See you next year!

Thank you all for making ISICEM 2016 a resounding success. We look forward to welcoming you again in 2017!

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Sepsis: 2026

A plenary lecture that took a journey through how we may treat sepsis in 10 years was featured on Wednesday evening, with Steven Opal (Rhode Island Hospital, Providence, RI, USA) stepping up to speak about the expectations, hopes and remaining challenges in the field.

In his opening slides, Dr Opal relayed the current burden of sepsis, stressing that it now is estimated at a global level of 31.5/19.4-million sepsis/severe-sepsis cases worldwide, with potentially 5.3-millions deaths annually.1

Framing the most pressing issue, he said: “Of course we are really in a difficult situation right now. We have got an impressive number of microbial pathogens who have acquired the capacity to resist our antibiotics.”

He added: “It is likely that we will continue to have problems. Some say it will get better, some say it will get worse – I’m not sure, but it is not going to go away, and will remain a major challenge for us over the next 10 years.”

Moving on to touch upon the third international consensus definition for sepsis and septic shock (‘Sepsis-3’), now published,2 he said: “It makes some points which are worth at least considering as we approach this problem.

“The definition of infection is the interaction with a microorganism that induces a local or systemic host response. If you don’t have any host response, most likely it is a colonization. Secondly, the term ‘sepsis’ should probably be reserved for what was previously known as ‘severe sepsis’, and that is a dysfunctional host response to infection which results in organ dysfunction remote from the site of the initial function.”

Speaking about ‘septic shock’, he added: “It is basically sepsis complicated by cardiovascular dysfunction, which will need vasopressors to maintain [adequate] circulation, and also an elevation of lactate.”

For infection, Dr Opal stressed that it is critical that we have rapid microbial diagnostics – with a genomic approach being hopefully established in the next 10 years. “For sepsis, we need to come up with better and earlier markers to determine who is getting into trouble,” he said. “And what are those early indicators of organ dysfunction that we should focus on, and what biomarkers might we use to make an early diagnosis of patients who are becoming septic.

“As far as septic shock goes, we need to come up with a better strategy to protect the endothelium.”

Delving deeper into microbial diagnostics, Dr Opal first cautioned that current standard diagnostics using cultures takes around 60 hours to complete, “which is way too long,” he said. “When you’re dealing with septic shock, you can’t wait for nearly three days to know what the organism is, and how to treat it.”

What will arguably save the most time, he added, was the use of amplification-based systems where you can take the blood directly from the patient, and use a PCR system to amplify the system of microbial genomes, and then make your diagnosis from there.

After emphasizing that another caveat of culture-based methods is that they rapidly disappear following antibiotic administration, and therefore lose their diagnostic capability (unlike PCR, which will remain viable for hours), Dr Opal cited a paper from Jean-Louis Vincent and colleagues on the use of PCR/electrospray ionization-mass spectrometry for rapid pathogen identification in 529 patients (616 paired samples). 3

“This takes blood directly from the patient, the samples are amplified, and then the nucleotide content of amplified genomic fragments from the bacteria are then analyzed via mass spectrometry [MS], and you then put it through an algorithm to determine what the organism would be,” he said.

Relaying the results, Dr Opal noted that using MS, there was a 37% positivity rate, versus 11% for culture comparisons. “And the mass spectrometry missed only 13 organisms, and resulted took about six hours, which isn’t bad,” he said.

“But what was particularly interesting, the top three organisms that were found in this clinical study to show about a 50% increase in yield with mass spectrometry were E. coli, staphylococcus aureus and enterococcus faecium – so these are not obscure microorganisms you have never heard about, these are common organisms, and all three of them would be of great importance for you to know about.”

He added: “So I think this shows the potential value, rather than waiting for a culture, particularly in patients who may have already received an antibiotic.”

Antibiotic resistance
As Dr Opal described, in the present day, there are multiple mechanisms of resistance against each antibiotic, thus there is pressing need to figure out optimal ways to combat microbials.

Introducing several different methods, he began with the concept of going after the toxicity of bacteria via injectable artificial liposomes that are tailored to effectively compete with host cells for toxin binding.4 “This is an interesting idea,” said Dr Opal. He continued: “I think we will also see an increased use of an old idea, which is using antibodies – i.e. designed monoclonal antibodies with very specific characteristics, and using them in combination with antibiotics as a support.”
Phage therapy was also detailed, in which bacteriophages — viruses that infect and replicate within bacteria — are employed to lyse bacteria without harming the host. “Once they rid the host of all the bacteria they are simply passed out in the urine and in the stool,” explained Dr Opal.

“Hundreds of thousands of patients over the last 100 years have received phage therapy, so it is not like it is a new idea, but it is catching interest because it is maybe able to bridge us along.”

Another important aspect that Dr Opal focused upon was how to discriminate between infection-positive and infection-negative systemic inflammation. Citing a paper by McHugh et al., he outlined how they were able to identify four genes (CEACAM4, LAMP1, PLA2G7, and PLAC8) that when used together were highly effective at distinguishing infectious inflammation from non-infectious inflammation.

“It looks very promising, and we will see how this holds over time,” said Dr Opal.

Organ dysfunction

An important section of his presentation was dedicated to early diagnosis of organ dysfunction, as he explained: “A great need now in sepsis research is defining those individuals who have an infection and are doing okay, versus those patients who are developing early organ dysfunction, and a dysfunctional host response.

He added that one of the challenges is that we need assays that can detect very small levels of proteins in very dilute solution that will contain lots of other different proteins. Aptamers could be one solution — RNA sequences of about 50-150 oligonucleotides which function like monoclonal antibodies. “When you link them with an optimized reporter sequence, you can come up with what is known as an immune-aptamer,” he said, noting that this would permit antibody-like specificity, but with the ability to measure as incredibly low zeptomolar (10-21) concentrations.

“Last but not least we need to have ways of protecting the endothelium,” said Dr Opal, adding: “There is a whole cascade of new agents being studied that are going to be designed to predict the endothelium from injury, and try to repair tight junctions and endothelial surfaces.”

Sepsis in 2026

In his closing remarks, Dr Opal gave an outlook of what sepsis management might be like in 10-years time. Beginning with his expectations, he first reiterated that fast, accurate and sensitive molecular microbial diagnostics will displace cultures.

He went on: “Treating pathogens will be more precise but more complicated; rapid genomics will be readily available and used to assess host response (SNPs and gene expression); and (there will be a) new generation of early organ injury markers.”

Lastly, he focused on less-certain “hopes” for the future, saying: “I am hopeful that we will have micro- and nanoscale lab-on-chip technology that will deliver the information that we need, essentially at the bedside … we have got to the point now where these are so good, and not very expensive.”

He added that “eventually” we will figure out how to assess antibiotic resistance — although replacing standard antibiotic resistance testing with genetic arrays will not be easy — and he was also hopeful that microbiome analyses will be readily available for diagnosis and infection prevention. He concluded: “I am hopeful that we will have a large number of sepsis drugs to improve outcomes in specific patients.”

References
Danger! A confounding story for Big Data

Delegates packed into the Arc Room on Wednesday morning for a series of sessions dedicated to clinical trials, focusing on topics including ‘big data’, as well as recommendations for best study outcomes. In his presentation, Theodore Iwashyna (Ann Arbor VA Center for Clinical Management Research, Michigan, USA) walked the audience through the dangers of big data, stressing that, in many cases, we are simply providing increasingly confident wrong answers.

