ICU

MANAGEMENT & PRACTICE

INTENSIVE CARE - EMERGENCY MEDICINE - ANAESTHESIOLOGY

VOLUME 18 - ISSUE 2 - SUMMER 2018

Pre-ICU

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You are Cordially Invited to Our Scientific Symposium at Euroanaesthesia 2018 in Copenhagen

Caring for the Critically Ill and High Risk Patients: New Frontiers in Advanced Monitoring and Patient Safety

Location : Turquoise Room, Bella Congress Center Copenhagen, Copenhagen, Denmark

Date and Time : **Sunday June 3rd • 12:15 - 13:45**

Lunch will be provided

Chairperson : **Basil Matta, BA, BAO, BCh, MB, FRCA, FFICM**

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Hyperoxia in Septic Shock: Temptations and Pitfalls

Luciano Gattinoni, MD

Professor of Anesthesiology and Intensive Care, Guest Professor at the Department of Anesthesia II Zentrum Anaesthesiologie Rettungs und Intensivmedizin Universität Klinikum Göttingen Göttingen, Germany

The Oxygen Reserve Index (ORi™): Novel Strategies to Monitor Oxygen Therapy

Thomas W.L. Scheeren, MD, PhD

Professor of Anaesthesiology, Head Cardiothoracic Anaesthesia Department of Anaesthesiology, University Medical Center Groningen Groningen, The Netherlands

Cerebral Oxygenation: New Insights, New Challenges

André Denault, MD, PhD, ABIM-CCM, FRCPC, FASE, FCCS

Professor of Anesthesiology and Intensive care Department of Anesthesiology, Critical Care Program Montreal Heart Institute, and Centre Hospitalier de l'Université de Montréal, Université de Montréal Université de Montréal Montreal, Quebec, Canada

Post-Operative Cognitive Dysfunction (POCD) & Delirium: Preventing Damage and Improving Outcome – Clinical Advances in Brain Monitoring and Cerebral Oxygenation

Basil Matta, BA, BAO, BCh, MB, FRCA, FFICM

Divisional Director, MSK. Digestive Diseases, Major Trauma and Perioperative Care Medicine Clinical Lead – Cambridge University Hospitals Trust Consultant, Anaesthesia and Critical Care Associate Lecturer, University of Cambridge Cambridge, UK

Oxygen Delivery (DO_2): Latest Hemodynamic Monitoring Strategies & Optimal Perioperative Oxygen Therapy

Azriel Perel, MD

Professor of Anesthesiology and Intensive Care Department of Anesthesiology and Intensive Care Sheba Medical Center, Tel Aviv University Tel Aviv, Israel

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Monty Mythen (London, UK)
Clinical need for optimized fluid management

Marit Habicher (Giessen, Germany)
Successful implementation of perioperative goal directed therapy in orthopedic patients

Alexandre Joosten (Brussels, Belgium)
Perioperative goal directed therapy using automated closed-loop fluid management: the future?

Denise Veelo (Amsterdam, The Netherlands)
From big data to smart data: how predictive monitoring will shift your paradigm

Thomas Scheeren (Groningen, The Netherlands)
Why hypotension matters and how Machine Learning will change our practice

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Pre-ICU

What happens before patients arrive in the ICU? We know that status pre-ICU is associated with outcomes after patients leave the ICU. We also know that we want patients to come to the ICU only if it is needed. This ties in to having an adequate emergency medicine system and innovative techniques in trauma as well as monitoring hospital patients at risk of clinical deterioration. Our cover story on pre-ICU looks at some of the issues we need to consider before patients arrive in the ICU, from the clinical as well as organisational point of view.

First, Rinaldo Bellomo, a pioneer of the rapid response system concept, outlines the development of rapid response teams, reviews the evidence on their usefulness as well as current controversies and challenges. He observes that even though categorical evidence for their utility is not available, "the logic behind their development is compelling."

