The first presentation delivered during the Opening Session on Tuesday was a fascinating report from the Round Table Conference on ‘ICU populations: from syndromes to phenotypes’, which took place 18–20 March, in Brussels, right before ISICEM 2023.

The report was delivered by Carolyn Calfee (University of California, San Francisco, CA, USA) and Anthony Gordon (Imperial College London, UK), who condensed the outcomes from the three-day Round Table into just 15 minutes at the podium. “We had an amazing list of fantastic speakers from around the globe, bringing lots of different perspectives, and I really want to thank all of them because their participation and engagement was really what made the Round Table an exciting and dynamic event to participate in,” began Professor Calfee.

“I want to particularly highlight our rising stars – a new program that we had this year where we invited Round Table faculty to nominate rising stars to help us both to nurture the next generation of investigators in the field, and to make sure that we are adequately representing the diversity of perspectives that are important for a topic like the one that we’re going to be covering.”

“Precision/personalized medicine, the core of the Round Table, can be defined as an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person. “That is kind of a generic definition,” said Professor Calfee.

“In the context of the ICU, it is thinking about when, how, and whether we should move from thinking about syndromes, like acute respiratory distress syndrome [ARDS] and sepsis, and perhaps move towards thinking about phenotypes. Why would we do this? Because we want to quantify both the obvious and clinically apparent, as well as the latent or hidden heterogeneity of critical illness to develop better treatments, and ultimately to improve patient outcomes.”

Quoting DeMerle et al. in their 2021 paper in Critical Care Medicine, Professor Calfee relayed that, if we are honest, what we really want is ‘clinically relevant, nonsynonymous, biologically plausible, treatment-responsive, and reproducible [and easily determined] subgroups.’ “So, a tall order,” she noted.

“There are numerous examples in ARDS and sepsis, said Professor Calfee. In the former, latent classes in ARDS have been termed hypo- and hyperinflammatory, and there are physiological phenotypes that have been described. In sepsis, gene expression profiles have included SRS 1 and 2, MARS 1–4, and inflammopathic, adaptive, coagulopathic subgroups, as well as classifier systems that use clinical data only.”
"There are also some really interesting examples from traumatic brain injury," noted Professor Calfee. "[Wilde et al.] developed a nice framework for thinking about biomarkers to help them understand severity, progression, and response to intervention. And using that approach, they developed multi-omic endotypes of traumatic brain injury that don't just have different probabilities of survival, but seem to respond differently to treatment."

Similarly, acute kidney injury (AKI) is very heterogeneous, both in terms of its underlying risk factors, and diagnosis of pathophysiological mechanisms, she said. "Yet, all of these types of AKI are diagnosed via creatinine."

Professor Calfee added: "We've also thought about pediatric critical care, where there is additional heterogeneity introduced by developmental differences in the immune response as you move from infancy through adulthood."

Finally, she touched on the heterogeneity in pathogens. Specifically, viruses, bacteria, and fungi may all cause or contribute to sepsis, ARDS, and organ failure, but what aspects of host response are shared, and what aspects are pathogen-specific? "Many cases of sepsis are culture-negative, so will molecular diagnosis of pathogens help us understand the heterogeneity of our critical illness syndromes?" Professor Calfee said as she passed the podium to Professor Gordon.

Understanding these sub-phenotypes is very interesting, he began, but there needs to be clinical utility if our treatment choices are to be affected. "There is evidence of that," noted Professor Gordon.

Showing results from the HARP-2 trial looking at the latent class clusters of hypo- and hyperinflammatory ARDS, Professor Gordon relayed that, in the overall population, there was no significant benefit from simvastatin, but it did look like there was a mortality benefit in the hyperinflammatory group when taken on its own.

Similar examples can be seen in the VANISH trial, said Professor Gordon, which looked at the role of corticosteroids in sepsis. "According to the gene expression profile where patients were randomized to steroids or placebo, you can see the SRS 2 group, which have been shown in multiple cohorts to normally do very well in sepsis, actually seemed to be harmed when they were randomized to corticosteroids," he said.