As Dr Iwashyna and colleagues noted in a paper on the topic, when clinicians administer different treatments to sicker patients, any treatment comparisons will be confounded by differences in severity of illness between patients. This ‘threat’ stems from patients being given therapies doctors think are better for them, rather than true randomization (a.k.a. a ‘coin flip’). It follows that the severity of illness is the factor driving the decision, thus there is the chance that ‘confounding by indication’ can be observed.

“That is what you call it when it is bothering you,” said Dr Iwashyna, noting that when this does not cause an issue, he would refer to it as “clinicians using their judgement.”

He added: “That is precisely the thing that we want, and we value, because our entire system is designed for clinician’s to use their judgement. But that is one of the challenges we will always have for observational data.”

To illustrate this simple yet powerful flaw in observational data, he showed comparative pictures of a child in the intensive care unit, versus a child receiving what appeared to be a simple adhesive bandage for a minor cut. The inference, he argued, could be that — should both children be entered into a comparative trial for mortality from infection — an adhesive bandage was 100% likely to protect from infection, but of course this would be a ridiculous interpretation.

Although a exaggerated example, it does demonstrate the profound effect of confounding. “The solution for this is risk adjustment,” he said.

Indeed, to overcome confounding, there are sophisticated methods such as severity of illness risk-adjusters, e.g. AUROC – utilizing the Area Under the Receiver Operating Characteristic (ROC) curve. This can allow ‘high’ values such as 0.8–0.9 in ICU patients, but unfortunately may also report lower values, especially with external validation, or with replacement by less-accurate comorbidity adjustment scores such as the Charlson index.

But, as Dr Iwashyna described, one potential benefit of ‘big data’ is that it allows us to measure more data points, and hopefully diminish confounding: “The question is, are we there yet?” he said.

Framing a typical scenario, Dr Iwashyna used the example of midazolam — recalling that there have been several papers in the last few years showing that patients receive more midazolam consistently do worse. “That has been based almost entirely on observational data showing that, after you control for enough things, people who get more benzodiazepines do worse … I have no opinion on whether benzodiazepines are deleterious … I am just trying to use this as a motivational example!”

Moving on to share different hypothetical/simulated trials to investigate how confounding affects results – which was the focus of the aforementioned paper he co-authored – Dr Iwashyna began with a scenario using a hypothetical drug with an odds ratio (OR) of 1.0 – i.e. in reality, no effect. In this situation, medical conclusions could make one of two conclusions: a) correctly conclude the treatment had no association with mortality, or b) incorrectly conclude the treatment was harmful.

Dr Iwashyna questioned: How good would the risk adjuster have to be, and how often will you get a study that shows false harm?

In a study population of 1,000, even when no confounding was present, the treatment was deemed harmful 5% of the time, in-line with the threshold for statistical significance (P = 0.05). Further exploring how results would shape up with either a ‘low’ or ‘high’ confounding, the effect of risk-adjustment with AUROC was investigated.

With values ranging from 0.6 (which Dr Iwashyna described as being comparable to a Charlson index value), to 0.76 (more akin to “decent” APACHE II scores), put briefly, a higher risk-adjuster value led to fewer studies demonstrating harm. More specifically, at a value of 0.70, for example, approximately 50% of studies (at n=1,000) in the low confounding group would report a statistically significant harm from what is, in reality, a truly safe treatment. This escalates to almost 90% in the high confounding scenario.

Testing the same hypothetical scenario with 10,000 patients, Dr Iwashyna cautioned that while one might think it would produce better results, instead it could inflate the confounding effect: “If you don’t turn up the risk adjustment, what you turn up here is the just the ability to publish your confounding … with much better levels of accuracy,” said Dr Iwashyna.

Indeed, for n=10,000, both low and high confounding groups would already be producing 100% ‘harmful’ study outcomes at a risk-adjuster value of 0.70. “So you are now publishing a strong study showing that this, in truth, completely [benign] drug that you just happened to give sicker people, looks like it is harming them.”

Moving on to other examples using drugs that are markedly- or very beneficial (OC = 0.8/0.6 respectively), in these examples the simulator studies could make one of three conclusions: a) a statistically significant benefit (accurate); b) no effect (false negative); and c) statistically significant harm (false harm).

A similar picture could be seen in the outcomes of these scenarios as well. In all stages, a higher risk-adjustment would produce more accurate results, but looking at specifics, for either-sized population, increasing...
The debate continues: hypoperfusion versus inflammation in AKI

In a session dedicated to the topic of kidney failure and recovery, held yesterday morning, a number of aspects of pathogenesis and therapy were discussed. A look at the roles of perfusion and inflammation preceded a talk by Didier Payen (Hôpitaux Universitaires Saint Louis - Lantiboisier, Paris, France), who argued that multiple factors should be considered together in the understanding of acute kidney injury (AKI).

The key, said Dr Payen, is in looking at the factors that feed into the disruptions in microcirculation that bring about symptoms of AKI.

Speaking to ISICEM News before his presentation, he described the questions underpinning the session: “The issue is just to respect the fact that AKI is not so perfectly settled: that is, when you have AKI, is this related to hemodynamic issues first, or to inflammatory issues?”

“These two approaches are the most important potential mechanisms underlying AKI in acute situations. The presentation [focuses on] the relatively modest impact of hypoperfusion by the reduction in renal blood flow and pressure, and the relatively high role of venous congestion, that may participate in AKI.

“I will then spend two-thirds of my talk on inflammation, which can alter renal function by the urinary filtration of mediators and substances activating the inflammation; then, on the blood side of the kidney, having some infiltration by immune cells, which may in turn alter renal function and tubular function.”

“The approach to inflammation is to know if you have immune cell modifications in the blood which may be related to the renal function or dysfunction.”

The activation of immune cells and the infiltration of inflammatory mediators have a disruptive effect on renal homeostasis, leading to the departure from normal renal tubular function and altered glomerular filtration. But the role of inflammation does not preclude the involvement of hemodynamic factors, hypoperfusion and ischemia, explained Dr Payen.

“Rather, such factors can too feed into and propagate the processes of tubular damage: “These modifications of the kidney are at the microcirculation level, and at the microcirculation level you see abnormal microperfusion,” he said. “But this abnormal microperfusion is related to interactions between endothelial cells and immune cells; and you [end up with] microclots and platelet clotting. But of course, if you have clotting in the microvessels, the vessel does not flow any more. So you can have some perfusion parameters that may tell you that something is happening in terms of inflammatory conflict.”

On the topic of what the study of mediators of inflammation that go on to disrupt renal tubular function could yield, he continued: “For the moment, it is difficult to say, with different molecules or mediators that might be changed or induced by the occurrence of AKI, that if you block this one or stimulate that one that you will change the outcome of AKI. For the moment, nobody can say that – it is too early.

“The issue is just to respect the fact that AKI is an inflammatory dysfunction, and that this dysfunction may even be protective for the tissue – who knows – and that stopping its function might be beneficial for the organ, protecting it. If the organ continues to work, filtrating and creating urine with abnormal tubular cells might be dangerous for these tubular cells to continue to work in a bad environment.”

References

“How do the kidneys fail... and recover? 100 Hall Thursday 08:00

The debate continues: hypoperfusion versus inflammation in AKI

"Neither data nor computing will reduce the need for well-formulated questions and meticulous attention to detail in the search for truth."

Theodore Iwashyna

While more detailed treatment on how risk-adjustment may be calculated and utilized is reserved for the paper itself, Dr Iwashyna offered a conclusion about the era of big data: “It’s a brave new world. Massive amounts of incidentally generated data and new computing possibilities are transforming how we do research, practice, and evaluate quality of care. But neither data nor computing will reduce the need for well-formulated questions and meticulous attention to detail in the search for truth.”

