Go with the flow
Making a case for permissive hypotension

O
veremphasis of blood pressure during resuscitation may carry serious pitfalls, delegates heard on Wednesday morning during a presentation dedicated to so-called ‘permissive hypotension’. The message was delivered byJan Bakker, Clinical Professor at New York University School of Medicine, and Adjunct Professor at Columbia University College of Physicians & Surgeons (New York, NY, USA), who is alsoTenured Professor at Erasmus MC University Medical Center, the Netherlands.

The ultimate goal of resuscitation, Professor Bakker notes in his recent paper,1 is restoration of tissue perfusion, however targeting inadequate endpoints implies the risk of over- or under-resuscitation, both of which worsen outcome. While current recommendations suggest targeting a mean arterial blood pressure (MAP) of at least 65 mmHg, from his view and clinical experience, this approach puts too much emphasis on blood pressure instead of flow, and may lead to a high risk of overusing vasoconstrictor drugs, and aggravating tissue hypoperfusion.

Speaking to ISICEM News, Professor Bakker framed the core issue at stake here: “The misunderstanding is that hypotension is hypoperfusion,” he said. “But there are a few steps in between that we forget.”

As he underlined, it boils down to the fact that hypotension, by definition, is related to mortality, and so there is no question that hypotension is likely to be a signal that something is wrong. “There are a few circumstances where patients are hypotensive from baseline, but if you’re a healthy person and have a normal blood pressure, and you come to the emergency room with hypotension, something is definitely wrong,” he said.

However, Professor Bakker reiterated that this does not automatically translate to a perfusion problem: “Is hypotension associated with hypoperfusion? Yes, in some cases, but not always, and this is where it gets complicated. The relationship between pressure and flow is not as stable as we think. In some patients you’ll give fluid and the blood pressure goes up, and in some patients you’ll give fluid and the blood pressure goes down. In some patients nothing happens.”

Returning to the guidelines, he continued: “The guidelines don’t address this. They only usually tell you that the blood pressure, at least if we think about septic shock, should be above 65 mmHg. There is no guidance as to which patient might benefit from aiming somewhat lower; there is only guidance for patients who might benefit from aiming somewhat higher.”

As such, Professor Bakker stressed that these “broad numbers” do not give enough clarity when facing a patient with hypotension. “You end up with a MAP somewhere above 65 mmHg. And so, the recommendations never help you to titrate your treatment, or optimize it in individual patients,” he said.

That, he continued, is where the concept of permissive hypotension comes to light – the most important part of it being context. Specifically, he underlined that it is the assessment of the perfusion state of patients which

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Improve the care of critically ill patients – palliative care into the ICU is an important area for improvement. “We have demonstrated that the integration of palliative care into the ICU is an important area for improvement.”

J. RANDALL CURTIS

The study involved two hospitals, where 168 eligible patients were randomized and 268 family members participated too. Outcomes, including depression, anxiety and post-traumatic stress disorder (PTSD) among family members were measured three and six months after ICU and resource use. “We showed in this randomized trial that this intervention was associated with reduced depression symptoms in family members at six months after critical illness,” said Professor Curtis.

Innovative models for improving palliative care in the ICU

Measuring and improving the integration of palliative care into the ICU was the focus of a discussion by J. Randall Curtis, a professor of medicine and Director of Cambia Palliative Care Center of Excellence at UW Medicine in Seattle (WA, USA). Professor Curtis has spent the last 25 years building a research program that has designed and evaluated a number of interventions shown to improve the quality of care of the ICU for patients with critical illness and their families. “We have demonstrated that the integration of palliative care into the ICU is an important area for improvement,” he told ISICEM News.

The research program at the Cambia Center aims to measure and improve the quality of patient-clinician communication about end-of-life care, barriers to patient-clinician communication, and to develop interventions to improve the quality of such communication about end-of-life care. It also aims to improve the quality of care at the end of life, as well as to develop a series of process and outcome measures that can be used as endpoints in evaluations of end-of-life care.

Professor Curtis spoke about a rigorous evaluation conducted to measure the value of a so-called ICU communication facilitator – a nurse specially trained by his team. Communication with the family of critically ill patients is often poor, and poor communication is associated with family distress and increased intensity of care at the end of life, said Professor Curtis. The facilitator, in theory, could help identify the communication styles and needs of family members of critically ill patients and then help the ICU team communicate more effectively with them.

