patients are less good. The study concluded that survival worsens considerably with organ failure, especially with sepsis, and that, given the extremely high mortality in patients with multi-organ failure, support should be limited or withdrawn in such patients.2 “We need to understand why that is,” commented Dr Wendon, “And manipulate things appropriately.”

Dr Wendon highlighted the SOFA-CLIF score, which is modified in terms of creatinine, coagulation, circulation, and lung factors for cirrhosis specifically. Investigators Moreau et al. sought to define acute-on-chronic liver failure, using organ failure and mortality data to stratify it. Mortality correlated with number of organ failures (1 organ failure, mortality 14.6%; 2 organ failures, 32.0%; 3 organ failures, 68.0%; 4 organ failures, 88.9%).3

Putting together data from a series of studies4-7, Dr Wendon noted that ICU mortality variation is dependent upon SOFA score, citing this as the main driver of prognostication once a patient is admitted to ITU, as opposed to the classic liver scores of cirrhosis.

“The work from Levesque is very powerful,” she continued. “It clearly shows the importance of sepsis in this group of patients. The mortality in patients with or without infection is dramatically different, and it doesn’t matter whether that sepsis was at the time of admission or acquired during the ITU admission. Avoidance of sepsis, and aggressive urgent treatment of sepsis, is paramount in altering outcome.”

Moving on to the choice of scoring system in decisions whether to treat, and how to treat, Dr Wendon referred to the prognostic cut-off points and Youden indices as dictated by different scoring systems (SOFA, MELD and SAPS II), described by Levesque et al.8 “This study was published some years ago now. If we think that what we are doing is worthwhile, what happened five years ago can’t be applied to what is happening now. We have to view these scores as dynamic, otherwise yes we will be nihilistic and we will say no and nothing will get better.”

Dr Wendon did note improvements in organ failure number and mortality over recent years.4 “We need to drive this forward,” she said, “In the right cohort of patients.”

In 2014 the Royal Free Hospital (RFH) score was developed, incorporating lactate, urea, and bilirubin, demonstrating good discriminative ability and calibration.9 “This is quite complex, and difficult to do at the bedside,” commented Dr Wendon. “But importantly, again, it defines your prognostic models. In terms of organ failure and mortality, the mortalities are not as high as we would expect. So driving forward aggressive care will change outcomes.”

Julia Wendon

“Our aim is to try and treat those patients who have a reversible component, and thus not provide futile care.”

Jalan et al. (2014) developed the CLIF-C score, finding it superior to the MELDs and MELD-Nas in predicting mortality.10 “These are all large groups of patients,” summarized Dr Wendon. “Not the individual sitting in front of you. So can we predict futility? If we fix specificity at 95% and we then use bootstrap methodology to assess sensitivity, we use a cut-off value of 14 for CLIF-SOFA, that gives us a sensitivity of over 32% (26-40%). If you have a cut off of greater than 12 for SOFA that gives a 33% sensitivity (26-39%). That suggests that neither score provides you with an adequate measure of futility. Prognosis maybe, but not futility.”

References
Critical care: US perspectives

The concept of unified critical care is that it is really a great advantage if you have multiple ICUs and acute care units, major institutions and other institutions under one umbrella organization.

Stephen Pastores

International perspectives 400 Hall Friday 10:50

Critical care: US perspectives

I nternational perspectives on critical care come together this morning in a session that draws in viewpoints from different parts of the world. Stephen Pastores (Memorial Sloan Kettering Cancer Center, and Weill Cornell Medical College, New York, NY, USA) will discuss the organization and governance of critical care in different parts of the world, and the driving forces behind a unified and expansive organizational model that is taking hold in the US — namely, that of the critical care organization (CCO), which reflects the evolution of intensive care as a standalone department.

“The concept of unified critical care is that it is really a great advantage if you have multiple ICUs and acute care units, major institutions and other institutions under one umbrella organization,” Dr Pastores told ISICEM News.