"Does this explain some of our disparate results in steroid trials? Maybe there is some benefit, but in other populations we've not seen that because some of the patients were harmed. We need to understand that."

To take this kind of information forward, Professor Gordon underlined the importance of understanding the biological mechanisms, i.e., the molecular drivers. What the Round Table participants agreed upon would be to start with solid preclinical models that identify the pathways of the targets that are then developed into multicenter cohorts with rich clinical, imaging, and molecular data. To bring this to the bedside, there will be a need for rapid diagnostics and data science to accompany it, noted Professor Gordon. "But that information, and that technology, is out there," he said.

"There are now point-of-care devices that are being used in many intensive care units around the world, and we can incorporate those into our clinical trial design. We will need to change the paradigm under which we do our randomized controlled trials [RCTs], but again, we are becoming more familiar with some of the more novel techniques that we will need to use. But it's not just all moving forward. We will learn while we do our trials. If we collect the right information, we will also have a backwards translation, where we will understand more about the mechanisms, leading to further treatments if we go down this path."

The Round Table panel discussed many ways that that might happen, including the use of mediation analysis in RCTs, allowing a better understanding of the effect a treatment is having on potential mediators that affect the outcome. That way, one can learn about the pathway itself, and the mechanisms in action, rather than just collecting data on the treatment used, and overall survival at the end.

"We all agreed that to understand the biology, and how it affects our treatments, we need to follow the trajectory of our patients – it is not all about measuring at baseline," continued Professor Gordon.

"But this is complicated: how do you follow patients over time, i.e., a trajectory analysis? There are multiple techniques available, and we've started hearing about some new ideas, for example dynamic time warping."

In terms of how to improve clinical trial designs, many different options were discussed during the Round Table, but Professor Gordon boiled the key considerations down to a few broad aspects. "If we have a biomarker that we are sure is going to determine a response, we can select just that group of patients for that trial, and enrich our population to hopefully show benefits from our treatments," he said.

"Where we're less sure, we can bring both groups – biomarker positive and negative – into the trial. If we realize it doesn't work in one group, we can use adaptive designs where we perhaps drop that arm, and still continue to find the right treatments for the right patient."

So-called treatable traits are another potential focus when designing 'basket' trials, noted Professor Gordon, where an illness feature is targeted by a specific drug, even though the

<table>
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<th>Table 1. Summary of agreed themes from the Round Table</th>
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<td>Treatment response is the goal (better targeted treatment)</td>
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<td>Need to agree on terminology and taxonomy</td>
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<tr>
<td>Need to harmonize subtypes/phenotypes: including clinical, biological, imaging, physiologic. Need for multi-disciplinary engagement (e.g., informaticians, bench scientists)</td>
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<td>Need for international cooperation/organization</td>
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<td>Shared values of equity, generalizability, population impact</td>
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<td>Need for indicators of treatment response</td>
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<td>Importance of trajectories of phenotypes</td>
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<td>Need to understand mechanism/s better</td>
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<td>Comparison of compartments/organ systems is important</td>
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<td>It's time to start (prospectively) with well-replicated, pragmatic phenotypes with parallel interrogation and iteration of the paradigm</td>
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underlying condition may differ between patients in the trial (e.g., pancreatitis, trauma, surgery, or infection patients all sharing the treatable trait).

“We realize, though, that while this is exciting, we need to be careful, and be aware of the pitfalls,” noted Professor Gordon. “All models are influenced by the characteristics of the data going in, so we need to make sure we’ve included the right data, avoid exacerbating medical disparities, and update continuously as we learn more about our diagnostic systems. Though they may be complex, we can still ensure transparency and reproducibility.”

In conclusion, Professor Gordon summed up the agreed themes from the Round Table (Table 1), including the need for: better targeted treatments; agreement on terminology and taxonomy; harmonized subtypes; international cooperation and sharing of values; development of indicators of treatment response; recognition of trajectories of phenotypes; better understanding of mechanisms; and comparisons of different compartments/organ systems.