References
In other words, the ICU communication facilitator did integrate well with the ICU team. “Family members are hearing a unified message from all clinicians and the intervention is adapted to the individual ICU culture,” he explained.

A further study investigated the economic viability of such an intervention. “We also showed this intervention was associated with reduced costs of ICU care per day, and reduced ICU length of stay among patients who died in the ICU,” added Professor Curtis.

The next step of this research will be taken within two large, randomized trials conducted in the US with Professor Curtis’ group, and another in France with Drs. Elie Azoulay and Nancy Kentish-Barnes. The groups have randomized 376 critically ill patients in the US and 400 in France to intervention or usual care. They are assessing effectiveness with patient- and family-centered outcomes, including symptoms of depression, anxiety and post-traumatic stress, at one, three and six month follow-up. Results should be available soon.

There have been important improvements in the integration of palliative care principles and communication with families in the ICU over the past two decades, said Professor Curtis. “In my career, I started by having to argue why these are important topics,” he said. “I don’t have to do that anymore as it is widely accepted as very important. However, there is still much room for improvement in the way that we do this.”

“Although we have made important improvements in this area over the last two decades, there is still progress to be made.”

J. RANDALL CURTIS

And today there is still tension around applying the principles of palliative care and communication across multiple countries and cultures, Professor Curtis added. “Some areas of the world remain very paternalistic in their approach to medical decision-making with patients and family members,” he said.

In other places – such as the USA – the opposite is true. “They have swung too far on the autonomy-paternalism spectrum to make patients and family members responsible for decisions without providing adequate support,” he added.

Although there is still considerable variability, many places in the world are moving towards the middle of this spectrum with shared decision-making. “And yet, it remains important to support local culture, and follow local regulations while still providing high-quality patient and family-centered care,” said Professor Curtis.

That’s why it is not trivial to roll out innovative interventions. “There are many challenges, because ICUs are very busy places, and ICU clinicians have many things they are trying to accomplish,” said Professor Curtis. Communicating with and supporting patients and family members takes time and it can be a challenge, understandably, to find that time. “However, there is increasing awareness of the importance of making the time and developing innovative models and approaches to provide that support to patients and their families,” he added.

Professor Curtis said he’d like to see more research looking at skills in communication, prognosis, goals of care, and treatment decisions. “Skills for providing emotional support are also essential for ICU clinicians, and it is clear that these skills can be learned,” he added. To that end, some institutions, schools, and professional societies are offering training that may be very beneficial. “Large ICUs can also build their own communication training programs. My advice is to develop and use these programs,” said Professor Curtis.

In closing, Professor Curtis said that palliative care should be an important part of high-quality ICU care for all critically ill patients and their families. “Although we have made important improvements in this area over the last two decades, there is still progress to be made,” he said. A yet-to-be-published systematic review suggests that most of the work in this area has been done in just a few countries. “Many countries have much more work to do,” he concluded.

References
Therapeutic advances in resistant Gram-negative pneumonia

This morning’s session will feature a clinically relevant discussion of the antibiotics most recently approved for the treatment of Gram-negative pneumonia. The newest developments in this field will be explored by Richard G. Wunderink, a professor of medicine in the Pulmonary and Critical Care Division of Northwestern University’s Feinberg School of Medicine and medical director of the Medical ICU at Northwestern Memorial Hospital, Chicago, IL, USA.

In discussion with ISICEM News, Dr. Wunderink outlined the context for his talk, giving some insights into the therapies he will cover. He began by highlighting the urgent clinical need for new treatments in this field, explaining how rising levels of multidrug resistance is placing ever greater strain on the beta-lactam backbone of therapy for patients with Gram-negative pneumonia. “In particular, the rapid spread of resistance to carbapenem is a major concern as we rely on these drugs as the last line of defense among the beta-lactams,” he said. “In my talk, I’ll focus on new treatments that are potentially effective against carbapenem-resistant pathogens, as that is the really critical need.”

The main carbapenem-resistant pathogens of concern in pneumonia are carbapenem-resistant Enterobacteriaceae (CRE), Pseudomonas (P.) aeruginosa and Acinetobacter species. Resistance to carbapenem in these bacteria is mediated by a variety of different mechanisms; the production of carbapenemase enzymes is a major issue in all three pathogens, while the overexpression of porins to decrease outer membrane permeability and the overexpression of efflux pumps is particularly important for P. aeruginosa.