References
DOAC reversal enters the arena

The direct oral anticoagulants (DOACs) emerged into broad clinical usage despite a limited number of specific reversal strategies. But this is no longer the case, says Menno Huisman (Leiden University Medical Center, the Netherlands), who presents the latest on the topic during this morning’s session on massive bleeding.

“There is exciting development,” said Dr Huisman to ISICEM News. “There is now one product, registered and available, which is the specific antidote against dabigatran’s anticoagulant activity – idarucizumab.”

A monoclonal antibody fragment, idarucizumab avidly binds dabigatran, both free and thrombin-bound, and consequently renders it ineffective. It is currently under evaluation in a cohort study of very severely bleeding patients, including those with intracranial hemorrhage and patients needing urgent interventions with a high bleed risk.

In a phase III study, RE-VERSE AD, in two cohorts of patients either presenting with severe life-threatening bleeding or the need for urgent operation with high bleeding risk, the safety and the maximum reversal capacity of 5 g of idarucizumab was evaluated upon the anticoagulant effect of dabigatran within four hours of its administration, based on the laboratory determination of diluted thrombin time (dTT) or ecarin clotting time (ECT). Restoration of hemostasis formed a secondary endpoint.

Interim results from RE-VERSE AD, featuring its first 90 patients, were published last year by Pollack et al. in the New England Journal of Medicine, and included 51 patients who were administered the agent due to serious bleeding, and 39 due to an urgent procedure. The study demonstrated a rapid, complete reversal of anticoagulant effect in 88 to 98% of those enrolled patients who had elevated clotting times at baseline. Among the 36 patients who underwent an operation, hemostasis was reported as normal in 92% of patients (mild to moderate in the remaining 8%).

“This is not a clinical outcome study, because that needs very large numbers of patients,” commented Dr Huisman. “But it has been evaluated by FDA and EMA, and they concluded that you can give this to patients needing this reversal. And it is working well in terms of a very short action of a complete normalization of coagulation tests, which had been prolonged due to dabigatran activity.”

Reversal of direct Xa inhibitors, such as apixaban, rivaroxaban, and edoxaban, is also currently being studied, noted Dr Huisman: “There is a drug – andexanet [alfa] – but it is still under evaluation; it is not registered.”

Andexanet alfa affects Xa inhibitors by binding to the active site of Xa inhibitor molecules with high affinity. The expectation is that andexanet alfa, which is currently undergoing fast-track evaluation at the FDA and EMA in the coming months, will be available for clinical use during the course of 2017.

The recently-published results of its preliminary studies, ANNEXA-A and ANNEXA-R, demonstrated its efficacy in reversing the anticoagulant activity of either apixaban or rivaroxaban in older patients. In the two-part trial, 101 patients were randomized to either andexanet or placebo. In apixaban patients administered andexanet alfa, anti-factor Xa activity was reduced by 94%, and by 92% in rivaroxaban patients (compared with 21% and 18%, respectively, in those given placebo).

This work has formed the basis of the ANNEXA-4 trial, whose estimated primary completion date is 2022. The prospective, open-label study looks at patients receiving a factor Xa inhibitor who have acute major bleeding.

FDA and EMA approval for andexanet is earnestly awaited, but in the interim we must continue to rely on the so-called ‘old’ ways of antagonizing or replenishing, said Dr Huisman. These include pro-hemostatic therapies such as prothrombin complex concentrate (PCC) in addition to other supportive measures, which suffice in the absence of more specific agents.

“For the Xa blockers, PCC seems to work quite well,” he noted. “We don’t know the mechanism, but outcome of bleedings is not much different from the vitamin K-antagonist-associated bleedings.”

“The good news is that, when renal function is adequate, the Xa blockers and dabigatran have a short half-life. So when you stop the drug, the anticoagulant action will wane away quickly itself. This is where we are right now.”

In the absence of reversal agents, certain protocols are in place in addition to reversal agents to produce best outcomes, explained Dr Huisman: “You have to find the origin of the bleeding – of course this is well known but it is very important. So when there is, for instance, gastrointestinal massive bleeding, you have to go to where the lesion is by endoscopic procedure. And then you have to give red blood concentrations, you have to give blood platelets, replenish with fresh frozen plasma. These are the normal, classic procedures.”

Asked whether the routine use of monitoring assays will ever form a part of DOAC management strategies, Dr Huisman was clear: “Not at all. The new anticoagulants are very straightforward in their action, and this is very expected in every patient but the extreme ones, such as extreme obese patients. We do not advocate monitoring – it is not needed. That is a big advantage over vitamin K antagonists.

“In patients presenting with massive bleeding, laboratory testing is useful if you have the time; otherwise it takes too long. If a patient comes in with what seems to be dabigatran-associated intracranial hemorrhage, we do not await coagulation tests. We may measure them for a post-hoc knowledge of what has been going on. So the laboratory tests have a moderate role in the new anticoagulant world.”

The RE-VERSE AD trial is well on the way to recruiting its hoped-for 500 patients.
Antibiotic resistance: A political bugbear?

The worrisome increase in the rate of multi-drug-resistant (MDR) organisms is a global concern, and one that does not discriminate between richer or poorer economies — although the problem is indeed costly in more than one respect. A session this morning examines at length the possible strategies that we could and should be adopting in hospitals, in the laboratory, and in the corridors of power. Discussing the political issues surrounding the battle against MDR organisms will be Djillali Annane (Raymond Poincaré Hospital, Garches, France), who concludes the session. In an interview with ISICEM News, he shared the main points of his presentation.

Regarding political interest in the issue of antibiotic resistance, what involvement do we currently see on the global and national levels? The World Health Organization (WHO) has already, on several occasions, alarmed governments about this issue. Subsequently, antibiotic resistance was put on the agenda of the G7 summit. Last year at the G7 summit, concerns rose about the rising incidence of antibiotic resistance, and they mandated their ministers of health to work on this issue. Last October, the G7 summit of the ministers of health put the Ebola crisis and MDR as the two main topics on their agenda.

They shared a number of ideas, and they also shared what they are doing in their own countries. In France, the minister for health Marisol Touraine mandated Professor Jean Carlet to work on recommendations for France to fight against MDR. The prime minister of France has taken this issue on his own agenda, and next spring there will be an inter-ministerial committee in France that will establish a number of actions that France will take to handle the issue.

Germany, Japan, and the US government have also initiated such plans. And among the issues they are working on is how to promote innovation, both in terms of discovering new molecules and in terms of improving the fast diagnosis of bacterial infections.

A recent WHO report noted other areas of importance that could be better regulated, such as quality assurance in drug manufacture, public awareness and the correction of the misuse of medicine. There are obviously a lot of difficulties here conflated by the need for cheap access to medicines for poorer economies. How can these be tackled? This is an important issue. It has been recognized that the fight against antibiotic resistance can only be a success if there is global involvement, and also by taking into account agricultural issues and veterinarian issues — in what is called the One Health global action. More than 100 countries have so far endorsed the One Health global plan, which gathers countries from different parts of the world (regardless of each country’s resources) to integrate actions towards agricultures and animal care and actions towards human beings.

At the G7 meeting in Berlin, ministers of health were discussing the obligation of limiting the prescription of antibiotics in animal care, and the obligations of restricting the duration of antibiotic use in both animal and human care. This is a key point in the fight against antibiotic resistance.