“Our next steps are to help bring these conceptual frameworks and investigational pathways into clinical practice, and into trials, so that we can actually implement them properly,” said Professor Gordon. “To achieve this, we need an independent infrastructure to allow collaboration and cooperation. And our first step in that will be to disseminate this work, not just here, but through a publication.”

He concluded: “Of course, we also thought about how new technology, data approaches, and artificial intelligence can help us do better for our patients going forward.”

References
Is sepsis very different in children?

Taking to the podium on Wednesday afternoon, Adrienne Randolph (Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children’s Hospital, MA, USA) delved into the current burden of sepsis in children, with specific focus on the challenges faced, and where they may differ from the adult population.

Professor Randolph has a long history in leading the charge against sepsis and other infectious/pathogenic diseases. In 1999, she embarked on a randomized clinical trial to look at weaning of children from the ventilator. Ten pediatric centers in the US and Canada came together to do the trial, forming the first initiative of the Pediatric Acute Lung Injury and Sepsis Investigator’s (PALISI) Network, which then merged with other trials that were ongoing.

In 2002, the expanding network of around 40 people from 25 sites got together in Vermont, USA, and since then it has grown to more than 90 hospitals in the USA and Canada, predominantly, but with collaboration with other networks internationally. With two meetings each year, there have been more than a dozen randomized trials and upwards of 370 publications associated with the network.

“There are also numerous subgroups, one being focused on outcomes in specific clinical trials, and one being the Pediatric Intensive Care Influenza and Emerging Pathogens [PICFLU-EP] Network, which I still lead,” Professor Randolph told ISICEM News. PICFLU-EP focuses on mostly observational studies of children with critical influenza, trying to understand the disease better, and determine the effectiveness of vaccination in preventing critical illness.

“When the pandemic came, we had a pandemic preparedness protocol ready to go, thinking it would be a flu pandemic,” continued Professor Randolph. “But when it turned out to be COVID, we were able to pivot and change to be more focused on COVID.” From that, the Overcoming COVID-19 study team was established, seeking to track and characterize the development of complications in children and young adults as a result of exposure to the novel coronavirus, SARS-CoV-2, one such outcome being Multisystem Inflammatory Syndrome in Children (MIS-C).

“We have had up to 65 sites involved in different observational studies, and we published on MIS-C very early on in the pandemic, in June 2020,” noted Professor Randolph. “That was one of the largest case series of MIS-C patients. It really helped to describe the disease. And then, we looked at a lot at cardiac outcomes and treatments, as well as acute COVID-19 and vaccine effectiveness studies. They were observational, because severe disease in children is uncommon.”

Professor Randolph and colleagues used a test-negative case control design, which led to several publications in 5–18-year-olds, and subsequently the effect of maternal vaccination in those under 6 months old. A publication showing that vaccination also likely prevents MIS-C followed.

Such networks have been instrumental, but many challenges remain in the pediatric population, not least because adult treatment and care principles do not necessarily apply, for a number of reasons. In sepsis, communication in very young children is a crucial component, said Professor Randolph, as they are not able to describe their symptoms, so they often present to the hospital later. “If children do develop septic shock, it’s a much later sign that the disease has progressed quite far,” she said.

“The epidemiology of sepsis in children is also different. Neonates are at the highest risk of mortality, and some of this is from perinatal-acquired infections, but it is also because they are very vulnerable, only really having the immunity that’s been passed on to them through antibodies from their mother. Those wane over time, usually in the first six months.”

Globally, sepsis is one of the biggest killers of healthy children, stressed Professor Randolph, with comorbid conditions such as prematurity, congenital disorders, or lung disease being associated with the most severe illness. Yet, it is striking that some of the biggest causes – pneumonia, diarrhea, malaria, and measles – are preventable conditions. That being said, the mortality rates come down extensively with public health interventions, be they vaccination, clean water, clean air, etc.

A crucial aspect in how sepsis differs in children and adults is that the patient population is so much more heterogenous in the former. From neonates to infants, toddlers, school-age children, and then adolescents, each broad phase term has its own specific challenges when it comes to infection, and other nuances that need to be considered. “For example, what the age of an adolescent?” said Professor Randolph.