The profound clinical impact of carbapenemases is well-recognized as these enzymes have the capacity to hydrolyze virtually all beta-lactams, rendering ineffective a potent class of antimicrobials; furthermore, the genes are typically horizontally transferable on plasmids and can therefore be transmitted easily between bacteria. Dr. Wunderink explained that the rapid spread of certain carbapenemases among CRE is a rising clinical problem. “The frequency of carbapenem resistance among Enterobacteriales continues to increase, while carbapenem resistance and failure of standard therapy for Pseudomonas and Acinetobacter has been a longer-standing problem,” he observed.

While many different carbapenemases have been identified among CRE, Dr. Wunderink highlighted certain enzymes of particular clinical significance. In the 2017 European survey of carbapenemase-producing Enterobacteriaceae (EuSCAPE), the most commonly expressed of these enzymes was Klebsiella pneumoniae carbapenemase (KPC), found in 42% of carbapenemase-producing enterobacteriaceae isolates, and the second most common was OXA-48-like oxacillines (in 38% of isolates).

After outlining the context of carbapenem resistance, Dr. Wunderink moved on to discuss new therapeutic options, highlighting recent progress in both the development of newer beta-lactam agents and combinations with beta-lactamase inhibitors. With regards to combinations, Dr. Wunderink began by drawing attention to meropenem-vaborbactam, the first combination of a carbapenem with a beta-lactamase inhibitor to become available for clinical use. Dr. Wunderink led the TANGO II study, a randomized clinical trial that compared the efficacy and safety of meropenem-vaborbactam to best available therapy in patients with CRE infections. The study found higher clinical cure rates with the combination (65.6% as compared to 33.3%; p < 0.03 at end of treatment), as well as reduced nephrotoxicity.

Commenting on the evidence, Dr. Wunderink explained that while these results are encouraging, meropenem-vaborbactam is only effective against certain classes of carbapenemases. Overall, vaborbactam restores the activity of meropenem against KPC-producing bacteria, but it has minimal or no activity against P. aeruginosa, Acinetobacter species or CREs that produce other carbapenemases such as metallo-beta-lactamases or OXA-48-type enzymes. A combination with more activity against certain OXA-48-type carbapenemases in addition to KPC enzymes is CAZ-AVI – the combination of ceftazidime, a third-generation cephalosporin, with avibactam, a novel non-beta-lactam semisynthetic beta-lactamase inhibitor activity. The efficacy of this therapy was assessed by the landmark phase III REPROVE trial, which compared CAZ-AVI to meropenem treatment for patients with hospital-acquired and ventilator-acquired pneumonia. Results of this trial indicated that CAZ-AVI was non-inferior to meropenem in terms of both 28-day mortality and the clinical cure endpoint. “CAZ-AVI is a valuable new tool in our armory against some CREs, and also to some extent P. aeruginosa,” commented Dr. Wunderink.

A drug better known for its efficacy against P. aeruginosa is ceftolozane, the newest beta-lactam available, which is often used in combination with the beta-lactamase inhibitor tazobactam. While susceptible to hydrolysis by carbapenemases, it has potent activity against P. aeruginosa.

Dr. Wunderink and colleagues assessed the clinical efficacy of ceftolozane-tazobactam in the ASPECT-NP trial, a double-blind randomized controlled trial enrolling patients with Gram-negative nosocomial pneumonia. The study found that ceftolozane-tazobactam was non-inferior to meropenem treatment, both in terms of 28-day all-cause mortality and clinical cure at test of cure.

Moving on to discuss another new agent, Dr. Wunderink highlighted the potential of cefiderocol, a siderophore cephalosporin with structural characteristics of both ceftazidime and cefepime. This drug has a slightly unusual mechanism of action in that it is taken up through iron channels, which is useful given the tendency of many resistant gram-negative bacteria to take up iron avidly. “Cefiderocol is an extremely broad-spectrum agent with enhanced stability to a wide variety of carbapenemases,” summarized Dr. Wunderink, explaining that he was involved in two phase III trials published earlier this year that evaluated its safety and efficacy. The first randomized multicenter trial, CREDIBLE-CR, assessed cefiderocol versus best available therapy in adults with serious infections caused by carbapenem-resistant Gram-negative bacteria. In this heterogeneous patient population, cefiderocol showed similar clinical and microbiological efficacy to best available therapy, but mortality in the cefiderocol group was higher, primarily in those patients with Acinetobacter infections.