As described by Dr Pastores in the most recent edition of the Handbook of Intensive Care Organization and Management, calls to increase care quality and safety in US health-care come at a time of intensivist workforce shortage and increasing service demand. A response to these calls must come in the form of new approaches to organization and management. In contrast to many European countries, where freestanding ICUs are commonplace, in the US ICUs are traditionally under the direction of academic or hospital departments.1

“For quite some time we have been trying to make the case that in the current landscape of critical care — the complexity, the aging population, the advances in technology, and treatment modalities — there is going to be ongoing increases in volumes of patients and how sick they are. It would be best if that care is streamlined and made more efficient by having more of a unified workforce with defined roles and responsibilities — the ICUs working in concert under one umbrella organization.

“Triage, governance, quality and safety initiatives, retention and hiring of people: all of these things are going to potentially improve, and hopefully we will also do better on the outcomes and reimbursement front. So you can make a business case. A financial case is a little tougher, but clearly on the efficiency side, there is a lot to be said about why critical care units have to be organized and led by critical care folks — rather than the way that ICUs are organized, in silos, which makes it a challenging.”

While the vast majority of US ICUs continue under preexisting structures, the perception of critical care management is changing, noted Dr Pastores, with hospitals more open to examining their infrastructures in order to reap the benefits of increased accountability, standardization, and data-gathering capabilities1. “There are so few of us that have this in place in North America; there were only 25 that could be identified that have an organized process of critical care.

“Is the US the best? I am saying, I don’t know! But I think this is what we should be doing. We should move to a new paradigm of delivering critical care.”

Stephen Pastores

“But every year more come up. I hope that this will lead to more CCOs being created, because there are driving forces and a good reason as to why they need to be in place.”

This change began with larger academic medical centers (AMCs) creating freestanding critical care management departments or CCOs in a similar vein to those existing for other specialties such as cardiovascular disease or cancer. Dr Pastores and others determined the structure, governance and experience to date of the few established CCOs in North America in a 2015 article in Critical Care Medicine. The study identified that, as it stood, nearly 80% of existing CCOs were primary AMCs, with an overall impression that they vary in organization and are continuing to evolve.2

“Out of that work and the publication of the paper on the survey, the Society of Critical Care Medicine decided to create a Task Force called the Academic Leaders in Critical Care Medicine (ALCCM). This task force is led by me and by Vladimir Kvetan (Montefiore Medical Center, NY, USA). The members of this ALCCM are all the leaders of the 25 CCOs. Our inaugural meeting was held last year during the society of Critical Care Congress (Orlando, FL, USA). We talked about our major goals, one of which is hopefully to see the creation of more CCOs over the next five years. We seem to be gaining ground.”

The ALCCM Task Force is creating toolkits and resources for those interested in creating a CCO, outlining ideal leadership and workforce characteristics. Upcoming publications explore these themes. One of the central ideas is integration — both horizontal, by which ICUs are brought under one umbrella organization, and vertical, by which individual patient care is a continuum that includes post-ICU care provided by a communicating network of affiliates. Vertical integration, said Dr Pastores, deals with the significant issue of post-ICU health issues (such as PICS), with a possible positive effect on readmission rates.

Obstacles to the expansion of the CCO concept, continued Dr Pastores, include issues of staffing, finances, individual hospital missions, and perhaps even personal issues. In his concluding statements, he outlined the three major themes he will be discussing this
morning: “Critical care delivery has to be more efficient and more effectively targeted.

“I and my other colleagues who are interested in making this happen think that creating the CCOs and having more of them provides that edge, in aligning operationally and financially the incentive to delivering great outcomes to patients. And there are many benefits to doing that, but it’s not easy to do. You have to make sure you have the manpower; you have to make sure you have the folks with the vision to do it; and you have to have leaders willing to govern. A lot of us who have the CCOs in place are an aging group, so we need people that will come behind us to carry the torch once we are no longer able to. We need to groom the leaders of the future, now!”

“The talk that they wanted me to do is asking, ‘Is the US the best?’ I am saying, I don’t know! But I think this is what we should be doing. We should move to a new paradigm of delivering critical care. To do it, it has to be of high impact, high value, patient-centered, and financially viable. In the end, critical care is really the only discipline that is so multidisciplinary and that is how it should be.”

Dr Pastores speaks during ‘International perspectives’, which takes place in 400 Hall from 10:50 today.

References

Fact or fiction: Could suspended animation be feasible in the ICU?

Peter Radermacher

“Pharmacologically induced suspended animation would be very exciting.”