“It varies across different studies. The World Health Organization considers adolescence to be 10 to 19... but some people define it as post-puberty, and that age is getting younger and younger: 8–13 for most girls, and 9–14 for boys. The body really changes a lot after puberty. There are major, major, developmental changes.”

A key aspect to consider throughout discussion of pediatric sepsis, said Professor Randolph, is how to define best practice interventions for this population. She was involved in the 2020 Surviving Sepsis Campaign guidelines process: “The great majority of those surviving sepsis guidelines have a low level of evidence – they were more consensus-based,” she said.

Indeed, she spoke of the difficulty in performing trials in sepsis. In high-resource countries, the mortality rates are relatively low – less than 20%, noted Professor Randolph – thus it is difficult to show an effect using mortality as an outcome measure. “So, we use these composite outcomes where mortality, of course, has to be part of it, but also where we look at health-related quality of life, organ failure, and other outcomes as well,” she said.

It can be especially challenging to collect data in children, continued Professor Randolph: “Routine health-related quality of life [questions] often rely on a parental report, and cognitive outcomes can also be a challenge to assess. There’s a great burden of disease in the under-five age group, but it’s hard to look at neurocognitive effects.”

In developing countries, however, mortality rates in sepsis are higher, and thus examining mortality as an outcome becomes more viable, said Professor Randolph. For example, the Fluid Expansion as Supportive Therapy (FEAST) trial in African children was designed to investigate the practice of early resuscitation with a saline bolus...
as compared with no bolus (control), and with an albumin bolus as compared with a saline bolus. Fluid boluses were associated with significantly increased 48-hour mortality in critically ill children with impaired perfusion in these resource-limited settings in Africa, noted Professor Randolph, adding: "The point here is that we can’t necessarily extrapolate trials done in high-resource countries to those in countries with few resources, and different epidemiology."

Wrapping up with her take-home messages, Professor Randolph re-emphasized that the global burden of sepsis in children is actually driven in many cases by preventable causes. Thus, it is very important for public health interventions to help bring down numbers. "But even when mortality rates are at their lowest, many children are still left with long-term disabilities, and they have a whole life span head of them," she said in closing.

**"There's a great burden of disease in the under-five age group."**

ADRIENNE RANDOLPH

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**References**

2. PICFLU. Available at: https://www.picflu.org/; accessed March 2023.

"There's a great burden of disease in the under-five age group."
Heterogenous treatment effects (HTE) of therapeutic-dose heparin for patients hospitalized for COVID-19 were explored on Tuesday morning, with Ewan C. Goligher presenting results from a study simultaneously published online in JAMA the very same morning.1

“The problem we take up in this paper is very much the one that was discussed at length over the weekend at the Round Table*, which is this issue of HTE,” began Dr. Goligher. “And with respect to what randomized trials report, they primarily report a single estimate of treatment effect, which might be termed the average treatment effect in the trial population. But in truth, we know that the treatment effect can vary markedly.”

Showing a hypothetical situation where it would appear that the mortality in an intervention group and control group are the same when taken as a single estimate, he stressed that in reality the treatment effect may vary between individuals, and consequently, the results of the trial may be misleading for specific subgroups of patients. This is the concept of HTE that he delved deeper into.

“Why is this occurring? Because trial populations, particularly with heterogeneous critical illness syndromes, represent a mixture of patients with widely varying relevant characteristics,” said Dr. Goligher. “And if those characteristics exert competing treatment effects, then that introduces significant noise into the trial, which attenuates and modifies the overall observed effect.”

The standard noise reduction strategy in the analysis of clinical trials is conventional subgroup analysis, continued Dr. Goligher, where sources of heterogeneity are considered one at a time — i.e., a one-dimensional approach.

“There can be substantial residual heterogeneity, and still a substantial variation within the subgroups,” he said. “And because each subgroup, or each subgroup effect, is considered separately, and no one subgroup effect is pre-specified as the primary analysis, you’re vulnerable to significantly increased errors, and all the problems attached to multiple hypothesis testing. So, such analyses are generally considered exploratory, and hypothesis generating.”