From your standpoint, in what ways could and should politicians be more involved? There are two major issues. One issue is to get, as much as possible, laypeople to not ask for antibiotics, even though it is not a bacterial infection. Here, there is a point for accurate communication towards lay people, to let them know that antibiotics are not automatic, and even that they might be dangerous. That is one major way, and that would be likely the most efficient way to reduce antibiotic consumption.

The second key pathway is in restimulating industries to invest in the development of new molecules. These could be antibiotics, or new types of molecules, that may help to solve the issue of MDR bacteria. These are the two major points. Just to take the point of view of a CEO of a big company: why would he or she invest to develop new molecules for conditions for which national governments and regulatory agencies will restrict the use? So there is no market. So why invest in something which there is no market? This is something that regulatory agencies and governments need to think about: how to find a new business model to make the development of new molecules attractive for industry.

Despite this, can we be optimistic? One thing that is very important and warrants optimism is that when you apply the plan, you will get a reduction of antibiotic use. I will present some data from France, from the veterinary side, where the implementation of the One Health global policy was associated with a 50% reduction in the use of antibiotics for animal care in France, within a four-year period. So implementing a plan is efficient.

Second, of course, there are public-private consortia that are currently working on developing new molecules for preventing or treating bacterial infection. There is large funding from the EC for this type of consortia for developing these new molecules, I will likely cite some examples in my talk of new molecules that may prevent Staphylococcus aureus infection in the lung, or similar infection in the lung. There are also types of molecules that I will mention — they have been developed by a very small young company (Eligo Bioscience) and they have invented the so-called “eligobiotics” (which are not antibiotics) that apparently are extremely efficient in preventing the development of MDR bacteria. So there are hopes. A third point is that the UN has put this issue on its own agenda. The next general assembly of the UN will discuss the issue and the importance of fighting against antibiotic resistance. The WHO has limited concrete resources, but the UN has the power for obligation towards nations to follow rules, and it has the power to control diseases. The Ebola crisis is a good illustration of that; things where changed at the time when the UN took it up on its agenda.

References

The latest on targeted hemostatic therapy in the emergency setting

Yesterday afternoon's CSL Behring-sponsored symposium on targeted hemostatic therapy brought together a number of experts in the fields of hemostasis, anesthesiology, trauma and intensive care medicine, examining current and future advances in the management of bleeding in the emergency setting.

Fibrinogen concentration in the initial resuscitation of severe trauma

Barto Nascimento (University of Toronto, Canada) presented the results of a recently-completed randomized-controlled trial (RCT), FiiRST (Fibrinogen in the initial Resuscitation of Severe Trauma), which provides evidence that fibrinogen concentration can be delivered rapidly to bleeding trauma patients as part of initial resuscitation. Bleeding and coagulopathy remains the number one cause of death in trauma. Most hemorrhagic deaths in trauma happen in the few first hours of hospitalization, meaning that everything you do to a bleeding trauma patient needs to be very, very quick.  

Fibrinogen depletion of course occurs due to factors surrounding trauma, including blood loss, hypothermia, and others, explained Dr Nascimento. Hypofibrinogenemia is common, occurring in around 80% of trauma patients, he added, citing his center’s own data; furthermore, low fibrinogen levels on admission are associated with increased rates of transfusion, bleeding and death.  

“{'There is no RCT published in trauma showing that, if you give fibrinogen upfront, it improves coagulopathy, reduces bleeding and improves survival rates in trauma. In fact, the most recent European guidelines say that you have to aim for a higher fibrinogen level.”'}

In North America, fibrinogen concentration is not licensed for trauma, and cryoprecipitate represents the standard of care. However, cryoprecipitate may have to be thawed, pooled and diluted before use, explained Dr Nascimento, delaying the time to fibrinogen replacement that is so critical to survival. The FiiRST feasibility RCT results are expected to be published shortly. The blinded study included patients at risk of bleeding and bleeding trauma patients, defined by blunt and penetrating hypotension (≤100 mmHg) at any time from injury until 30 minutes after their admission and the ordering of blood transfusion. These patients were assigned to receive either placebo or 6 grams of fibrinogen concentrate within one hour of admission. Because of the narrow window of recruitment, 50 patients out of a total of 1061 screened were randomized. 95.6% of patients received the study intervention within one hour of hospital arrival, demonstrating the feasibility of the use of fibrinogen concentrate. No difference was found in time to infusion between the two study arms. Plasma fibrinogen concentrations differed significantly at three hours after administration, with 1.8g/L in the placebo arm and 2.9g/L in the intervention arm (p<0.01). “You can maintain hemostasis and fibrinogen levels higher throughout resuscitation if you use upfront fibrinogen concentrate in these trauma patients,” commented Dr Nascimento, adding that this difference was no longer apparent after 12 hours – which is significant with respect to avoiding thromboembolic events. “This was a small study,” he stressed. “It was not powered to show any differences in clinical endpoints. You cannot make any definitive conclusions, but at least you had enough data to show that we can study this drug further, and that is what we are planning to do. But there were no safety concerns.”

Treatment of trauma-induced coagulopathy using factor concentrates and/or fresh frozen plasma

Dietmar Fries (Medical University Innsbruck, Austria) followed to describe the latest knowledge on the use of factor concentrates versus fresh frozen plasma (FFP). In a publication from Karim Brohi1, he showed that mortality increased by more or less 100% when your patient is, additionally to his injury, coagulopathic,” he began. “So we are at a cornerstone. We can move on with a 1:1:1 ratio, and there are some good arguments to do that.”

“However, side effects are that plasma is not very effective; you have a time delay, you have to perform a prophylactic transfusion in your patients. On the other side, there is targeted transfusion management, where you just replace what the patient needs, but you have to measure what you give.” Dr Fries explained that, compared to whole blood, transfusions of FFP/red blood cell (RBC)/platelets conter reduced platelet counts, coagulation factors and fibrinogen concentrations. He added that massive trauma protocols cannot avoid low fibrinogen and, consequentially, high mortality in this patient group.

Schöchl et al. demonstrated that FIBTEM assay provides early prediction of massive transfusion in trauma. Because FFP contains such low fibrinogen concentrations, explained Dr Fries, it is infeasible for it to deliver the required dose without additional cryoprecipitate or fibrinogen concentrate administration.

Dr Fries went on to cite the work of Innerhofer et al3, who compared the exclusive use of coagulation factor concentrates (fibrinogen concentrate and/or prothrombin complex concentrate) against the additional use of FFP transfusion. The investigators found that the use of coagulation factors alone effectively corrected coagulopathy in patients with severe blunt trauma and concomitantly decreased exposure to allogeneic transfusion, which may translate into improved outcome.
Morbidity, sepsis and multi-organ failure was significantly greater in those receiving additional FFP.3

“The guidelines tell us that, with a very high evidence level A1++, to be restrictive with al-
lergenic blood products,” concluded Dr Fries. “We should do everything to avoid massive transfusions, or at least massive transfusion protocols.”

Fibrinogen in post-partum hemorrhage
Rachel Collis (University Hospital of Wales, Cardiff, UK) demonstrated how targeted therapy in post-partum hemorrhage (PPH) could help a sub-group of patients who demonstrate low fibrinogen levels, demonstrating that point-of-care testing could have a valuable role in identifying those in need of it.

Coagulopathy in obstetrics is rarely associated with trauma or atony, she explained, with abruption being a more common factor. “More than 90% of women with PPH have atony, she explained, with abruption being a more common factor. “More than 90% of women with PPH have normal clotting,” she noted, “And most women, if you started giving them FFP, will be diluted.