The intriguing concept of pharmacologically-induced ‘suspended animation’ as a protective strategy in the ICU was presented yesterday afternoon by Peter Radermacher, from the Institute of Anaesthesiological Pathophysiology and Process Engineering, Ulm University Medical School, Germany.

In their 2014 paper1 on the topic, Professor Radermacher and colleagues note that suspended animation is, by definition, a hypometabolic state that is characterized by “the slowing of life processes by external means, without termination.”

It was arguably the study by Blackstone et al. in 2005 that sparked a great deal of interest in the concept of suspended animation. In the paper, the authors demonstrated in mice that inhalation of hydrogen sulfide (H2S) reversibly decreased energy expenditure, associated with a fall in core temperature. As such, should pharmacologically-induced suspended animation be translatable into the ICU, it could offer a protective strategy for patients, whilst avoiding some of the pitfalls of direct cooling-based hypothermia (e.g. metabolic acidosis, coagulopathy, prolonged inflammation, and impaired host defense). Speaking on Blackstone et al., and the wider data, Professor Radermacher said: “Data from large animal (sheep, swine) models have been contradictory: some authors (Li Pediatr CCM 2008; Haouzi Respir Physiol 2008; Derwall Shock 2010, Crit Care 2011; Drabek Shock 2011) in fact were unable to reproduce any effect similar to Blackstone’s paper. In contrast, during much longer exposure times, we could demonstrate a (fairly moderate) temperature effect of both inhaled H2S (Simon Shock 2008) and infusing Na2S (Simon Shock 2011; Bracht CCM 2012) in porcine models of I/R-injury and hemorrhage and resuscitation.

“However, due to the experimental design, it was impossible to answer the question whether this effect was due to H2S per se, and/or attenuated inflammation etc.” He went on to note that animal size is a major component that affects the success of suspended animation: “During anesthesia, mice in particular become hypothermic without any further intervention. In human-size swine, this takes hours,” he said, adding his comments on the so-called ‘non-shivering thermogenesis’ that small rodents are able to undergo. “This represents the fundamental metabolic difference between rodents (in particular mice) and larger mammals. In larger mammals, such an effect is only present during the peri-natal period (Radermacher & Haouzi ICMexp 2013).

Moving on to human study, Professor Radermacher began by commenting on the observation that inhalation of H2S during exercise in healthy volunteers had a toxic restriction on aerobic capacity.” Clearly, during maximal exercise (low dose, 5 ppm) H2S inhalation markedly increased lactate concentrations, which coincided with increased maximal VO2, associated with a fall in RER, i.e. suggesting reduced aerobic substrate oxidation together with (presumably) increased O2 consumption used to detoxify H2S.

“Since the VO2 max, however, was even higher than without inhaling H2S, it remains open to which extent mitochondrial respiratory activity was stimulated by H2S feeding into the respiratory system via the sulphide-quinone-reductase-system (SQR) (Szabo Bouilleaud Br J Pharmacol 2014).”

Conversely, he added his thoughts as to whether H2S could be protective for organ injury when applied at the right moment: “There is indeed ample evidence (even in large animal models) that H2S is protective in I/R-injury models. Currently, it seems that, to a large extent, these effects are NOT related to metabolic modulation. Whether or not this might play an important role, e.g. due to protection of mitochondrial function and/or morphological integrity is an open question (Szabo Bouilleaud Br J Pharmacol 2014).”

The talk that they wanted me to do is asking, ‘Is the US the best?’ I am saying, I don’t know! But I think this is what we should be doing. We should move to a new paradigm of delivering critical care. To do it, it has to be of high impact, high value, patient-centered, and financially viable. In the end, critical care is really the only discipline that is so multidisciplinary and that is how it should be.”


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Fact or fiction: Could suspended animation be feasible in the ICU?

Continued from page 15

until a measurable effect on core temperature could be detected. "Moreover, there was considerable time lag between the effect on metabolic rate (VO2, VCO2) and temperature (Simon Shock 2008)," he said.

In their paper1, Professor Radermacher and colleagues touch upon prolonging tolerance against damage in the critically ill by using hypometabolism – something he described as a "tempting concept", adding: "This also relates to the concept that 'Multiorgan failure is an endocrine-mediated metabolic response to overwhelming hyper-inflammation' (see Singer Lancet 2004).