A much stronger potential approach would be to use multi-dimensional HTE analysis, stressed Dr. Goligher. Here, the goal is to estimate what is called the conditional average treatment effect. “This is the treatment effect that is simultaneously conditioned on multiple characteristics,” he explained. “This might allow you to see how the treatment effect varies according to all combinations of relevant characteristics.

“But there are challenges, of course, in doing this. Which characteristics or phenotypes need to be considered? How do we combine these together in a single model to get a primary pre-specified analysis? And if we use different approaches to doing this, do we get consistent results?”

To answer these questions, Dr. Goligher and colleagues set up an exploratory analysis of a multi-platform randomized controlled trial (RCT) of therapeutic-dose heparin for moderate or severe COVID-19. Upon secondary analysis of the RCT, originally released as two separate papers in critically ill or noncritically ill patients with COVID-19 — both in 2021 — significant heterogeneity was found in the latter, along with a high probability of benefit. In critically ill patients, there was a high probability of harm.

“But because these patients were all enrolled and randomized in one overarching, multi-platform trial, it provided a good opportunity to look at the how these HTE analysis techniques were performed,” said Dr. Goligher. “And in particular, our goals were to establish, empirically, the threshold of severity distinguishing between benefit and harm, and to look at consistency across the methods.”

In their paper,1 to estimate the conditional average treatment effect, two approaches were used. The first was a risk-based analysis with a single effect-modifier variable, which is quantified in terms of the risk of a poor outcome. Here, multiple patient characteristics are combined into a single model that predicts risk, represented by a risk score. Then, the observed treatment effect in the trial is stratified by the risk score, to look at risk-based HTE.

The second approach is what is called the effect-based approach to analysis, where the single effect modifier is the predicted treatment effect. Multiple characteristics of patients and disease state are combined to estimate the predicted treatment effect, and then again, the observed effect is stratified by the predicted effect to look at HTE.

Sharing the results, Dr. Goligher continued: “The average treatment effect in the overall multi-platform trial was consistent with a neutral non-significant effect odds ratio.

“The potential impact is a more personalized approach to treatment for safer care, better outcomes, and a greater return on investment for the healthcare research enterprise.”

Ewan C. Goligher

“There is potential in the future to incorporate real-time HTE analysis into the design of adaptive trials, to uncover treatment-responsive phenotypes, and to adapt to the trial accordingly.”

Ewan C. Goligher
of 1.05, so a low probability of superiority. Using conventional subgroup analysis, we identified a number of possible predictors of HTE effect. For example, body mass index seemed to have a significant influence on treatment effect. Patients with low body mass index were much more likely to experience a benefit from therapy. Treatment effect also differed according to sex, and according to severity of illness as we’d expect based on the primary reports.

Again, it was determined that patients on low or supplemental oxygen were more likely to benefit from therapy, and other patients were more likely to be harmed, noted Dr. Goligher.

When using the risk-based approach to analysis, the true spectrum of heterogeneity across the spectrum of risk was revealed. “You can see that across the range of risk, the treatment effect monotonically varies according to predictive risk,” said Dr. Goligher. Patients in risk groups 8–10 had substantial probability of harm, and all of these patients were on high flow nasal cannula or higher levels of respiratory support. By contrast, patients in risk groups 1–6 had a fairly high probability of benefit. None of these patients required higher levels of respiratory support.

In the risk model, the major predictors of risk, and therefore treatment effect, were age and (again) body mass index, and the baseline level of respiratory support.

Finally, in the effect-based approach, using a causal forest model, the most influential predictors of effect were a predicted risk of poor outcome, and body mass index, said Dr. Goligher, adding: “And although the observed effect is not monotonically related to the predicted effect in the lowest predicted effect decile, there was a significant difference in treatment effect in comparison to the other patients.”

Summarizing the findings of the study, Dr. Goligher began: “We identified some key consistent predictors of HTE across the different methods, body mass index, and the severity of illness as best represented by the level of respiratory supportive baseline. And given the fact that the overall average treatment effect in the multi-platform trials was neutral, and that there was such significant HTE, in retrospect, we can say it was truly fortuitous that the investigators chose to stratify the treatment effect and the primary analysis by severity when the trial was initially designed. In essence, it was very, very, lucky.”