Next, Tobias Gauss, Marc Maegele and Tim Harris address the challenges of pre-hospital coagulation management in trauma. They argue that there is a strong rationale for starting to treat trauma-induced coagulopathy (TIC) in the pre-hospital phase, and suggest what a pre-hospital TIC strategy should comprise.

Then two acute emergency medicine systems are described—from Norway and Greece. Guttorm Brattebø and Øyvind Østerås explain how acute healthcare is organised in Norway, where they observe that is it unusual for a patient to arrive in a hospital emergency department without seeing a general practitioner first. While the system is well-organised, in such a long, sparsely populated country, they acknowledge the constant need to identify patients in need of ICU care, and also to maintain quality of care at smaller hospitals that do not see trauma or seriously ill patients regularly. In recent years, Greece took in a large number of refugees, whilst dealing with its own severe financial crisis. Theodoros Aslanides describes how these challenges led to changes to pre-hospital emergency medicine services.

In the Matrix section, point-of-care ultrasound (POCUS) is the focus for the first article, from Gulrukh Zaidi and Seth Koenig, who remind us of how POCUS has changed ICU practice and argue the case for its use for physicians not yet converted.

Great advances have been made in liver support, both for patients with acute liver failure as well as acute-on-chronic liver failure. Mohammed Faisal Sheikh, Karla Lee and Rajiv Jalan describe the mechanism of action and science behind the types of extracorporeal liver assist devices now available, and take a look at emerging technologies currently being trialled.

Next, Ecaterina Scarlatescu and Dana R. Tomescu present a practical view on different aspects related to the management of bleeding in visceral and liver surgery. They emphasise the need for a comprehensive perioperative coagulation treatment algorithm adapted to the local conditions of each institution.

It is not uncommon for ICU patients to experience drug-induced immediate-type hypersensitvity. The incidence is not well known, but there are steps to take to manage reactions. Cristina Petrișor, Natalia Hagău and Nadia Onițiu-Gherman give practical advice on emergency treatment for hypersensitivity reactions as well as allergological investigations.

Mikhail Zamyatin, Vitaliy Gusarov, Natalia Petrova, Natalia Lashenkova, Maria Dementienko, Dmitriy Shilkin and Ekaterina Nesterova present the results of antimicrobial stewardship programme (ASP) implementation in their 600-bed multidisciplinary hospital. One outcome was a reduction of length of stay of patients with infection in the intensive care unit (ICU), and they note that an ASP is a permanent instrument for improving quality of care.

In the Management section, we continue our series of articles on the roles and responsibilities of the multidisciplinary ICU team. Jackie McRae describes the scope of practice of the speech and language therapist (SLT), with the aim of increasing awareness of the value of SLTs as part of the wider team. Allison Gonzalez and Robert Klugman explain how the ICU social worker can be an integral member of the critical care team. The skills and training of social workers make them invaluable additions to the holistic care of critically ill patients and their families, they note.

In our Interview section, we speak to Hussain Al Rahma, Head of the Emergency and Critical Care Services Directorate at Al Zahra Hospital in Dubai, United Arab Emirates. Prof. Al Rahma is also President of the International Pan-Arab Critical Care Medicine Society and President of the Emirates Intensive Care Society. He chairs the Emirates Critical Care Conference, which recently concluded its 14th event. As our Country Focus we share from our sister journal *Health-Management.org The Journal* an interview with Temie Giwa-Tubosun, CEO and founder of LifeBank, which has developed crucial infrastructure in Nigeria to enable efficient transportation and storage of blood, saving thousands of lives. As always, if you would like to get in touch, please email **JLVincent@icu-management.org.**

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IN EVERY ISSUE

COVER STORY

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POINT OF VIEW

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Lighter emergency breathing tubes associated with higher survival after out-of-hospital cardiac arrest

Image credit: Dwight Andrews, UTHealth

When paramedics used a new, more flexible laryngeal breathing tube to give oxygen to patients who had had an out-of-hospital cardiac arrest, these patients survived longer than patients who received oxygen via the traditional endotracheal tube, according to the results of a large randomised controlled trial conducted in the USA.

