The 40th ISICEM has arrived – welcome to Brussels!

This year’s meeting has been a considerable challenge, and entailed a lot of effort and hard work, not only from our team here in Brussels, but also from our faculty members, our sponsors, and of course our participants. But we made it. Here we are, at the start of an exciting four-day program of high-quality presentations, pro-con debates, meet the expert sessions, and real-life interaction! You will see new data on new therapies and optimal respiratory management in COVID-19, oxygenation targets, and extracorporeal CO₂ removal presented for the very first time, with simultaneous publications in JAMA and the Lancet.

Over the last 18 months or so, we’ve been obliged to find alternative methods of sharing information and keeping up to date. We’ve made huge progress with using Zoom, Webex, and Teams to communicate virtually, and indeed, we’ve all become much more tech-savvy over the last year and a half. But regardless of how good (or easy to use) the technology is, online conferencing can never be the same as physical meetings. Web- or video-conferencing is great for short discus-

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sions around a specific question among a very limited number of people, but for large scientific events online presenting cannot replace actual physical presence and interaction.

Of course, it is more comfortable to speak from home or from our office, but these sessions are then often slotted into a busy day, and we are easily distracted or less available. Often a speaker will remain connected just for his/her presentation and perhaps a couple of questions, and then leaves the meeting. Moreo-ver, lively discussions are impossible for international meetings across time zones. Also, some presentations have to be recorded a while in advance, so that last minute developments cannot be easily incorporated.

Speakers at physical meetings are usually present for several days, and can dedicate their time and attention to their presentations and other discussions during the conference. Conversely, at online meetings, participants often connect, but then get sidetracked by other tasks as the meeting proceeds, so that they do not really concentrate on what is being said. Attending recorded talks after the conference sounds appealing, but the opportunity is often missed when there is no strict deadline. How many times have we said: "I’ll definitely at- tend that talk", and then postpone and postpone, and finally never log in.

It’s difficult for a tennis- or football player to play well without spectators, or for a singer to perform optimally without an audience. It is equally challenging for a speaker to give a talk without being able to see who is listening. Do people understand what is being said? Do they seem to support what I am saying? Do they need more explanation? Feedback is so important to be able to adapt the content for the specific audience, and so difficult to obtain when those watching are not present in the same room. Question time is definitely not the same in virtual meetings, and it is even more difficult to maintain a debate. Meet the expert, pro/con debates, round table discussions – all the less formal meeting formats we love – are just impossible without face-to-face interactions. Not to mention the fact that talking to a screen is just so boring!

Importantly, this is not a winner-takes-all competition – it is not one or the other. Both physical and digital conferencing complement each other, and can be combined to ensure the best possible educational solution, and the best experience possible. I am not so much alluding to so-called ‘hybrid meetings’ combining live and video presentations, but rather to the possibility of having a physical meet-}

ing followed by video presentations later on. Participants of the physical meeting can view a presentation that they were unable to attend, review one they didn’t fully understand, or re-watch one that they found particularly helpful. All sessions at ISICEM are therefore being recorded and will be available for all our registered participants to watch online after the meet- ing – until our next ISICEM in March 2022!

Throughout the planning of this meeting, we’ve had encouraging comments from our speakers, for example: "I’ll be there - definitely! Thank you for taking on this chal- lenge"; "It may be complicated to travel, but you can count on me!"; "I’m so happy we can meet again for real, rather than on a screen"; and "Great to get back to face to face meetings!". We are so grateful to all our faculty members who accepted the challenge and have found their way through the multiple different regulations and tests to come to Brussels and share their expertise with their ISICEM colleagues. We really appreciate the extra effort that has been put into attending this year by our faculty, our participants, and our sponsors."

JEAN-LOUIS VINCENT

ISICEM Chairman

The multiple organ dysfunction syndrome: a history Salle M (Bozar) Tuesday 17:40

All roads lead to Rome: A 2,000-year history of multiple organ dysfunction syndrome

In the first plenary lecture of the 40th ISICEM meeting, John C. Marshall (University of To- ronto, ON, Canada) will offer a potted history of multiple organ dysfunction syndrome (MODS), taking the audience through its origins, evolution and persistent challenges. Professor Marshall will begin the story in ancient Rome (38–30 B.C.), where Celsus described four card-inal signs of inflammation: redness (rubor), swelling (tumour), heat (color), only applicable to the extremi- ties and pain (dolor).1 Galen (A.D. 130–200) then added a fifth, loss of function (functio levis). Fast forward to the last 200 years, and it’s clear that a number of key touchpoints in recent history have led to the modern-day concept of MODS. “The first notions of being able to resuscitate patients with intravenous fluids appeared back in the 19th and early 20th century, and the concept of support-
the 1960s reports came out about jaundice and respiratory failure in people who were being kept alive in an ICU. “And then by the late 1960s, the first notion came that when you see renal failure, jaundice and sepsis occurring, maybe this is a syndrome,” said Professor Marshall.