This should prompt some ‘soul-searching’ about the general approach to interpreting and deriving meaning from RCTs, noted Dr. Goligher, who submits that the relevant estimate from trials is not so much the average treatment effect in the population, but the conditional average treatment effect, conditioned on characteristics, that are relevant for patients and clinicians making medical decisions at the bedside.

“Therefore, we would propose that conditional average treatment effects be routinely pre-specified and reported in the analysis of trial,” said Dr. Goligher. “There is potential in the future to incorporate real-time HTE analysis into the design of adaptive trials, to uncover treatment-responsive phenotypes, and to adapt to the trial accordingly. "I think the potential impact here is significant. We may as a result have more informative randomized trials with fewer negative results. And for some truly salient examples, you could look at recent HTE re-analyses of the BASICS and BOUGIE trials that were recently published.”

He concluded: “Overall, the potential impact is a more personalized approach to treatment for safer care, better outcomes, and a greater return on investment for the healthcare research enterprise.”

*See page 1 of this issue of ISICEM News for more information about the Round Table.

**References**


**“It was truly fortuitous that the investigators chose to stratify the treatment effect and the primary analysis by severity when the trial was initially designed. In essence, it was very, very, lucky.”**

*EWAN C. GOLIGHER*
Poster Awards  Gold Hall  Thursday  10:30

Congratulations to this year’s Poster Award winners!

P015: The effect of differing loading conditions on ultrasound assessment of diaphragm function
Idunn S Morris & Ewan Goligher (Canada)

P070: Geodemographic factors associated with COVID-19 mortality in indigenous population in Colombia
Jairo Cárdenas & Juanita Leon (Colombia)

P 177 (ISF Sepsis Best Abstract Award):
Hydrocortisone treatment in septic mice increases cholesterol availability without improving adrenal function and with exacerbated wasting of lean tissue
Lauren De Bruyn & colleagues (Belgium)

P271: A novel role for ADAMTS13 in trauma-induced hyperfibrinolysis
Pieter H Sloos & colleagues (the Netherlands)

P297: Identification of an optimal threshold to define oliguria in critically ill patients: an observational study
Nathan Bianchi & colleagues (Switzerland), received by Céline Monard
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What is the role of drugs in cardiac arrest?

Adrenaline, amiodarone, and other drugs used in cardiac arrest will be placed under the spotlight this morning, with Gavin Perkins, Professor of Critical Care Medicine at the University of Warwick, UK, taking the audience through a discussion of short- and long-term outcomes, evidence-based utilization, and future perspectives. “Cardiac arrest continues to claim far too many lives each year around the world,” Professor Perkins said in conversation with ISICEM News.

“Whilst initial resuscitation efforts that comprise basic life support and defibrillation are highly effective at restarting the heart of people who have sustained cardiac arrest, it leaves a group of about three in four people in whom, despite those initial resuscitation efforts, return of spontaneous circulation (ROSC) is not achieved, and they require pharmacological treatments, principally with vasopressors, to improve their chances of survival.”

A core issue within the discussion of the role of drugs in cardiac arrest comes from the comparison of short-term and long-term outcomes. “For example, adrenaline is highly effective at restarting the heart, but its impact on longer-term outcomes is much smaller,” said Professor Perkins. Indeed, in an narrative review published in Critical Care, Professor Perkins and co-author Keith Couper stated that Adrenaline (1 mg) is highly effective at achieving return of spontaneous circulation (number needed to treat 4) but is less effective on long-term outcomes (survival to 30 days, number needed to treat 111) with uncertain effects on survival with a favorable neurological outcome.2

“However, one explanation for disappointing long-term outcomes is that adrenaline is often given late in the course of resuscitation,” explained Professor Perkins. “Whilst the heart is resilient for ischemia for longer periods than the brain, if treatment is left too late, it is highly likely that the brain will reach a point from which it can’t recover.”