The results from the Pragmatic Airway Resuscitation Trial (clinicaltrials.gov/ct2/show/NCT02419573) were presented at the Society for Academic Medicine annual meeting by lead author, Henry Wang, MD, MS, professor and vice chair for research in the Department of Emergency Medicine at McGovern Medical School, University of Texas Health Science Center at Houston, USA.

Prof. Wang commented in a media release: "Intubation in the pre-hospital setting is very difficult and fraught with errors. This is the first randomised trial to show that a paramedic airway intervention can improve cardiac arrest survival."

In the study, the largest of its kind, survival rates for 3000 adults who had had a cardiac arrest and were treated by paramedics from 27 emergency medical services agencies between December 2015 and November 2016, were analysed. Around half received the laryngeal tube (LT) supraglottic airway, and the rest received traditional endotracheal intubation.

Results

In the LT group, 18.3% of patients survived 72 hours in the hospital, compared to 15.4% in the intubation group. From the LT group, 10.8% survived to hospital discharge, and only 8.1% in the intubation group. The proportion of patients from the LT group who survived with good brain function was also higher.

The study was conducted by the Resuscitation Outcomes Consortium research network and funded by the U.S. National Heart, Lung, and Blood Institute (NHLBI). ■

Bioengineering approach to artificial tracheas

A new paper reports an approach to growing tracheas by coaxing cells to form three distinct tissue types after assembling them into a tube structure.

The research, led by Eben Alsberg, professor in Biomedical Engineering and Orthopaedic Surgery and director of the Alsberg Stem Cell & Engineered Novel Therapeutics (ASCENT) Lab at Case Western Reserve University, is published in *Advanced Science* (Dikina et al. 2018).

Patients with damaged tracheas have limited options currently. Other techniques for artificial tracheas use a scaffolding approach, in which cells are seeded on the scaffolding. Difficulties have included uniformly seeding cells on the scaffolding, recreating the multiple different tissue types found in the native trachea, tailoring the scaffolding degradation rate to equal the rate of new tissue formation, and recreating important contacts between cells because of the intervening scaffold.

The research at Case Western University uses self-assembling rings that can fuse together to form tubes of cartilage and 'prevascular' tissue types (i.e., tissues potentially ready to participate in the formation of blood vessels). The cartilage rings are formed by aggregating marrow-derived stem cells in ring-shaped wells. Polymer microspheres are incorporated that contain a protein that induces the stem cells to become chondrocytes (i.e., cells that form cartilage). The prevascular rings include the stem cells and endothelial cells. The fusion of the different tissue ring modules, along coating the resulting tube lumen with epithelial cells, enables the creation of the complex multi-tissue structure of the trachea: cartilage with ridigity, epithelium for immunoprotection and prevascular tissue to ultimately allow blood flow into the new trachea tissue.

Prof. Alsberg told *ICU Management & Practice* in an email: "A scaffold-free approach has several potential advantages over a scaffold-based approach. The cellular condensations are more mimetic of natural development. A scaffold can interfere with vital cell-cell contact and communication, and it is also necessary to tune its degradation rate to match that of cell growth and tissue production, which can be challenging."

So far the team has engineered highly elastic 'neo-tracheas' of various sizes, including tissues similar to the human trachea. When these were implanted under the skin in mice, there was evidence the prevascular structures could join up with the host vascular supply.

Alsberg confirmed that the research is continuing: "We are working on enhancing vascularization and epithelialization of the constructs, and look forward to testing them in an in vivo model." ■

Reference

Dikina AD, Alt DS, Heberg S et al. (2018) A modular strategy to engineer complex tissues and organs. Adv Sci, 5: 1700402.