“In the 1970s, Arthur Baue, who was an American surgeon, suggested that it wasn’t any one of these complications in isolation, but actually the combination of them that was responsible for people dying. And so he coined the concept of multiple organ failure, and really established the notion that maybe there is some common underlying thread to this process.”

In the coming years, studies quickly followed showing that a large number of people who had multiple organ failure had occult and undetected infections, typically intra-abdominal, thus there was some interest in performing laparotomies in patients with organ dysfunction for some time. “But then it became apparent that maybe they didn’t have infection after all,” said Professor Marshall.

“And so we began to think about the possibility that bacteria from another location were responsible for the syndrome – maybe as a result of bacteria that are in the gut, of which there was some evidence. However, it was then clear that in addition to this simply being a consequence of the persistence of an inflammatory response, regardless of the cause – whether an infection or not – there was a significant additional component, namely the inadvertent consequences of what we were doing in the ICU to keep people alive.”

Indeed, as Professor Marshall writes in his recent paper, the most cogent concept underlying MODS is that the syndrome is inescapably iatrogenic: it only arises in patients whose lives have been saved by resuscitation and support. At the same time, its subsequent evolution is heavily shaped by the inadvertent and often unrecognized consequences of that resuscitation and support.

By way of example, use of a ventilator to resuscitate patients actually evokes a response that could lead to further lung dysfunction, and it is this almost paradoxical treatment-based harm that is part and parcel of MODS itself.

Professor Marshall expanded on this concept: “What we are really talking about with MODS is something really quite fundamental, which is a group of diseases or physiological abnormalities that occur in people who otherwise would have died. MODS only happens because we are able to intervene to prevent the person from dying and, as a result, then see consequences that simply don’t have a precedent in the absence of the capacity to support.”

Nevertheless, confirmation of MODS is now based on three main assumptions: 1) it involves systemic changes in the function of more than one single system; 2) it entails graded degrees of severity and is potentially reversible; and 3) it arises through a common biologic process or processes, and so comprises a syndrome.

In terms of our understanding of MODS, however, Professor Marshall stressed that when considering that the majority of deaths in an ICU are anticipated, and upwards of 90% of those who die, die with, if not because of, MODS, it follows that there is genuine need for increased understanding of the pathogenesis of disease. “Often we don’t really know why a patient is dying,” he said. “Nor do we know why they get better.”

“[Arthur Baue] coined the concept of multiple organ failure, and really established the notion that maybe there is some common underlying thread to this process.”

JOHN C. MARSHALL

During his lecture, he will touch upon some of the salient points regarding what we know, and what we don’t know, about MODS, including its measurement, clinical management, and underlying mechanisms of action. While the ISICEM audience will have to wait until this afternoon to find out more, he offered a glimpse of some of these messages for ISICEM News. “Our measures are pretty crude,” he said. “They are measures of what we think is wrong with the patient, for example their kidneys are failing (so their creatine is going up), or they are measures of what we do because we think things are wrong, such as dialysis.

“When you put all of those kinds of things together, which you can do in a score or a scale, you can come up with something that associates, in a dose-dependent way, with the risk of mortality.”

Then again, added Professor Marshall, one could argue that such descriptors are largely trivial. “You are saying that patients who are sick are going to die. You’re not really describing the biology of a process – you’re simply describing the crude consequences. There may not be a single, underlying abnormality behind the deterioration, but until we can identify a specific defect, it’s harder to measure it as a disease.”

Professor Marshall presents ‘The multiple organ dysfunction syndrome: a history’ this afternoon at 17:40 in Salle M (Bozar).

References
ECMO for COVID-19 rescues the most severe patients

Alain Combes, Professor of Intensive Care Medicine at Sorbonne University Paris, and head of the ICU department at Pitié-Salpêtrière hospital (Paris, France), has extensive experience in the care of patients with the most severe forms of cardiac and respiratory failure, at one of the busiest units in the world. This morning, he will talk about treating patients in need of extracorporeal support, mainly for the most severe forms of COVID-19. In 95% of such cases he has experienced, patients received extracorporeal membrane oxygenation (ECMO) for respiratory failure, although some experienced cardiac failure too, he told ISICEM News.

Before COVID-19, Professor Combes’ department had an average of 300 cases requiring ECMO each year. In France, the average for most hospitals would have been around 50, he said. Since March 2020, his unit has seen more than 250 patients with the most severe forms of COVID-19. “We are gathering a lot of cases from greater Paris, also because we have a very active mobile retrieval team which is able to travel to remote hospitals, insert the device and then bring the patient back to our center,” he said.