“We started to look at how useful hemostatic tests are in our obstetric population,” she continued, explaining that from very early on in bleeding, fibrinogen levels start to drop, suggesting a useful role as an early predictive biomarker of progression to major PPH in this context. “Fibrinogen does seem to be the key to understanding the progression to severe post-partum hemorrhage,” she said.

Turning to how this could be harnessed in a time-sensitive scenario, Dr Collis noted that point-of-care testing machines, such as TEG and ROTEM, provide rapid results. “In our practice they will probably help us along quite considerably.”

Dr Collis cited the OBS1 study, in which consecutive women were recruited with experience of PPH. Along with regular coagulation assays, the group performed FIBTEM fibrinogen assay on the ROTEM machine, demonstrating that fibrinogen concentrations of less than 2g/L were associated with a 50% risk of PPH.

Dr Collis and colleagues are currently testing the hypothesis that FIBTEM can identify those women at greatest risk of PPH in the OBS2 study.7 The results, which are set to emerge in full this May, identified a subset at risk, although it was difficult to find those women with low fibrinogen concentrations due to their relative rarity.

“Whether it is rare or not, it is important to target these particular women so that you can prevent them from bleeding,” noted Dr Collis, concluding: “Point of care testing really takes the guess work out of what to do in PPH. But there are still more questions than answers.”

References

Poster Awards Gold Hall Thursday 10:30

Congratulations to this year’s recipients of the ISICEM Poster Award!
(From left to right) M Soares, N Yamamoto, RM Bateman, G Nicolaes and C Goossens, along with Jukka Takala (President of the Poster Jury) far right.

Posters
A. M Soares, et al. Organizational factors, outcomes and resource use in 9,946 cancer patients admitted to 70 icus
B. N Yamamoto, et al. Neutrophil Extracellular Traps (NETs) production under hypoxic condition
C. RM Bateman, et al. Sepsis impairs the capillary response within hypoxic capil-laries and decreases erythrocyte oxygen dependent ATP efflux
D. G Nicolaes, et al. Extracellular histone H3 levels are inversely correlated with am-thrombin levels and platelet counts and are associated with mortality in sepsis patients
E. C Goossens, et al. Premorbid obesity, but not nutrition, prevents critical illness-induced muscle wasting and weakness
The future of critical care

Ever since Florence Nightingale placed the sickest patients near the nursing station during the Crimean War, critical care has made advancement after advancement, surging forward through natural and man-made disasters, polio outbreaks, World Wars and so on.

Providing a whirlwind tour of critical care, as well as a projection up to 30 years into the future, Craig M Coopersmith, a professor of surgery at the Emory Center for Critical Care, Atlanta, Georgia, USA, reviewed the history and possible future of ICUs in a talk on Tuesday entitled ‘The future of critical care’.

He pointed out that it had taken thousands of years to reach the point where sick patients were grouped together near the nurses station, 70 years to develop a three bed post-op unit, 50 years to develop the first modern ICUs in the US with four beds, and 50-60 years to get from there to continuous renal replacement therapy (CRRT), extracorporeal membrane oxygenation (ECMO), ventricular assist devices (VADs), or Molecular Adsorbent Recirculating Systems (MARS; Gambro/Baxter).

“Actually, changes are occurring incredibly fast,” he asserted, before discussing projections for the next 5 years, 5-15 years and 15-30 years in turn.

Regarding the next five years, Dr Coopersmith noted that some ICUs might already be familiar with certain developments, whilst others units might find the advancements a thing of the future.

Referring to the Surviving Sepsis Campaign (SSC), he discussed how ICUs would benefit from better implementation of existing data.

“The longer a hospital is in the SSC then the lower their mortality, reducing by 0.7% per quarter,” he said.

“Also importantly, mortality was 38.6% with low resuscitation bundle compliance, and 29.0% with high compliance.”

Early mobilization was also highlighted by Dr Coopersmith over the next five years. Asking for a show of hands on who in the room actually walked their patients, only three hands were raised. “The bottom line is that the more we mobilize patients early in the ICU, then better the deal. The future is now,” he said, showing data that supported that all patients should be exercised.

“Fifteen years ago I used to think the right thing to do was put everyone on benzodiazepines and keep them asleep to avoid post-traumatic stress disorder, from being in the ICU,” he said. “I could not have been more wrong. Now we are trying to minimize sedation and treat pain, agitation and delirium, but how are we doing on early mobilization? We should all be mobilizing our patients.”

Moving to telemedicine, only four audience members admitted to using this. Eleven percent of critically ill patients in the US are supported by telemedicine. “This is associated with lower ICU and hospital mortality, and associated with shorter ICU and hospital length of stay,” explained Dr Coopersmith.

“If you don’t have enough intensivists at the bedside you can’t wait an hour for someone to come in, so you make a call with a camera to a board-certified intensivist. They can proactively tell you before something happens that an issue could start.”

However, he added that currently telemedicine is not reimbursed, nor are there enough physicians trained in critical care to manage ICU patients in many countries. “Intensivists provide care to only one third of ICU patients in the US, and with increase in ICU demand and relatively no change in supply, there’s a worsening shortfall projected by 2020.”

As a solution to this situation, Dr Coopersmith pointed out that nurse practitioners (NP) and physician assistants (PA) represent a novel solution to workforce needs. “While this may sound quite different from the way some think of ICU care being delivered, integrating NPPAs into the ICU has already started to occur in multiple countries,” he said.

He emphasized that, “the NP or PA can do 90% of what I do, and that makes me someone who cares for the sickest 10% when really needed. They are very good at what they do.”

Study design change is another area that is going to alter from the single randomized controlled trial to the adaptive trial over the next few years, said Dr Coopersmith. “This is really changing the way we do clinical trials. This allows pre-specified changes in key trial characteristics during the conduct of the trial in response to information accrued during the trial. It also allows for re-estimation of sample size or variable randomization proportions.”

The adaptive design would facilitate enhanced investigation into certain subgroups that show benefit and make it possible to enrich sub-populations of interest. “It also means that different platforms can be investigated at the same time rather than using sequential investigation,” said Dr Coopersmith. “Not all patients are going to benefit from an intervention, what we want to know is which group is going to benefit and study them more and get an answer ASAP.”

Looking ahead to the next 5-15 years, Dr Coopersmith presented ideas that he considered were all plausible, namely: personalized medicine, immunotherapy, and restoring diversity and preventing virulence with the microbiome.

“In cancer they don’t say someone has cancer, or even just breast cancer, or even stage I breast cancer, they say the patient has stage I or II, Hercep-tin-[trastuzumab] positive, with a molecular fingerprint, and this determines whether a patient receives a certain therapy or not,” he explained, illustrating his point about personalized, precision medicine and how cancer therapies were already ahead in this approach.

He added that it was misplaced to think that in critical care trials—all patients with sepsis, for example—should be enrolled into the study and be expected to have similar outcomes. “There’s tremendous host variability just like there is with cancer. In patients with sepsis, for example, there are endotypes that suggest benefit from therapy versus other endotypes that suggest potential harm from a therapy.”

According to Dr Coopersmith, another possible progression in the next 5-15 years will be delaying the timing of therapy in cases of sepsis. He acknowledged the widespread understanding that significant amounts of sepsis were in the hypo-inflammatory phase of immunosuppression. “When do we treat? We are taught to stabilize as soon as possible. At some point the patient will have a suppressed immune system and this allows for augmentation of the immune system. So by delaying the timing of therapy, until such time as a patient is known to be immunosuppressed,
should improve survival as shown in mouse models. Just like transplant surgeons change the immune system, we’ll be able to do the same thing.”