Dr. Wunderink will discuss the implications of these results in his talk, and relate them to the findings of APEKS-NP, a randomized, double-blind, multicenter non-inferiority trial that assessed the efficacy and safety of cefiderocol in comparison to high-dose, extended-infusion meropenem for adults with Gram-negative nosocomial pneumonia.
study found cefiderocol to be non-inferior in terms of all-cause mortality at day 14, and to have similar tolerability to meropenem treatment.7

“Overall, these results indicate that cefiderocol has similar effectiveness to current therapies in treating carbapenem-resistant Gram-negative infections,” said Dr. Wunderink. “It is a little disappointing, however, that we have not seen superior efficacy to best available therapies.”

As well as the therapies discussed above, Dr. Wunderink will also review the evidence-base for imipenem/reboxabactam, and will touch on the issue of New Delhi metallo-beta-lactamases in his talk. Looking toward the future more broadly, Dr. Wunderink gave his take on the role of other clinical advances besides the development of new therapies. Strategies with the potential to aid the management of resistant Gram-negative bacterial pneumonia include improved use of biomarkers to facilitate better antimicrobial stewardship, advancements in drug delivery systems such as aerosolization, and new tools to rapidly detect antimicrobial resistance. This latter approach, Dr. Wunderink believes, could be particularly significant.

“I would emphasize the importance of new diagnostics such as multiplex PCR as part of the hope for delaying the emergence of resistant pathogens,” he commented. “Alongside therapeutic advances, these new developments could help relieve the pressure on the beta-lactam backbone and improve clinical outcomes for patients.”

References

Standard therapy is a must for COVID-19 critical care

The recently published randomized controlled trials on anticoagulation therapies for COVID-19 patients in critical care will be the focus of a talk by Beverley Hunt, a professor of thrombosis and hemostasis at King’s College London, UK. A consultant at Guy’s and St Thomas’, Professor Hunt is director of its Hemostasis Research Unit, and has been involved in developing care specifically targeting the problem of thromboprophylaxis.

Professor Hunt told ISICEM News about her experiences in hospital when the pandemic began in March 2020. “We started to receive a lot of very sick patients with COVID-19 pneumonia,” she said. “It became evident very quickly that they had very sticky blood and high rates of thrombosis, especially in the lungs.”

As a consequence, the choice was made to increase the doses of low-molecular-weight heparin (LMWH) given to such patients routinely. “When we started, many intensivists were appalled at the rate of thrombosis that we saw,” she said. “We were very worried that patients were having so many clots, despite standard thromboprophylaxis, and on that basis the dose of LMWH was increased without any clinical evidence.”

Last month, however, the results of two large important randomized controlled trials were published in the *New England Journal of Medicine* (NEJM). One suggested that in critically ill patients, standard thrombosis remains the best therapy. “If we give more heparin to critically ill patients, we don’t seem to improve clinical outcomes, and patients have a lot of bleeding,” said Professor Hunt.

Professor Hunt plans to go through both trials in detail. “They’re quite difficult trials because they use a Bayesian analysis and not everybody is used to that type of statistical analysis.”

In addition, there has been a little confusion as to the true breadth of the trials. “I’m aware, from Twitter, that there is a misunderstanding of the trials. I think it’s really important I get back to the basic study and really go through it in a very clear way,” she added.

In both trials, when comparing therapeutic anticoagulation strategies with the standard-of-care, it was shown very clearly that full-dose anticoagulation has no benefit, rather the potential for harm, noted Professor Hunt. However, the confusion has arisen because only some critical care units regard standard-of-care as standard thromboprophylaxis. “Some thought that it was a comparison with intermediate dosing,” she added, “so I will present the randomized controlled trial as cleanly as possible so that delegates can see the data and agree that standard-of-care should be standard thromboprophylaxis.”

Indeed, Professor Hunt says an intermediate dose may not benefit patients. To that end, she will be talking about another study, perhaps less well known, called INSPIRATION, which compared 562 patients treated in an ICU. INSPIRATION saw more bleeding in the intermediate-dose group. “It strongly suggested that there is no point using intermediate-dose coagulation,” she said. “It doesn’t improve outcomes, and certainly not in critical care patients.”

What’s interesting about the two NEJM randomized controlled trials was that they were originally conducted by three groups across the world. Specifically, they encompassed the REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia), ACTIV-4a (A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic Strategies in Hospitalized Adults with COVID-19), and the ATTACC (Antithrombotic Therapy to Ameliorate Complications of COVID-19) trial groups. “They agreed to join together and published results because they were very similar studies – all of them compared full anticoagulation with some form of standard-of-care,” said Professor Hunt.