Today, Professor Combes will be talking about experiences gleaned during the various surges within the pandemic. His research, comparing the first weeks and months of the pandemic last year, showed that the mortality rate for patients who received ECMO was 30–35%. New variants had an impact, especially the UK variant which caused mortality rates to rise to 45% this year. “The increase in mortality was not only because of increased virulence, but also because strategies of care for patients before COVID-19 were different,” he said.

What’s important to stress however, said Professor Combes, is that outcomes for these patients would have been very different without ECMO. “We are talking about COVID-19 patients who probably would have died if they did not have ECMO,” he said. To that end, he will talk about a new unpublished paper which found that mortality rates reached over 90% for patients denied ECMO in the greater Paris area (either because it was too late for the intervention, or due to other reasons related to indication).

Professor Combes will discuss an important multicenter cohort study1 which looked at all adult patients with laboratory-confirmed SARS-CoV-2 infection and severe acute respiratory distress syndrome (ARDS) requiring ECMO who were admitted to 17 Greater Paris ICUs between March 8 and June 3, 2020. This research revealed several epidemiological characteristics that influenced mortality rates. For instance, a shorter time between intubation and ECMO, a younger age and those with no pre-ECMO renal dysfunction were independently associated with improved 90-day survival.

Professor Combes went on to stress that more precise criteria for ECMO in COVID-19 patients should be discussed as a result of these data. “We are more stringent now about age, severity of the disease, and the co-morbidities of the patient,” he said. “We start discussing if ECMO is feasible at 60 years old, and we never canulate patients over the age of 70.”

Criteria should almost certainly take into account a center’s experience in venovenous (VV) ECMO, for example. The same study found that 90-day survival among ECMO-assisted patients with COVID-19 was strongly associated with the volumes of patients treated at different centers. “Mortality is significantly lower for centers who were treating more than 30 VV ECMO patients a year before the COVID-19 period,” explained Professor Combes. “It is a volume–outcome effect which is very strong for ECMO.”

Professor Combes will also discuss the duration of high-flow oxygenation, also proven to be of value in COVID-19 patients. As detailed in another piece of research, his team came across an interesting effect when looking at patients who received high-flow oxygenation before moving over to ECMO. The protocol in place in 2020 was to intubate much more rapidly, and in hindsight, this yielded better results. “This probably has a major impact on the outcome of patients, should the high-flow oxygenation strategy be failing,” said Professor Combes. Importantly, however, use of ECMO still had a positive effect compared to no ECMO. “We still have a survival rate which is over 50%, but it was clearly better last year.”

According to results that he will present this morning, patients seem to pay a higher price when they fail to respond to non-invasive strategies. “This could be what we call ‘patient self-inflicted lung injury,’” explained Professor Combes. “It seems to arise from high-frequency, high-respiratory volumes because of the hypoxemic disease caused by COVID-19, that is more common in these patients. This could be very interesting to discuss.”

A major challenge going forward, said Professor Combes, is how to mitigate risks from extended periods on ECMO – something which has risen sharply in patients with COVID-19. Before the pandemic, the median time that patients remained on ECMO was two weeks. “It’s completely different now. Patients can be on ECMO close to one month, and there are some who are weaned from the machine after over two months of support.”

The next step now is to find more effective treatments once the patients are on ECMO, Professor Combes and his team are conducting a study – PRONing to Facilitate Weaning From ECMO in Patients With Refractory Acute Respiratory Distress Syndrome (PRONECO)2 – evaluating the impact of prone positioning on ECMO in these COVID-19 patients. PRONECO, conducted in France, will enroll over 200 patients who will be randomized to early prone positioning vs. no prone positioning while on ECMO.

Until then, Professor Combes’ team is still awaiting the effect of a surge in vaccinations and how that might affect ICU numbers, and by extension, ECMO patients. What’s clear, however, is that ECMO is a vital intervention during the pandemic. “ECMO can rescue the most severe forms of COVID-19,” he concluded.

References
Are you using ketamine routinely in your ICU practice? If not, perhaps you should be!

PAUL WISCHMEYER

Join the Edwards Lifesciences Symposium at ISICEM 2021

Prediction of haemodynamic instability in the ICU

Salle M (live and streaming)

31st August 2021, 12:30 – 13:30

Chaired by
Thomas Scheeren

Speakers
- D. Veelo, Academisch Medisch Centrum Universiteit, Amsterdam
- T. Scheeren, Universitair Medisch Centrum, Groningen
- J. Mesquida, Hospital de Sabadell, Corporacion Sanitaria y Universitaria Parc Taulí, Barcelona
Corticosteroids: toward personalized medicine?

At a time when corticosteroids have become a first-line treatment for severe COVID-19, tomorrow, Djillali Annane, Director of the Intensive Care Unit at Raymond Poincaré Hospital (Versailles, France) will speak about ground-breaking research into the more frugal use of these drugs.