"In fact, the term 'suspended animation' was always associated with 'metabolic inhibition' (Webb Ann Surg 1963). This concept is already used via induced hypothermia after CPR. On the other hand, induced hypothermia was detrimental after TBI (Andrews NEJM 2015). Any pharmacologically induced suspended animation would be very exciting. Interestingly in this context, the above-mentioned original experiments (Webb Ann Surg 1963) used MgSO4 during normothermic conditions!"

Speaking frankly, Professor Radermacher went on to emphasize that inhaled H2S is most likely is a "dead end", due to the mucosa irritation possibly associated with its application, and the environmental toxicity that would require substantial protection measures for the personnel involved. He added that dosing and timing of H2S is also a fundamental problem for any other H2S donor: "So far, there is no gold standard for the measurement of H2S concentrations (Cook Nitric Oxide 2014), and clearly, there is no simple relation between concentrations and biological effects," he said.

"Moreover, when sulphide salts (e.g. Na2S, NaSH) are administered the (pH-dependent) presence of sulphide in its gaseous form, the aqueous dissolved forms and the sold molecule have to be considered. Finally, the dosing-timing window at least for sulphide-releasing salts seems to be extremely narrow (Bracht CCM 2012)."

Turning to the lingering question at hand, does Professor Radermacher believe that suspended animation will be realized within our lifetimes? "It'll certainly take a lot of time," he said. "Maybe using molecules that are already recognized for other indications (and for which possible undesired side effects are known) could be worth trying."

But should focus be on evaluating the mechanisms behind the H2S effect? "Yes, this is definitely a major challenge: as a small, gaseous mediator, H2S is easily diffusible and does not need any receptor. Hence, it will have ubiquitous biological activity, with toxicity and protection being theoretically possible simultaneously, even at comparable concentrations."

Concluding with his thoughts on whether further study to try and achieve isolated organ protection should be a nearer-term goal, he said: "This is already ongoing, since it is of course an interesting concept in the context of transplant surgery (e.g. Lobb Am J Transplant 2017). Combin- ing this approach with the above-mentioned use of recognized molecules might be an option."

References

Stimulating potential for immunotherapy in sepsis

Tuesday afternoon’s plenary lecture by Richard Hotchkiss (Washington University School of Medicine, St Louis, MO, USA) took a fascinating journey through sepsis-induced immunosuppression, outlining the clinical relevance, impact and – importantly – the vast treatment potential that immunotherapy could provide.

While septic shock is more traditionally viewed as a disease of excessive systemic inflammation, the vast majority of patients survive the initial ‘insult’, only to succumb to sepsis-induced multigorgan dysfunction days or weeks later, suggesting that there is an overarching shift to an immuno- suppressive phase. Indeed, sepsis has been previously described as a ‘race to the death’ between pathogens and the host immune system.2

"If you look at most ICU patients, they survive the first few days, but they die later," Dr Hotchkiss told ISICEM News. "A lot of them will develop secondary infections, with organisms that are not very virulent, i.e. pathogens that would not affect people who were healthy."

With sepsis being the leading cause of death in the ICU, studies on treatment have abounded in recent years, but for the most part have failed, leaving the door open for novel approaches.3,4

To explore the mechanisms of sepsis, Dr Hotchkiss and colleagues have performed rapid autopsies at the bedside, examining the types of cells that die during sepsis. "A lot of the cell death in sepsis was occurring in the spleen, in the lymph nodes and in the GI tract," he said. "These were lymphocytes and dendritic cells that were dying, i.e. very important components of your immune system."

With animal models confirming the same cellular death, Dr Hotchkiss was confident that he and his team were really onto something: "We subsequently went on to show that the death of the immunne effector cells was an important pathophysiological event," he said.

Crucially, he noted that further studies in mice were able to show that halting of sepsis-induced death of lymphocytes could be achieved (via a variety of independent methods), then there was a marked improvement in survival. Further validation of the post-mortem findings came from other groups, who also saw a profound loss of immune effector cells in neonates, and in pediatric populations. "So this same finding of apoptotic death and depletion of immune effector cells has now been verified across patient age groups," said Dr Hotchkiss.