That being said, while one trial looked at the therapies for critically ill patients and found no benefit in using higher doses of heparin, the other trial, for non-critically ill patients, did. “If we look at the moderately ill patients, so those who aren’t in critical care and just needed a ‘whiff’ of supplementary oxygen in the ward, they actually do benefit from a higher dose of anticoagulation,” said Professor Hunt.

“These results are really interesting when compared with steroid trials being conducted by the RECOVERY (Randomised Evaluation of COVID-19 therapy and Related Interventions) trial platform because steroids are also showing this benefit.” She added that the benefit of steroids is in the ward, where patients have moderate COVID-19 pneumonia, but are not yet sick enough to require mechanical ventilation in critical care.

Taken as a whole, this research raises yet more questions as to mechanisms guiding these kinds of effects. “Really what comes out of this is, what is the hell is heparin doing here?” said Professor Hunt.

During her talk, Professor Hunt will discuss some of the possible mechanisms heparin might be using. “It looks like it’s acting as an anti-inflammatory drug, which we know it can do. Is it anti-inflammatory, and how much of the benefit is due to anticoagulation? We know it has antiviral properties too. Is that important?”

Going forward, more research is required, especially in how to better determine the effects that different doses of heparin may have. “We really need a bigger study comparing intermediate and standard doses to absolutely convince everybody that we don’t need to go up to the intermediate dose,” said Professor Hunt. “This is actually what’s happening with the REMAP-CAP trial.”

What’s clear now is how important randomized controlled trials will be in this arena. “It is so important not to base care on theories, or on the fact that when you look at a disease you may find that a certain pathway is activated,” stressed Professor Hunt. “Switching off the pathway may not be of benefit.”

She concluded: “We have to do randomized controlled trials.”

References


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The crucial role of mitochondria in sepsis will be addressed this afternoon by Arthur van Zanten, Head of the Department of Intensive Care Medicine at Gelderse Vallei Hospital (Ede, the Netherlands), and a professor at Wageningen University & Research. He will be speaking about its role in ICU-acquired weakness and increasingly in long COVID. “Long COVID is sepsis, at least in the ICU,” he said. “Stays in the ICU can come with long-term consequences including psychological problems, and a lot of functional difficulties.”

For many years, Professor van Zanten has studied the role of nutrition and how to restore muscle mass, which drops dramatically over the course of a stay in the ICU. This research into optimal feeding in the ICU has evolved into what happens after ICU discharge. “We know that it takes months and sometimes years and many of the patients never recover their pre-existing functioning capacity,” he explained. “Why is this huge catabolic response – this breakdown of the muscles and tissues in the ICU – so severe?”

What research has now established is that patients who do not survive ICU have lower levels of adenosine triphosphate (ATP) in their muscles. Additionally, more data suggests that ICU-acquired weakness is associated with lower ATP production and, importantly, dysfunctional mitochondria. “In critical care medicine we have focused a lot on how to optimize nutrition, flow to the tissues, and the microcirculation,” said Professor van Zanten, “but while you can have all these building blocks, maybe a cell cannot utilize them because the function of the mitochondria has shut down.”

What’s unclear is whether this reduced level of ATP is acting as a kind of hibernation, and whether it is positive or negative in effect. “Maybe this is an adaptive response to sepsis. Maybe it’s beneficial,” commented Professor van Zanten. If cells effectively hibernate to survive a traumatic event, it begs the question of whether it is wise to provide interventions in the first phase of a stay at the ICU, later during this period of critical illness, or in the latter phases of convalescence?

Certainly, research into nutrition in the early phases of the ICU suggests this is a critical period where less is more. “We now know we have to be very careful because overfeeding in this phase is not very well tolerated, and is associated with high mortality,” he said. Therefore, research should look more into the importance of this phase (and subsequent ones) in terms of ATP function. “How can we prove what to do in these phases?” asked Professor van Zanten.

“Importantly, in some patients mitochondrial function recovers and resumes over time. That’s interesting, because in some patients it does not.” In his work, Professor van Zanten has been looking at how medication affects mitochondrial function. In addition, many micronutrients, such as vitamins and trace elements, are essential co-factors in the function of mitochondria. In fact, could it be that the foods consumed by patients in the run-up to admission to hospital for sepsis are able to determine how their ATP levels behave subsequent-

"Micronutrients may be a limitation for optimal mitochondrial function. This is a focus of study in the future."