A seasoned veteran of ISICEM for over 17 years, Professor Annane is very pleased to once again return to a face-to-face meeting this year. During a session dedicated to pharmacological therapies for COVID-19, he plans to outline the last 20 years of research into corticosteroids in the treatment of severe infection and sepsis, particularly the rise of corticosteroids as a treatment for severe COVID-19. “It’s amazing to see what has happened if we go back a short time. The WHO guidelines in March 2020 were against corticosteroids. There were no corticosteroids recommended for COVID-19,” he said. “Then, the new WHO guidelines in September 2020 stated that corticosteroids were for everyone; now we think it might save lives.”

Professor Annane plans to present preliminary data from work that tries to personalize the use of corticosteroids in patients with severe infection. “The idea is that not all people respond in the same way to the same drugs, and this is true for corticosteroids in patients with sepsis or COVID-19,” he said.

Specifically, Professor Annane’s team has been able to identify the couple of transcriptomic signatures, or individual fingerprints, indicating whether an individual patient may or may not respond to corticosteroids. “We have been working on this topic now for about two years or so, and we have ended up using a multimetric approach,” he said.

The research should ultimately prevent patients from being unduly exposed to corticosteroids. For example, if corticosteroids are likely to cause adverse events such as super infections or metabolic disorders – yet providing no gain in terms of controlling inflammation or respiratory/vascular support – they should be avoided, stressed Professor Annane. “Really, the idea is to highlight interesting molecular findings at the level of individual. This may help physicians decide whether they should be giving the drugs or not.”

Professor Annane’s team has already published preliminary data on their findings using artificial intelligence. Here, they asked whether machine learning-derived estimates of individual corticosteroid therapy effects yield better results than treat-all or treat-no-one strategies in adults with septic shock. The first transcriptome-based data will be presented today at ISICEM, before being submitted to a major journal early in September.

“The research could lead to a profound change in the way corticosteroids are prescribed. As Professor Annane underlined, the pandemic has resulted in frequent use of corticosteroids worldwide for COVID-19 and other severe infections, and that has probably led to many side effects. Now, his research could change that. “When our primary data is confirmed, we will then be in a situation where physicians could change their practices because they will have a point-of-care test with a turnaround time of about one hour,” he explained. "We can see if a patient is corticosteroid-resistant, in which case we would need to choose another way of controlling the inflammation." By contrast, patients with corticosteroid sensitivity will draw maximum benefit from the treatment with a low likelihood of harms such as super infections or neuromuscular weakness,” he said.

The next step is to validate the accuracy of these transcriptomic signatures or fingerprints in a randomized controlled trial. Professor Annane said a consortium of researchers in Germany, Spain, the UK and the US are currently in the process of setting up an international randomized controlled platform adaptation trial that will be biomarker stratified. Critical illness-related corticosteroid insufficiency, endocan, glucocorticoid-induced leucine zipper, CPD, endotype B and transcriptomic sepsis response signatures will be tested. Importantly, this next study, called International Rapid Recognition of Corticosteroid Resistant or Sensitive Sepsis (iRECORS), will randomize patients to corticosteroids or placebo according to their fingerprints.

ISICEM is likely to be the site of much discussion as to the future use of corticosteroids. Professor Annane said the pandemic has placed corticosteroids as a first-line drug in severe pneumonia as well as COVID-19. “It will continue to be the practice for the next 10 years or so, and I think it’s all the more important to try to avoid unnecessary exposure of patients who are corticosteroid-resistant, just like in asthma,” he explained. “I think we are now moving on the same path for corticosteroids in sepsis and identifying the right population to be treated.”

Whether corticosteroids should be used to treat severe flu in the coming winter season will become a source of great debate at ISICEM, Professor Annane predicts. After such a quick U-turn in the guidelines for management of COVID-19, Professor Annane anticipates discussions will turn to changes to guidelines on influenza too. “The current guidelines for severe flu say no to corticosteroids,” he said. “Some may say that we are placing patients in danger by not giving them corticosteroids. It’s going to be a hot topic for sure.”

Professor Annane added that there may be arguments for corticosteroids for severe flu without randomized controlled trials (today there are more than 18 randomized control trials for corticosteroids in COVID-19, but none for severe flu). “For severe COVID-19, I think there is now sufficient information from randomized controlled trials to have these drugs as routine treatments,” he stressed. “That’s not the case for severe flu.”

Luckily, there are likely to be more firm answers about corticosteroids for severe flu from existing adaptive platform trials, such as REMAP-CAP and RECOVERY, which Professor Annane said are all planning to test corticosteroids in severe flu. “That’s why I am very confident the guidelines will change for severe flu,” he said.