Finally, Dr Coopersmith drew attention to the microbiome and its use as a possible development for critical care in the next 5-15 years. Noting that more than 100 trillion microorganisms live in the human colon, he explained how there are more bacteria in the body than its own cells. “There’s an increasing recognition that the microbiome plays a crucial role in the maintenance of health,” he said. “Today we increase good bacteria by offering probiotics, prebiotics, and synbiotics, and use fecal transplants of bacteria among other procedures.”

Dr Coopersmith went on to suggest that bacteria might sense the patient’s environment – when healthy or sick. “They sense intraluminal phosphate,” he said. “A patient could live for 70 years in a perfectly happy and healthy state but as soon as they get critically ill then the low phosphate state means the bacteria change and start attacking the patient,” he explained. “Maybe if we could give intraluminal phosphate we could alter the microbiome and trick the bacteria so they no longer attack the patient.”

This would be a totally new way of treating the patient suffering the harmful effects of microbes. Dr Coopersmith pointed out that the antibiotic pipeline would never be good enough because of resistance. “By reprogramming the bacteria, so they ‘think’ the host is not sick, then biodiversity increases and outcomes improve.”

He also noted that recent evidence suggested that cancer drugs, namely immunotherapy, were found to be more effective depending on the patient’s microbiome status. “If we can reprogram the stool and improve biodiversity then we might be able to change how we use immunotherapy in the ICU.”

Drawing his talk to a close, he referred to the distant horizon, and suggested that in the next 15-30 years it might be possible to regenerate or reanimate failing or hibernating organs. There also might be scope to instantaneously assess the immune system, microbiome, and other compartments and predict decompensation before it starts.

“This sounds crazy but it’s not. It will be possible to predict that someone will get worse 12 hours from now, before it happens,” he said.

In conclusion, he noted that it would take less than three decades to realize a future that may seem unimaginable today. “This is within our grasp … and it will be unbelievably exciting.”
Can we prevent VAP, even if we cannot define it?

This afternoon the Silver Hall stages the continuing dialogue on the complex issues surrounding the prevention of ventilator-associated pneumonia (VAP). Michael Niederman (Weill Cornell Medical College, NY, USA) will be asking whether we can prevent VAP, even if we cannot define it, and he caught up with ISICEM News ahead of the session to discuss his thoughts on the topic.

Professor Niederman has previously described that a combination of diagnostic scores and microbiological or biomarker evaluation could improve the treatment of drug-resistant pathogens in the ICU, and avoid the over treatment of non-resistant cases. But understanding one’s own ICU setting comes first in the developing preventative strategies, he explained, because the frequency of multidrug-resistant (MDR) pathogens is highly variable from country to country, and from ICU to ICU.

“The starting point is that every ICU doctor needs to know the prevalent pathogens in their hospital and what the susceptibility patterns are,” he said. “And if they have very susceptible pathogens and not a lot of the resistant organisms, then a lot of the things I’m going to talk about probably become less important.

“On the other hand, if they identify the resistant pathogens, and there are many countries in Europe that have this problem, then the management is complex. Because if you try to use a narrow-spectrum antibiotic empirically in an effort to avoid the overuse and abuse of antibiotics, you may be doing a good thing from a stewardship standpoint, but if you don’t treat the pathogen correctly that may tremendously add to mortality.”

There is, therefore, a real challenge that doctors face, in identifying the best strategy for the responsible use of antibiotics within their own ICU, while at the same time covering the pathogens and protecting the patient. Current approaches involve profiling patients based on risk factors, and applying broad-spectrum therapy when patients possess risk factors for MDR pathogens.

Professor Niederman’s vision for the future is, of course, to include biomarkers within this strategy: “If we had biomarkers and rapid molecular diagnostic tests on lower respiratory tract secretions, we could be more selective as to whether we use antibiotics and whether we need to use a broad-spectrum antibiotic.”

On the prevention side, Professor Niederman went through a number of strategies, centered around an understanding of pathogenesis, that are largely effective: “The general pathogenesis that is trying to be interrupted is that, as patients get critically ill, their oropharynx becomes colonized by potentially pathogenic organisms.

“Those organisms can be aspirated into the lower respiratory tract, even around the endotracheal tube cuff, and they can be inoculated into the lower respiratory tract and progress from colonization to tracheal bronchitis to pneumonia.

“Based on that pathogenesis, a variety of different prevention strategies have been developed. The first perspective on prevention that I have is that it is very effective. Probably with the existing prevention strategies, there has been a reduction in the frequency of VAP, probably by about half. A number of studies suggest that around half of all VAP is preventable. Not all of it – but at least half of it. Where there is some controversy is that, within the US, the Institute for Healthcare Improvement has pushed this idea of ‘zero VAP’, meaning that with prevention you can eliminate VAP completely. But I think most clinicians don’t really believe that it can be zero.”

Ventilator bundles typically include measures such as increasing elevation of the head of the bed and daily interruption of sedation. Two other interventions, gastrointestinal (GI) bleeding prophylaxis and deep vein thrombosis prophylaxis, are not pneumonia-specific but are appropriate for ventilator patients, noted Professor Niederman, because such complications can prolong mechanical ventilation and hence add to the risk of pneumonia. Oral hygiene is another important component of prevention, he added, in whatever form.

Running through some of the other approaches that ICUs may adopt, he continued: “Most ICUs try to use non-invasive ventilation wherever possible and try to avoid intubation. Typically we put the endotracheal tube and the gastric tube through the mouth, not through the nose. Anything that goes through the nose can lead to nosocomial sinusitis, which can also lead to pneumonia. There has been a lot of study of ventilator circuits – not changing them too often and only changing them when they are soiled.

“A more controversial intervention – which I believe in – is that for anybody who is urgently intubated, there is some fairly strong data that they aspirate during urgent emergent intubation and that a 24-hour course of antibiotics at the time of urgent intubation can be prophylactic for very early-onset pneumonia.”

For Professor Niederman, one of the most controversial of these areas is oral care. Chlorhexidine is widely used, but some recent meta-analyses have suggested that oral chlorhexidine can increase mortality, possibly due to its aspiration.

Certain of the problematic areas, such as the vulnerability of the endotracheal tube cuff itself, have also been addressed: “There are some very interesting devices that monitor cuff pressure and adjust it, maintaining continuous cuff pressure to prevent aspiration around the cuff,” explained Professor Niederman. “Even prophylactic PEEP at 5 to 8 cm can keep the cuff inflated and prevent aspiration. A lot of hospitals use closed suction catheter systems, and when they are doing enteral feeding, sometimes they try to place the feeding tube in the post-pyloric area into the jejunum.”

Despite the establishment of the ventilator bundle, ongoing study has continued to throw up new evidence around its many facets. For example, the Europe Gravity VAP studied the use of the lateral Trendelenburg position in comparison to the semi-recumbent position to prevent the incidence of VAP, with the idea that the former may promote secretion drainage from the lungs.

There are also devices designed to target the biofilm on the inside of the endotracheal tube, by either removing it physically or washing it away, explained Professor Niederman, adding that there endotracheal tubes made of different materials and in different shapes, which may also be beneficial.