ARTHUR VAN ZANTEN

Importantly, Professor van Zanten plans to show some preliminary results from a current study. The MIC (mitochondria in ICU) trial looks at what happens with ATP production in sepsis patients. The trial included patients with sepsis from whom blood samples were analyzed. He has established that during the first week of an ICU stay, mitochondria do not function normally. “What we see in the first few days is that down-regulation is the most marked, and the most severe, and then over time it recovers,” he said. Professor van Zanten’s group is now in the process of analyzing whether there is an association between the severity of down-regulation and the outcome of patients, as well as the relationship to other factors including nutrition and inflammatory mediators.

“The interesting thing is that when function decreases, we can stimulate the mitochondria to work harder in the lab,” he said.

The next step will be to establish during which phase of a patient’s recovery would be the optimum time to restore the mitochondria. “Particularly in patients with persistent mitochondrial deficiency, we may need to think about medication and optimum vitamin feeding, as well as exercise – we know demobilization is not good for mitochondrial function and muscle protein synthesis,” he said. “So we probably need multi-modal interventions.”

However, it will be at least two or three years before studies establishing the right course of action will appear, said Professor van Zanten. “This research area is still in its infancy because we don’t have strong data yet to support the fact that if we change the course of the mitochondria it will lead to a better outcome.”

Professor van Zanten stressed it is crucial to understand that, in sepsis, it’s common to see down-regulation of mitochondria, an association with lower ATP and organ failure, as well as other consequences. “Let’s not just focus on anti-coagulation therapy, anti-inflammation therapy, or on optimizing the circulation as we do as intensivists,” he said. “If we have an energy path that doesn’t work, it doesn’t help to improve cardiac output or oxygen saturation.

“We need more data to prove what helps resolve mitochondrial dysfunction over time.”
Setting our sights on the endothelium as a target for sepsis

Treating the endothelium as a target in sepsis to limit organ failure will be the focus of a fascinating talk by Nicole Juffermans, a critical care physician at the Department of Intensive Care at Onze Lieve Vrouwe Gasthuis (Amsterdam, the Netherlands). A professor of translational intensive care medicine at the University of Amsterdam’s faculty of medicine, she will discuss both her own work and a rich and growing research field looking at endothelial permeability.

Targeting the endothelium as a therapeutic strategy has not received much attention to date, Professor Juffermans told ISICEM News. “We have always neglected it, even though it’s a hallmark of critical care illnesses,” she said. “We see endothelial leakage all the time in the ICU, and we haven’t really turned our attention to it.”

A key characteristic of sepsis is the inflammatory response, and a severe inflammatory response can lead to leaking of the vessel wall, driven by many contributory factors. “The interesting thing is that endothelial permeability is not really a characteristic of sepsis, per se,” said Professor Juffermans. “It is really a generic pathway in different types of shock.”

For example, endothelial permeability occurs in both traumatic shock and sepsis. “In terms of vessel leakage, trauma and sepsis are quite similar,” she said. “However, obviously, the cause differs: in sepsis the causative factor is microorganisms, and in trauma it’s the content of injured cells that cause endothelial activation, but these different entities share similarities in pathways leading to endothelial leakage.”

Regardless of the specific initiation, many elements of the cascade that follows shock are quite similar between shock types, continued Professor Juffermans, including neutrophils, cytokines, and activated platelets. “These are all different mechanisms, and all of these provoke a response in general, and contribute to the endothelial permeability,” she said.

“What’s important too, said Professor Juffermans, is recent research in the field which has investigated the effect of fluid resuscitation in the treatment of sepsis – particularly organ edema and organ failure. “We have learned that being restrictive with our fluids is associated with better outcomes in sepsis,” she said. “This is most likely related to restriction of the gradient of leakage of the fluid. The more fluid you give, the more it will leak if your vessel wall is permeable – it’s not rocket science. But that makes it a relevant therapeutic target.”

More indirect evidence supporting this notion is the action of the endothelial glycocalyx, the inner lining of the vessel wall. “If someone is in shock, you will be able to find constituents of this glycocalyx circulating in their blood, because it’s being shed,” explained Professor Juffermans, adding: “Glycocalyx can really be a biomarker for mortality; this is indirect evidence, which is important.”