For now, Professor Annane advocates the use of corticosteroids under specific circumstances. “For severe COVID-19, please use a regimen of dexamethasone 6 mg/day for 10 days. For patients with bacterial sepsis, use hydrocortisone 200 mg/day for one week,” he said. “Hopefully, within a year or two, we will have an accurate point-of-care test available to better select the patients that need to be treated with corticosteroids.”

References


“We can see if a patient is corticosteroid-resistant, in which case we would need to choose another way of controlling the inflammation.”

DJILLALI ANNANE

“For severe COVID-19, I think there is now sufficient information from randomized controlled trials to have these drugs as routine treatments.”

DJILLALI ANNANE
Post-ICU and post-acute COVID-19 syndromes side-by-side

Longer-term ICU- and COVID-19 survivorship will be the focus of a talk on Wednesday by Shari Barnett Brosnahan, an assistant professor at the Division of Pulmonary, Critical Care and Sleep Medicine at the New York University (NYU) Langone Health System (New York, NY, USA). At NYU Hospital she works on both the inpatient critical care and pulmonary teams, and her research interest lays in both pulmonary vein thromboembolism and ICU survivorship. Her talk tomorrow will focus on whether post-ICU syndrome (PICS) is different when someone is critically ill from COVID-19.

"Prior to COVID-19, the appreciation of PICS was still in its infancy. COVID-19 has inadvertently brought PICS up to the main stage," Dr. Brosnahan told ISICEM News.

During the COVID-19 pandemic, Dr. Brosnahan was uniquely positioned to help compare COVID-19 survivorship and COVID-19 thrombosis. By breaking down the major contributors and outcomes of ICU survivorship and its toll on mental, physical and cognitive health, Dr. Brosnahan will now compare it with the major outcomes of what’s now called post-acute COVID-19 syndrome (PACS).

These are not mutually exclusive diseases, points out Dr. Brosnahan. "PACS symptoms vary from PICS to some degree, however there is no reason to think that people who have PACS and require an ICU stay would not also be at risk for PICS. The mechanism behind both PICS and PACS can vary from person to person, as they are both syndromes. There are likely to be overarching principles which are helpful in preventing both."

More knowledge on the topic is published all the time, noted Dr. Brosnahan. "There are new data that PACS can occur in patients who don't even have symptoms during their acute infection. However, there are signals that patients with worse acute COVID-19 infections are more likely to have lingering symptoms than those with only mild acute illness."

Therefore, implementing similar strategies to mitigate PICS maybe helpful, she said. There are estimates that PICS occurs in over 50% of ICU patients, even a year after survivorship. At present, the incidence of PACS is poorly understood but the symptoms linger – so far they have been observed for year.

At ISICEM, Dr. Brosnahan will present data from her home institution. Here, to determine whether symptoms improve or persist over time, researchers followed a prospective cohort of patients discharged after admission for severe COVID-19 to characterize overall health status, physical and mental health, and dyspnea at six months post-hospital discharge. They compared patients’ responses at six months post-hospital discharge to their responses a month after discharge, and to their reported baseline before COVID-19 illness.

This study found that even six months after hospital discharge, most patients reported that their health had not returned to normal. "We as ICU providers must stay vigilant to minimize sedation, paralytics and to reorient and normalize survivorship," said Shari Brosnahan.

COVID-19 infections are more likely to have lingering symptoms than those with only mild acute illness. At present, the incidence of PACS is poorly understood but the symptoms linger – so far they have been observed for year. At ISICEM, Dr. Brosnahan will present data from her home institution.

Here, to determine whether symptoms improve or persist over time, researchers followed a prospective cohort of patients discharged after admission for severe COVID-19 to characterize overall health status, physical and mental health, and dyspnea at six months post-hospital discharge. They compared patients’ responses at six months post-hospital discharge to their responses a month after discharge, and to their reported baseline before COVID-19 illness. This study found that even six months after hospital discharge, most patients reported that their health had not returned to normal.

"This is just part of the larger context of what is being learned," said Dr. Brosnahan. "At present, the best evidence we have is a meta-analysis showing the relative rates of symptoms that exists for PACS," she said. In addition, another piece of research is in the works.

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research suggests PACS occurs in a greater number of patients who come to the ICU.

“Therefore, it’s not simply the treatment of illness or the acute host response that causes PACS,” said Dr. Brosnahan. “It is likely some patients with PICS are the same. It’s not just our treatment, but the underlying disease which causes the lingering symptoms.”

How to best control and monitor for these symptoms will be important in the future, said Dr. Brosnahan. However, the amount of symptomatology that happens as the result of treatment should not be underestimated, she said. “We as ICU providers must stay vigilant to minimize sedation, paralytics and to reorient and normalize survivorship.” The best way to do this is to work to the so-called ABCDEF bundle; Assess/prevent/manage pain; Breathing trials (spontaneous awakening and breathing); Choice of analgesia and sedation; Delirium – assess, prevent, and manage; Early mobility and exercise; Family engagement and empowerment.