He continued: “I would say that the most controversial prevention strategy is selective digestive decontamination, and selective oral decontamination. These involve using antibiotics typically in the...
mouth and GI tract. Although some of the clinical trials show a clear benefit in mortality, the largest clinical trial, that was from the Netherlands, didn’t specifically measure VAP. So it is unclear if it was through a mechanism of pneumonia that the mortality was reduced.

“The other caveat about that trial is that it was done at a time when ventilator bundles were not standard and so there was no standardization of other prophylactic measures. Many of us who haven’t quite yet decided to use selective decontamination feel that we have already got such a low rate of VAP with our existing ventilator bundles (which might even include safer mouth hygiene, effectively an oral decontamination strategy). If we are doing those interventions, we might not get much more incremental benefit from additional measures.

“And, if we do use them, not only might we not get additional preventive benefit, but we might add to the risk of emergence of resistance. Because what’s different in, say, the US and in many other ICUs compared to the Netherlands, is that baseline rates of resistance are much higher than in the Netherlands. So the impact of prophylactic antibiotics when you have highly resistant bacteria I think is unclear, but it is a concern to a lot of people.”

References

Best Practices in Patient Blood Management

Red blood cell (RBC) transfusions are one of the most frequent procedures in every hospital and can increase risk to patients and costs to hospitals. Many transfusions are considered unnecessary, so there is a growing recognition of the need to reduce RBC transfusions. Laboratory hemoglobin values are used as a primary indicator for RBC transfusions, are only available intermittently, and are often delayed—leading to suboptimal transfusion decisions.

Masimo has invented noninvasive and continuous hemoglobin (SpHb®) monitoring, which helps clinicians optimize transfusion decisions by providing real-time trending in hemoglobin status. SpHb has been shown to help clinicians reduce blood transfusions in both low and high blood loss surgery, and has demonstrated its lifesaving potential to help clinicians detect occult bleeding in places like intensive care units and labor and delivery wards.

With the growing recognition of the need to reduce transfusions, noninvasive and continuous hemoglobin (SpHb®) can be a key tool to help overcome the limitations of existing approaches. The Joint Commission has introduced Patient Blood Management Measures that encourage hospitals to evaluate appropriateness of transfusions as a continuous quality indicator. The American Medical Association and The Joint Commission also recently identified RBC transfusions as one of the top five underused interventions.

Continuous hemoglobin means you can determine the directional trend of hemoglobin—whether it is stable, rising, or falling. This can help avoid unnecessary transfusions when the SpHb trend is stable and the clinician may otherwise perceive hemoglobin is dropping, or when the SpHb trend is rising and the clinician may otherwise perceive it is not rising fast enough. Inside and outside the operating room, a dropping SpHb trend may also allow clinicians to identify internal bleeding and permit earlier interventions.

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Don’t be so negative’ about our trials

Presentation that called for cessation of clinical research “bashing” took place on Wednesday at ISICEM, with Jean-Daniel Chiche (Hôpital Cochin, Medical Intensive Care Unit, Paris Descartes University, France) arguing that we need to rethink how we design, implement and analyze important research questions.

“You need to think of the study question, and its premise,” he told ISICEM News ahead of his talk. “If the premise is wrong, then the answer will be wrong.”

In essence, Professor Chiche reasoned that the right hypothesis should be set in place before any study begins, otherwise how can we expect the results to be anything but redundant? Design is another aspect that he emphasized, in particular noting that we need to modernize our approaches to a more dynamic style. He delved deeper: “Let’s say we start a trial testing drug ‘A’ or drug ‘B’ in septic shock, for example, and then we refer our patients to the protocol. If there already is a trend that shows that drug A is better than drug B, wouldn’t you like to have this information when it comes to making a decision for your relative?”

“If you have the information you will think, ‘Yes I would rather he or she has drug A.’ … But with traditional clinical design that is not what happens. If we have decided that we are going to enroll 1500 patients, and your relative is number 500 in the trial, despite the fact that we are starting to see scientific evidence, we wait. But with novel trial designs, it is going to enrich the recruitment in medicine is not mutually exclusive to clinician-led improvements of how we treat patients. “I think that there are three basic situations,” he said. “One situation – and I would say it is the easiest to follow – is a situation where you are facing a clinical problem in which there have been studies that actually unequivocally show what you should actually do, such as the recommendations from the Surviving Sepsis Campaign, or recommendations from scientific societies etc.

“Knowing that at each time you are going to think about guidelines, there is one preamble that needs to be considered. That is, if you have a patient, who will be the target of these guidelines? Who do they apply to very well? Who do they not apply to?”

By way of example, he mentioned a patient with acute MI. For them, there are plenty of guidelines, including giving anticoagulation therapy. “But let’s say that the patient now develops GI bleeding,” continued Professor Chiche. “Now which way around do you follow the guidelines? Do you follow the GI bleeding guidelines, or the acute MI guidelines? So each time you are thinking about guidelines you should think about who do they apply to, and who do they not apply to.”

The second scenario he mentioned was when there are no guidelines in place for a common occurrence, for whatever reason, in which case what we have to think of is, is this a problem that is frequent enough so that evidence can actually gathered for the future? “That becomes a scientific endeavor,” he said.

He described the third and final scenario: “And then we have the situation where the patient is not a target of any guidelines – because the patient is an outlier perhaps, or because the problem is very infrequent. If we do not have any evidence, what you have to do is basically bring back clinical reasoning and common sense at the bedside.”

He added: “It is good to say we will not follow guidelines and protocols, and actually treat every patient according to their physiology, but the people who actually have the sufficient knowledge to do this are not so numerous.

“That being said, I really think that we have been overly negative about trials, and sometimes people might say that the trials are negative when they actually have been well conducted, and they bring us an answer to a question that is, or was, important.”

Indeed, Professor Chiche was keen to emphasize the importance of interpretation when it comes to trials, arguing that in many cases, what someone may deem ‘negative’ could be actually a valid and important answer. For instance, the Rivers, et al. trial on early goal-directed therapy (EGDT) – a very famous and somewhat controversial study – is a good example to chew over.

“Today, most patients identified with infection receive some sort of fluid early on, and now we start to give antibiotics to patients who are infected. That is the outcome of the Surviving Sepsis Campaign. I think we can say it is a success story, because it has reduced mortality in sepsis.

“In this context, does it make any sense to use the Emanuel Rivers protocol, as compared to usual care? The question is important, and has been answered by three different groups [ProCESS®, ARISE® and ProMISE®]: multicenter trials that look at the patients who actually are admitted to the emergency department.”

Noting that the three trials showed no difference between ‘usual’ and EGDT fluid resuscitation, he said: “So are these negative trials? No … they are true positive, in the sense that the question that was addressed was an important question, the studies were well-conducted, and they gave us an important answer.”

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Brainstorming:
“Big Questions for the Experts”
Hotel Boscolo Exedra,
Nice, France, May 1-4, 2016

Coordinator
Jean-Louis Vincent (Brussels, Belgium)

The 10 experts
Massimo Antonelli (Rome, Italy)
Elie Azoulay (Paris, France)
Luis Blanch (Sabadell, Spain)
Stephen Brett (London, UK)
Niall Ferguson (Toronto, Canada)
John Kellum (Pittsburgh, USA)
Michael Quintel (Göttingen, Germany)
Mervyn Singer (London, UK)
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ECMO: To believe, or not to believe?

A session pitched the question, ‘Does ECMO [extracorporeal membrane oxygenation] save lives?’ was held on Wednesday afternoon, with a number of experts putting in their two-cents for its use in patients with acute respiratory failure (ARF), pulmonary hypertension and lung transplantation.