Turning to the possible realities of treatment, Dr Hotchkiss spoke primarily of interleukin-7 (IL-7) and anti PD-1 (programmed death 1) approaches.1,5 IL-7 is an antiapoptotic, immuno- nostimulatory cytokine, and PD-1 is a monocye-macrophage protein that impairs immunity by inducing apopto- sis, and preventing proliferation and ‘exhausting’ T-cells (i.e. anti PD-1 is the therapeutic strategy relevant).1

Several trials are now underway exploring these (and other) immuno- therapies, such as the IRIS-7 B trial – a multicenter, randomized, double-blind, placebo-controlled study of two dosing frequencies of recombinant Interleukin-7 (CYT107) treatment to restore absolute lymphocyte counts in sepsis patients. Dr Hotchkiss is Study Director, but there is also a par- allel study in France. "Bruno François and Thomas Daix have been leading the IL-7 study in France. We have some results on that, and we believe they are very exciting," he said.

In addition, studies are now under- way for nivolumab (a PD-1 inhibitor that has been extensively used for treating the immune system of cancer patients)5 in severe sepsis and septic shock.2

Relaying clinical case studies using immunotherapy in sepsis, Dr Hotchkiss spoke of a paper co-authored with David Grimaldi, Olivier Pradier and Jean-Louis Vincent,6 which describes a 30-year-old woman who was injured

"These drugs, IL-7 and anti-PD-1, could be highly effective … because they will boost the immune system, and then help get rid [of] pathogens."

Richard Hotchkiss
in the March 2016 Brussels terrorist bombings – injuries that included sustained pelvic and femur fractures, extensive soft-tissue abdominal and pelvic damage, pulmonary contusion, and second-degree burns. “She developed mucormycosis, which is a really virulent fungal infection,” said Dr Hotchkiss. “They were unable to control the infection, despite surgical therapy to remove it, and despite antimicrobial agents.”

Because of poor prognosis and immunosuppression, the authors used nivolumab, and interferon-γ, for treatment. “The patient subsequently cleared her fungal infection, and has survived. So that is an interesting case,” said Dr Hotchkiss.

Harking back to his earlier statement regarding the ‘delayed’ death of most sepsis patients – i.e. hospitalization due to secondary infections from normally less-virulent pathogens, which are exacerbated by a weakened immune system – Dr Hotchkiss stressed that there are lessons to be learned from the oncology world, saying: “Immunotherapy has revolutionized cancer therapy, and because of the overlap in the similarities of immune defects in sepsis and cancer, we think that immunotherapy is going to be highly effective in septic patients too.”

“Immunotherapy has revolutionized cancer therapy, and because of the overlap in the similarities of immune defects in sepsis and cancer, we think that immunotherapy is going to be highly effective in septic patients too.”

Richard Hotchkiss

Noting a few challenges, he added: “There has been a lot of concern about the autoimmunity of some of the cancer therapy drugs, but the autoimmunity problems usually occur almost always in patients after they have received multiple doses of the drugs (which is less likely in sepsis), and/or combination immunotherapy, so with sepsis I don’t think there is going to be a problem.”

“However, I don’t think we will be able to use these drugs in patients who have existing immune problems and get septic, or patients that have an organ transplantation, because they may reject their organs. So there are going to be people who are not good candidates, and there are going to be some people that are going to have autoimmune reactions.”

Wrapping up his key message, Dr Hotchkiss reiterated the importance of understanding that weakened immune systems could be a key driver of sepsis outcomes, allowing as they do less dangerous pathogens to invade and harm the host. “Recently, the World Health Organization highlighted so-called ‘superbugs’, i.e. multi drug-resistant organisms. Immunotherapy is ideal for that type of problem because ‘superbug’ is really a misnomer. Those bacteria are not all that virulent. They attack people with weakened immune systems. The people that are getting infected are those in the intensive care unit, in general, although there are some exceptions. “These drugs, IL-7 and anti-PD-1, could be highly effective against those, because they will boost the immune system, and then help get rid of those pathogens.”

References
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Looking forward to the future of personalized medicine, Raghavan Murugan (University of Pittsburgh School of Medicine, and the University of Pittsburgh Medical Centre, PA, USA) presented the recommendations of the Society of Critical Care Medicine (SCCM) Task Force, which set out a framework for precision medicine research and implementation in critically ill populations.