In other words, Dr. Brosnahan believes clinicians need to do a better job of controlling for the cohort of patients who develop PACS after the ICU. “Given the need for ventilator synchrony and length of illness from acute COVID-19, many who wound up intubated were given large amounts of sedimenting medications, pain medication, and paralytics,” she said. “These drugs were then used for longer than we do with most of our ICU patients – even those with other causes of acute respiratory distress syndrome.

At present, the best approach to PACS appears to be a good multidisciplinary team focusing on symptom-triggered care. It’s also important to help normalize the recovery for the patient, and give hope that people seem to continue to get better.”

She added: “It is hopeful that we have seen people continue to improve between nine months to a year. But we don’t have data much further than that.”

Going forward, more resources will need to be channelled into this area. “I think the major challenge is how to effectively set all of this up quickly in a time when the medical community has been focused on acute COVID-19 infections,” she said. “The ability to orchestrate a follow-up and treatment clinic during the pandemic, when healthcare is already strapped, has been extraordinarily hard.”

In addition, more standardized, multicenter research is required to answer the questions being raised in such a short period of time. For example, the US’ National Institutes for Health (NIH) just funded the RECOVER initiative: REsearching COVID for Health (NIH) just funded the RECOVER initiative: REsearching COVID to Enhance Recovery, The initiative will look at key questions such as how recovery from SARS-CoV-2 infection changes among different groups, whether symptoms persist after acute infection, or if patients develop new symptoms after acute infection. It will investigate the health effects and why some people do not develop them, and it will look at whether COVID-19 infection triggers changes in the body that increase the risk of other conditions, such as chronic lung, heart, or brain disorders.

Dr. Brosnahan’s institution at NYU has been selected as the Clinical Science Core (CSC) for the NIH’s Post-Acute Sequelae of SARS-CoV-2 Infection Initiative. They will take the lead in building the RECOVER research consortium, harmonizing and coordinating data within the consortium, and developing methods for monitoring protocols, including recruitment, data quality, and safety measures to identify adverse events. The CSC also will guide communication and engagement efforts with key stakeholders, including patients and healthcare providers.

“Both PACS and PICS are in their infancy, and desperately need good physician–scientists to help,” stressed Dr. Brosnahan. “These are both diseases without a home – critical care doctors seldom deal with outpatients, and infectious-disease doctors don’t heal after the infection is gone. None of us are experts on our own; this will truly be a team effort.”

References

“Critical care doctors seldom deal with outpatients, and infectious-disease doctors don’t heal after the infection is gone.”

SHARI BROSNAHAN

Issue 2 of ISICEM News
Available Wednesday!
Improving early management of patients in the general ward

Challenges in the early management of patients on the conventional wards will be laid bare this morning by Marc Leone, Professor of Anesthesiology and Intensive Care Medicine at Hôpital Nord (Marseille, France). “Every day in hospitals around the world there are several patients in conventional units or wards requiring ICU care, and there is no strategy in place,” he told ISICEM News. Specifically, this morning Professor Leone will speak about a novel triaging technique for conventional ward patients in need of ICU treatment.

Strategies to triage patients presenting at the emergency department from outside the hospital are well established, he said, but somewhere in hospital, the quality of early management for patients on the general wards is poor.

Indeed, early management of ward patients is rarely practiced, and severely understudied, particularly in Europe.

“In the US there are some mobile teams which are quite involved in the general wards, but in Europe that is less the case,” said Professor Leone.

That’s why he and his team began to think about training resident and senior doctors in point-of-care ultrasound (POCUS), developing algorithms to better manage patients. “With the assistance of ultrasound, and a few very simple images, intensivists are able to decide the best triage for patients, including whether ‘to ICU, or not to ICU, and what treatments should come first,’” he said.

Crucially, the team created algorithms designed to spot the warning signs for acute respiratory failure and cardiac failure. “Quite often, the picture is acute respiratory failure and acute cardiac failure,” noted Professor Leone. “So, with a little bit of training in algorithms, we can greatly improve practice.”

Today, Professor Leone will present a quasi-randomized study based on research at his hospital in Marseille. Recently published, the results have been compelling. “We showed a strong association between improved outcomes in the patients in the ultrasound group compared with the control group,” he said.

Patients in the ultrasound group had better survival rates, required less invasive procedures/ventilation, less medication (systemic steroids, vasopressors) and spent less time in the ICU. ICU mortality rates were 11% in the POCUS group and 25% in the control group (p = 0.04). In-hospital mortality rates were 17% in the POCUS group and more than double, at 35%, in the control group (p = 0.007).