Within the session, Alain Combes (Pierre Marie Curie University, Paris, France) and Roy Brower (Johns Hopkins University School of Medicine, Baltimore, USA) offered their ‘beliefs’ and ‘skepticisms’ for the evidence behind ECMO’s life-saving nature in equal measure.

Both speakers co-authored a comprehensive position paper on the subject in 2014, which gave in equal measure. For the evidence behind ECMO’s life-saving nature (Johns Hopkins University School of Medicine, Baltimore, USA) and Roy Brower transplantation.

Within the session, Alain Combes (Pierre Marie Curie University, Paris, France) and Roy Brower (Johns Hopkins University School of Medicine, Baltimore, USA) offered their ‘beliefs’ and ‘skepticisms’ for the evidence behind ECMO’s life-saving nature in equal measure.

Both speakers co-authored a comprehensive position paper on the subject in 2014, which gave a thorough treatment of several aspects including definitions (extracorporeal life support, for example), regional organization considerations for ECMO centers, staffing, equipment, research and many more areas.

While the ultimate conclusion of that paper was that ‘The role of ECMO for patients with severe ARF has not been definitively established, and further studies are needed to evaluate its impact’, Wednesday’s session was a chance to bring together their latest perspectives on the topic.

‘I am a believer’

Beginning with his views in favor of ECMO being a ‘life-saver’, Professor Combes said: “Definitely ECMO saves lives in acute respiratory failure patients. It saves lives of the most difficult forms, and those who are dying of hypoxemia. But to what extent should we use the machine, and what should be the indications for ECMO, to what kinds of severity threshold to initiate ECMO. This probably will remain on the table even after the [EOLIA] trial.”

The EOLIA trial, of which Professor Combes is principal investigator, aims to randomize patients with severe ARDS to ECMO or conventional mechanical ventilation. “It is ongoing, but should be wrapped up by the end of this year,” said Professor Combes.

He went on, noting the importance of such a trial. “We have a very small subset of patients who are dying with refractory hypoxemia (although not very frequent) clearly who will hopefully benefit from [the trial]. It is going to be very difficult to prove [ECMO is life-saving], as prediction of patient outcome in the ICU is very difficult, even for those who are the most severe.

“But still we all remember cases of patients dying of refractory hypoxemia, and those patients can be rescued by ECMO. This is maybe what constitutes ‘the evidence’, but it will never be based on strong data.”

For patients who are less severe, Professor Combes stressed that they may benefit from ECMO because it will permit a more protective mechanical ventilation strategy, decreasing tidal volume, and decreasing the driving pressure, which is now one of the main determinants of mortality in these patients. “So there is a strong rationale also for advocating the use of ECMO in this setting,” he said.

Speaking more generally about use of ECMO, Professor Combes was keen to emphasize that its efficacy is proportional to the volume of times it is used in centers. “The big centers with high levels of experience will help to manage the patient probably in the best way, and will likely also have the best knowledge of which population of patients might benefit most from ECMO,” he said.

He added: “Probably the minimum should be at least one per month – the strict minimum … but the higher the number, the better the outcome.”

Turning to directorship, staffing policies and regionalization, Professor Combes underlined there importance, making some brief comments, but notting that more detail can be found in the position paper. “Everything is written in that paper, as well as the minimum number of cases, what the experience of physicians should be, and what should the support from other departments,” he said, adding: “Also we insisted on the necessity of building a network of hospitals coordinating the activity, with an epicenter – probably also with a mobile rescue team for patients on ECMO – the most severe forms.”

Turning to the possible views that a skeptic such as Dr Brower may touch upon, Professor Combes noted that there are of course arguments from the other side. For example, because people are able to survive at the top of Everest, it is clear the human body can withstand very low PaO2 in the blood. “What's more, ECMO has many complications, ECMO cannot be set up in all ICUs, and ECMO causes hemorrhage and so on and so on,” he said.

He concluded: “It is still complicated, but we need an RCT to prove the benefit of ECMO.”

‘I am a skeptic’

When asked about the core question, ‘Is ECMO saving lives?’, Dr Brower hammered home that we are still simply lacking a suitable level of evidence for that. “I think it certainly makes physiologic sense that if somebody has severe respiratory failure, caused by something that is potentially reversible,
International Course
Echocardiography for Hemodynamic Monitoring 2016
with videotransmissions of live cases from the ICU
Brussels, November 15-17, 2016

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Daniel De Backer (Brussels, Belgium)
Michel Slama (Amiens, France)
Antoine Vieillard-Baron (Boulogne-Billancourt, France)
Paul Mayo (New York, USA)
Anthony McLean (Sydney, Australia)

Host Faculty:
Jacques Creteur (Brussels, Belgium)
Antoine Herpain (Brussels, Belgium)
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The first day will be devoted to revising the basics of echocardiography; the second and third days will describe how to use this technique to evaluate the hemodynamic status of critically ill patients.
such as pneumonia, that if we support gas exchange with an extracorporeal circuit, it buys time for antibiotics to work, and for natural healing processes to work. And if we don’t buy time then the patient may well succumb to inadequate gas exchange, hypoxemia and so on.”

Commenting on two randomized (but undisclosed) controlled clinical trials of extracorporeal gas exchange, he noted that these were done years ago, and neither of them support using ECMO for improvement of mortality. Despite this, given the advancements in technology and expertise in recent years, he agreed that it makes plenty of sense to revisit the question.

“There was a report that came out of New Zealand and Australia when H1N1 was having its first epidemic season there,” continued Dr Brower. “They performed ECMO on a large number of patients who had severe respiratory failure – but it was not a randomized clinical trial.”

He added: “They had, what is to some, a surprisingly low mortality rate, but it was apparent from the data presented in that report that those patients were not typical of ARDS patients in general, they were younger … and age is an important predictor of mortality. Also they had very few comorbid conditions, by that I mean liver failure, cancer, COPD [etc.]. These were basically young, previously healthy patients who had severe acute respiratory failure. I love those patients! And I have a low mortality rate on those patients without ECMO.”

Dr Brower therefore stressed that the study was not convincing, and was not alone in that aspect, with at least two other studies that he had seen examining a lower-risk group of patients, which again failed to offer convincing real-world data. Going on to discuss the CESAR trial – in which conventional ventilatory support was pitched against ECMO for severe adult respiratory failure – he commented on its design. “The trial randomized patients to either stay in their home hospitals without ECMO, or go to a tertiary center that has the capability of doing ECMO. The patients who went to the tertiary center did better, but they didn’t all get ECMO, and also we have reason to believe that the supportive care for those patients was different in the tertiary center, in a favorable way.”

“So it is really a trial of going to a tertiary center, versus staying in a home hospital.”

Staying on the topic of trials, Dr Brower said that while the large trial underway for ECMO is already hoped to be positive by many, he would like emphasis just placed on getting the trial done, and getting started on evidence evaluation. “Let’s see what it shows,” he said. “Medical history is strewn with results of randomized clinical trials of treatments we thought were working, and it turned out they were not.”

He added: “Everything you do, you pay a price. There are adverse effects, and for example with ECMO, you have to use some anticoagulation, and therefore patients are at a higher risk of bleeds. If they bleed they get more transfusions, and the adverse effects of those. Another risk of ECMO is that you have to put large catheters in, and although they usually go in OK, they don’t always, and can cause significant injury.”

He concluded: “We need a higher level of evidence, and until we have that, nobody really knows if doing ECMO the way it is being done is decreasing mortality rates.”

References
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