References
CRRT as a well-informed strategy

Sтеfano Romagnoli is an intensivist and anesthetist at Careggi Hospital, University of Florence, Italy. With fields of interest that include renal failure, acute kidney injury (AKI), and renal transplantation, Dr. Romagnoli took to the podium on Tuesday to discuss his recommendations for continuous renal replacement therapy (CRRT), and how it might achieve better management of critically ill patients with severe forms of AKI.

Dr. Romagnoli reviewed the most recent guidelines and international recommendations delivered by scientific societies and groups of experts, and discussed the challenges of translating constantly updated scientific knowledge into daily clinical practice.1 “Citrate anticoagulation management without the application of rigid protocols could be considered an example of how to translate scientific knowledge into clinical practice,” he said.

In conversation with ISICEM News, Dr. Romagnoli covered key aspects of CRRT in intensive care. He started with clinical data and the parameters that nurses and physicians routinely use to evaluate whether, when, and how to initiate renal support sustaining a holistic approach to critically ill patients. It is important to consider many clinical aspects, he said, in order to determine the optimal timing to start, but also the best modality, dose, and the other prescriptions. The choice of modality – continuous venovenous haemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD) or continuous venovenous haemodiafiltration (CVVHDF) – is also important and should be individualized although often based on local expertise.

Dr. Romagnoli outlined key aspects of the decision-making process, including indications for CRRT such as a limited physiological reserve leading to a reduced ability to tolerate the consequences of AKI. Clinicians might also consider whether non-renal organ dysfunction has worsened or is exacerbated by excessive fluid accumulation (e.g., impaired respiratory function), he added. A lower probability of rapid kidney recovery associated with renal and non-renal organ dysfunction might be taken into consideration too.

Lastly, Dr. Romagnoli discussed some possible contraindications to CRRT that should be considered before starting the treatment. These include a low likelihood of benefit (or futility), a patient who receives palliative care and/or is approaching the end of life.

“Another relevant, although frequently underestimated, issue is the need to train staff,” said Dr. Romagnoli. “Knowledge of equipment including CRRT machines, catheters, circuits and the basics of CRRT theory is essential.” Protocols, staff, and institutional organization must be assessed also before starting CRRT treatment. ICU performance and quality indicators must be measured regularly, including: actual delivered dose/prescribed dose, ultrafiltration removed/prescribed ultrafiltration, filter life, catheter dysfunction, and downtime.2

However, it is perhaps rather unusual to look at these quality indicators, said Dr. Romagnoli. “This approach may appear to be a novelty in the field of CRRT, but it is my opinion that careful monitoring of ICU performance will become standard procedure in our hospitals in the near future,” he said.

Finally, in the era of modern and highly technological intensive care, expertise, experience, and knowledge must be shared and disseminated, Dr. Romagnoli explained. “Technological evolution and innovation of dialysis machines and the parallel increase in clinical knowledge make meetings like ISICEM a necessary and optimal opportunity to improve the care of our patients.”

Importantly, he emphasized that CRRT should not be an afterthought. “It is not a ‘doesn’t-hurt-to-try’ technique – a holistic approach to patient care is crucial when deciding whether or not to start CRRT. Always individualize the modality, the dose, the vascular access, the anticoagulation strategy, and the net ultrafiltration. Prescriptions must be dynamic,” said Dr. Romagnoli. “Before starting a CRRT program in your ICU, it is paramount to train staff (nurses and physicians) and share knowledge of the basic principles of CRRT.” He added that it is vital that clinicians monitor quality indicators that will tell them if they are doing a good job.

Lastly, CRRT must be carried out in a way that is based on the most up-to-date data. Dr. Romagnoli concluded: “When considering renal replacement therapies, a crucial step toward improving daily clinical practice is to move from a situation where people say, ‘We’ve always done it this way,’ to a more efficient, evidence-based, expertise-based approach.”

**References**

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- 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.

**WE NEED YOUR SUPPORT**

If you consider more plasma should be collected across Europe to meet the growing need of patients for PDMPs

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.

**ABOUT US**

The Plasma Protein Therapeutics Association (PPTA) is steadfast in its mission to promote the availability of, and access to, safe and effective plasma protein therapies for patients around the world.

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1. Immune deficiencies, immune-mediated neurological diseases, hemophilia and other coagulation disorders, hereditary angioedema, alpha-1-antitrypsin deficiency, and many other conditions.

Learn more at ItsInUsAllToSaveALife.org