“It seems that the use of ultrasound, along with training, is associated with improved outcomes – and that’s just an association, because there is no true randomization,” commented Professor Leone. “When you look at the mortality rate at day 28 in the control group, it’s 35%. That’s fairly huge.” The method looks to be consistent too, noted Professor Leone; the team used different statistical approaches to analyze the data, and each time the training and use of ultrasound were associated with improved outcomes.

“That the area of conventional ward triage is so understudied might be because it requires a transversal approach, continued Professor Leone. “They are not ICU patients, and they are not inside the ICU. As such, they are not under an intensivist’s care. It’s a kind of gray area in the hospital.”

For his study, Professor Leone also had a distinct focus on technology. This kind of triage is only made possible because of a new generation of portable, handheld ultrasound devices. “These are very small, easy to keep in the pocket, and can be readily used all over the hospital. They have good resolution too, so you can obtain some very relevant data from the images,” he said. “Five years ago, these devices were not on the market.”

Professor Leone says there is something of an emerging interest in the use of this technology. However, at €10,000, the cost of a device may be a barrier for some institutions. Yet, Professor Leone suggests the cost is justifiable when compared to other costs in the ICU. In France, a daily ICU stay for a patient costs around €3,000, and is likely to be similar in other European countries. “I think that if we can save lives, and if we can reduce ICU stay by several days, then such a device will ‘reimburse’ itself very quickly,” he explained.

But the devices are not the only reason for the results they saw in the research, continued Professor Leone. “I really think that the technology drives the study, but also we have to consider the training and algorithms that we built to improve our practice,” he said. “We need to formalize or protocolize early management, and that’s probably as important as the use of the technology.” For example, such training enables the management of a patient showing a B-line at lung level, and gives them very early diuretics.

Ultimately, individual hospitals will have to devise a way in which such devices, training and algorithms can be optimally used. “Is the physician using the device going to be in a conventional ward, or do you have a dedicated group for mobile team triage?” he asked. At Professor Leone’s hospital, a group is available at the ICU 24 hours a day, visiting general wards with the devices as required. But other hospitals’ strategies may vary. “Would it be too resource intensive for some?”

Going forward, Professor Leone would like to see multicenter randomized controlled trials of the technology, in conjunction with training and use of algorithms. Crucially, there is a need to eliminate any center-based effect. “We need to confirm these good results in terms of outcomes first,” he explained. “If it is confirmed that the device could be used for routine patients, it could be implemented in each institution.”

Before such a study is completed, Professor Leone advises delegates to consider more ways to ensure early management of patients in general wards. “We suggest the use of this technology, with appropriate training; but we also need new ideas to improve the management of conventional ward patients with organ failure. We need to improve outcomes via early management,” he concluded.

“I think that if we can save lives, and if we can reduce ICU stay by several days, then [handheld ultrasound] will ‘reimburse’ itself very quickly.”

Marc Leone

References
Corticosteroids under the microscope

Approximately to corticosteroids should change in critical care. That is the thought-provoking message from Greet Van den Berghe, Head of the Department and Laboratory of Intensive Care Medicine at the KU Leuven University in Belgium. Her research focuses on endocrine and metabolic alterations during critical illness in adults and children.

Tomorrow morning, Professor Van den Berghe will be talking about critical illness-related corticosteroid insufficiency. “There is controversy ongoing, and with COVID-19 this topic is high on the agenda again,” she said. “That’s because guidelines advise to use corticosteroids as an immune-modulating, anti-inflammatory drug for this disease.

“Clinicians often use corticosteroids as a symptomatic intervention that increases blood pressure, and that is often considered a ‘good’ thing, whereas we advise a more conservative use of corticosteroids.”

Broadly, Professor Van den Berghe will discuss the so-called fight-or-flight response to critical illness. This relies on increased systemic cortisol availability, traditionally attributed to several-fold increased cortisol production via an activated hypothalamus-pituitary-adrenal (HPA) axis, which is essential for survival in critical illnesses. “However, recent studies provide evidence against this concept,” she explained. “I will discuss these new insights and explain the clinical implications.”

Specifically, Professor Van den Berghe will discuss the key role of cortisol in controlling inflammation and essential metabolic substrates, for fluid retention, and in the activation of the cardiovascular system to increase blood pressure and cardiac output. “For decades it has been understood that when patients cannot mount an HPA-axis activation in response to illness, survival is seriously threatened,” she explained.

Beyond the context of critical illness, however, adrenal failure can be due to pathology in one of the three levels of the HPA axis, noted Professor Van den Berghe. Primary adrenal failure refers to disease within the adrenal cortex, secondary adrenal failure to disease within the anterior pituitary gland, and tertiary adrenal failure to disease within the hypothalamus. Crucially, all three conditions present with low plasma cortisol, whereas only primary adrenal failure reveals increased plasma adrenocorticotropic hormone (ACTH) due to loss of feedback inhibition. “The two central forms of adrenal failure show low plasma ACTH, and low plasma cortisol, thus allowing differential diagnosis,” she said.