As such, the practice point that Professor Perkins made was to emphasize the importance of giving adrenaline, particularly in a non-shockable rhythm, as early as possible. Importantly, he underlined that for shockable rhythms, there are data from an in-hospital cardiac registry of several hundreds of thousands of patients showing that adrenaline should not be given prior to an attempt at defibrillation.

There is also some importance in examining the effect of drug use in cardiac arrest in terms of the trajectory of patients in hospital. If ROSC can be achieved before brain injury has occurred, then it would be expected that there is reduced need for ICU admission or prolonged hospital stay, in turn reducing the burden on resources. However, it is also worth considering if increased numbers of patients with unfavorable neurological outcomes would be expected to then require hospital care. “It is probably a societal question, informed by the values and preference of the society or the community that are served by the emergency ambulance response,” said Professor Perkins.

“In some communities, the preservation of life – irrespective of its quality – is an overarching priority. Yet in others, societies or parts of the population feel that it is the quality of life that is most important... so I don’t think that there’s going to be a single answer that is going to be relevant to across the whole of society.”

Another way of assessing worth it is to do a cost effectiveness analysis, noted Professor Perkins, looking at the cost of the intervention, the care that follows the intervention, and the impact that that has on survival and health-related quality of life. This has already been done for adrenaline, as he described. “The analysis had three components. If we considered the analysis purely from the data we have from the trials, then adrenaline is not cost effective, and in fact is very, very, costly, with limited benefit in the first six months following cardiac arrest.”

The next component is to take a modelling approach and say, well, after somebody has survived to six months, a number of people will survive for 10 years, so what impact did adrenaline have? “If you take what’s called the lifetime horizon, which is where you do modelling out for the lifetime of an specific person, then adrenaline still remains not cost effective by the measures that would typically be used, certainly in the UK, with a threshold of about 30,000 euros,” said Professor Perkins.

“But then if you consider that a small proportion of people who don’t survive after they are given adrenaline therapy will go on to become organ donors, if you add in the economic benefits of organ donation, then adrenaline does become cost-effective.”

Outside of adrenaline, other vasopressors such as vasopressin, phenylephrine, and noradrenaline have not been proven to be as effective as adrenaline, noted Professor Perkins. Anti-arrhythmic drugs such as amiodarone or lidocaine are included in current guidelines, however, for patients who remain in shock-refractory atrial fibrillation. “There is evidence that in cardiac arrests which are witnessed, amiodarone is effective at improving both ROSC and subsequent survival,” he said.

Conversely, neither calcium nor bicarbonate have been part of resuscitation guidelines for more than a decade, but observational data suggest they are still being used frequently, cautioned Professor Perkins: “We should draw attention to the recent Calcium for Out-of-Hospital Cardiac Arrest (COCa) trial, done by Lars Andersen and colleagues from Denmark, where they treated patients with calcium or placebo. The trial was terminated early because of a signal of harm in the calcium-treated group. So, it highlights the importance of guideline adherence, because guidelines are based on evidence.”

The group is also now recruiting for the Bicarbonate for In-Hospital Cardiac Arrest (BIHCA) trial. “In my personal practice I have complete equipoise as to whether bicarbonate is safe or effective,” said Professor Perkins, who is interested to see the results from the trial, and what impact they may have on routine clinical practice. Turning to the overarching question...
of what role drugs have to play in the chain of care for cardiac arrest, Professor Perkins stressed that while the incremental benefits of drugs compared to public access defibrillation and community delivered cardiopulmonary resuscitation may be small, and likely to remain that way, the fact is that several are indicated by the guidelines, and may continue to have a crucial role in the large number of patients who remain in refractory cardiac arrest despite initial interventions. “But there is absolutely a need for more research as we continue to learn about which drugs are the most effective, and importantly, what is the most effective route to administer those drugs?” he said.

To that end, examining whether intravenous or intraosseous administration of primary drug therapy is the most effective will be the aim of the Pre-hospitAl RAndomised trial of MEDIcation route in out-of-hospital cardiac arrest (PARAMEDIC-3) trial,4 of which Professor Perkins is chief investigator. “We’re a year into the study. We have around 2,400 patients enrolled, and have another 12 months to run with it,” Professor Perkins said in closing.

References
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