Dr Murugan explained to delegates on Wednesday that precision therapeutics is a response to the naïve expectation that data on average treatment effects are sufficient to inform decision-making for the individual patient. “Variability is the law of life,” he said. “Clinicians know this every day, because when you take care of these patients you are trying to figure out what is the best drug to use that would benefit them.”

Advances in technology have brought to life the field of omics, he explained, creating the possibility of integrating genomic, transcriptomic, proteomic, and metabolomics data to guide pharmacological or interventional selection. Today, a number of stark challenges persist in this sphere, namely: the definition of conditions’ sub-types by distinct functional or biological mechanisms (so-called ‘endotyping’); their linking with specific outcomes; and their applications in studies or trials that will precipitate precision medicine.

The SCCM Task Force developed guidelines on the development, conduct and design of trials for precision medicine in critically ill patients, which will shortly be published. The Task Force brings together leaders across SCCM from various domains, including systems biology, biostatistics, modelling, data analysis, trial design, and individual syndromes (e.g. sepsis, ARDS, AKI, trauma, etc.) Its aim is to discuss the significance of precision medicine paradigms to enhance the diagnosis, prognosis and treatment of critically ill patients; to summarize the science supporting precision medicine approaches in critical illness; and to provide recommendations on precision medicine research priorities in the years to come.

Why do we need precision medicine? “There is profound biological and clinical heterogeneity,” explained Dr Murugan. “Precision medicine is a powerful tool to leverage this, to come up with meaningful solutions for high-risk patients where we can optimize the risk-benefit ratio, because critical care is probably one of the most high-risk of all medical specialties. Also, we can reduce resource utilization, because intensive care medicine has some of the highest resource utilization of all the specialties.”

One of the things I want to put forward is the concept of heterogeneity of treatment response, Dr Murugan noted its implications for traditional RCT design – as well as for the development of new precision RCT designs. “One of recommendations for traditional RCT design is that we should incorporate a prespecified heterogeneity analysis at the trial end. You need to show the interaction that occurs with various comorbidities in that given patient in terms of the treatment outcome.”

Potential drug-by-phenotyping interactions must be explored, he added, as an exploratory analysis at the end of the trial, in order to generate hypotheses that could be tested in the future. A further recommendation was to incorporate standardized baseline clinical data, with the idea that these data could be used in individual patient data meta-analysis, as

“Variability is the law of life.”
Raghavan Murugan

“We should be moving away from diseases or syndromes or states towards a specific diagnosis.”
Raghavan Murugan
well as to explore the drug-response phenotype. Biosampling was a strong recommendation, where this includes the measurement of physiological parameters as well as the collection of biological data.

Further recommendations were made for novel RCT design: “Where there is strong evidence for candidate biomarkers, we should explicitly be stratifying or recruiting the biomarker-positive patients,” suggested Dr Murugan. “Whenever there are candidate biomarkers with therapeutic response potential, we should incorporate a biomarker enrichment design that tests and learns whether there is a treatment-by-biomarker interaction. This means, does the treatment affect the biomarker levels, and how does this affect the outcomes? There have been proposals to study some of the newer study designs, such as the sequential multiple assignment randomized trial (SMART) design, where they assign multiple interventions in a randomized trial.”

Another novel RCT design is the concept of ‘adaptive randomization’: “Patients are increasingly not willing to be randomized when there is a 50:50 probability of whether that drug will work or not. As the trial enrols, the study learns from the outcomes that accrue in the trial, so that subsequent patients are randomized to where the intervention actually works. These trials are already ongoing.

“Then there are platform trials, which evaluate multiple interventions, focusing on the individuals who receive the interventions, trying to understand which drugs work for which patients.”

Concluding his talk, Dr Murugan summarized: “We should be moving away from diseases or syndromes or states towards a specific diagnosis. There is ample evidence that treating pneumococcal pneumonia is associated with better outcomes as opposed to treating sepsis or severe sepsis. We should be using all these omics signatures that are out there, for early identification of the interactions that occur within the host as well as the outcome. Finally we should move away from manipulating the host to manipulating the pathogen. One of the strongest recommendations is to study the microbiome, which has got great potential to improve outcomes from sepsis and severe sepsis.”
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