“Although such ‘absolute’ failure of the HPA axis can be a cause of critical illness when not treated promptly and adequately, in the context of critical care medicine, the highly debated question is, can this system partially fail in patients suffering from other conditions?” questioned Professor Van den Berghe.

Of relevance to the discussion is the history of the term ‘relative adrenal failure’. Over twenty years ago, it would refer to patients suffering from septic shock who would have a maximally activated HPA axis, and thus adrenal cortex, which does not result in sufficiently high systemic cortisol availability for survival. Later, the concept was broadened to a relative failure of the entire HPA axis, which could also involve a failure of the anterior pituitary gland or the hypothalamus, besides the adrenal cortex. “The condition was then also re-named as ‘critical illness-induced corticosteroid insufficiency’, or ‘critical illness-induced corticosteroid insufficiency’, noted Professor Van den Berghe.

Almost a decade ago, Professor Van den Berghe’s research group began a series of pathophysiological studies of abdominal sepsis in patients, as well as in a validated experimental mouse model. The idea behind the studies was to question whether this relative adrenal failure or critical illness-induced corticosteroid insufficiency really represents a failure of the HPA-axis stress response, or not. “We had hypothesized that what was reported in studies could be also interpreted differently,” she said. Importantly, recent novel insights into the response of the HPA axis to acute and prolonged critical illnesses have challenged the concept of relative adrenal failure or critical illness-induced corticosteroid insufficiency, as currently defined, as well as the current practice guidelines for its diagnosis and treatment, stressed Professor Van den Berghe.

This new conceptual framework she’ll describe opens up opportunities for further research into preventive and therapeutic innovations. “The results from our recent work have generated a fresh perspective on how to interpret the HPA-axis response to the stress of critical illness, on its changes over time, and on the concept of relative adrenal failure or critical illness-induced corticosteroid insufficiency,” she said.

Professor Van den Berghe will discuss several published insights during her session. “One concerns dosing. “It is clear that all acute critically ill patients have high-free cortisol availability, which is predominately explained by low cortisol-binding proteins and reduced cortisol enzymatic breakdown, rather than by substantially increased adrenocortical cortisol production and secretion,” she explained. “That knowledge is important for determining the optimal dose of hydrocortisone for any suspected ‘absolute’ adrenal failure in the ICU.”

For example, absolute adrenal failure due to adrenal hemorrhage – or in the context of suspected central adrenal failure in prolonged critical illness – may require a dose that is likely much lower than that historically prescribed, i.e. 30–60 mg/day versus 200–300 mg/day, she said.

Another factor of high clinical relevance, said Professor Van den Berghe, is that the cosyntrropin (a synthetic derivative of the adrenocorticotropic hormone) test is not suitable to investigate adrenocortical integrity, or reserve, in critically ill patients. “In this context, the test is highly confounded by the increased cortisol distribution volume,” she said.

Together, the novel insights she will outline should provide a solid basis for further pre-clinical and clinical research focusing on the need, if any, and the timing of treatment of ICU patients with corticosteroids.

References
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WHY IS PLASMA IMPORTANT?

Human plasma is the unique and indispensable starting material for the manufacturing of PDMPs.

300,000 patients across Europe rely on PDMPs to treat a variety of rare, serious, chronic, many times genetic diseases and often severe, life-threatening medical conditions.

For individuals with these conditions, PDMPs replace their missing or deficient proteins.

Without these treatments, many patients would either not be able to survive or would have a substantially diminished quality of life and productivity.

Every year, more plasma donations are needed to meet the growing clinical need for PDMPs.

It is worth noting that it takes more than 130 donations per year to treat a single patient with a primary immune deficiency.

Each year it takes more than 900 plasma donations to treat 1 person living with alpha-1 antitrypsin deficiency.

It takes more than 1,200 donations to treat 1 person living with Hemophilia A for 1 year.

WHERE DOES PLASMA COME FROM IN EUROPE?

Plasma cannot be made artificially in a lab. Plasma and its lifesaving proteins can only be obtained from healthy donors who generously give their time to donate. Plasma can be obtained from whole blood donations (recovered plasma) or collected directly through a process called plasmapheresis (source plasma).

40% of plasma in Europe is collected by public and NGO blood-collection services.

30% of plasma imported in Europe is collected in the United States.

30% of plasma in Europe is collected through plasmapheresis by the private sector.

Plasma donations were in some decline this year due to the ongoing COVID-19 pandemic. The existing insufficient availability of European plasma coupled with declines in donations have the potential to restrict patients’ access to plasma-derived therapies.

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If you want to ask policymakers to put in place the most appropriate EU or national policy frameworks leading to significantly increased plasma collection in Europe.

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