Study: Aortic grafts are feasible to rebuild windpipe and airway

A French study of patients with lung cancer or end-stage tracheal lesions has successfully used cryopreserved human aortic grafts to rebuild the windpipe and airway sections removed because of disease. The study is published in *JAMA*, to concide with its presentation at the American Thoracic Society 2018 conference.

The study, Airway and/or Pulmonary Vessels Transplantation (TRACHBRONCAR) [clinicaltrials.gov/ct2/shAow/NCT01331863], was led by Emmanuel Martinod, MD, PhD, professor of thoracic surgery at the Assistance Publique Hôpitaux de Paris and University of Paris. The study included 20 patients, who had had sections of their windpipe removed, and followed those who received airway transplantation (5 tracheal, 7 bronchial, 1 carinal) between October 2009 and February 2017, with final follow-up in November 2017.

The surgery involved airway transplantation using a cryopreserved aortic graft, which was not matched by the ABO and leukocyte antigen systems, and a custom-made stent that was inserted into the graft to keep the airway from collapsing but was later removed, at a mean postoperative period of 18 months.

Results

One patient, who underwent carinal transplantation, died (5% 90-day mortality). No patients who underwent tracheal or bronchial reconstruction died after 90 days. After nearly four years 10/13 patients were alive, and 8/10 were breathing normally through newly formed airways after stent removal. In addition, new generation of cartilage was seen in the transplanted areas. The researchers report that there were no major complications related to the allograft or the stent.

The authors conclude that this approach is feasible for complex tracheal and bronchial reconstruction. They recommend further studies and multicentre randomised clinical trials to evaluate the benefit-risk balance of the approach for specific indications such as end-stage tracheal diseases, locally advanced thyroid cancer, and proximal lung cancer. They also note additional areas for research, including accelerating the de novo cartilage generation to enable earlier stent removal, and assessment of long-term quality of life in patients who receive a transplant.

In an accompanying editorial, Valerie W. Rusch, MD, of Thoracic Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, describes the study as an "elegant solution to challenges that have long bedeviled the field of tracheal surgery. For some patients with cancer, this approach may preserve lung function and quality of life by avoiding pneumonectomy while permitting an oncologically sound operation."

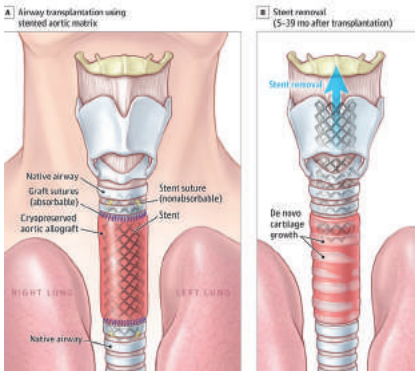

Image courtesy of JAMA network ® © 2018 American Medical Association

References

Martinod E, Chouahnia K, Radu DM et al. (2018) Feasibility of airway transplantation using a bioengineered stented aortic allograft. JAMA, 20 May. doi: 10.1001/jama.2018.4653

Rusch VW (2018) Has reconstruction of the central airways been transformed? From aorta to trachea. JAMA, 20 May. doi:10.1001/jama.2018.4652

Study: Air pollution associated with ARDS hospitalisation in over 65s

A comparison of hospital admissions of patients over 65 and air pollution in the USA has found an association between exposure to pollutants and admission for acute respiratory distress syndrome (ARDS). The study was presented at the annual meeting of the American Thoracic Society.

The researchers analysed data by zip code from nearly 30 million Medicare patients (65 years and over) discharged from hospitals from 2000 up to and including 2012 following a diagnosis of ARDS. Using these zip codes, the researchers computed annual average concentrations of fine particulate matter ($PM_{2.5}$) and ozone concentrations. The data was used in a statistical model to make associations between air pollution levels and ARDS hospitalisations. The analysis was adjusted for differences in weather, race, socioeconomic status and smoking status.

The analysis found statistically significant associations between yearly changes in $PM_{2.5}$ and yearly changes in ARDS hospitalisation rates for elderly patients. Admissions for ARDS increased when $PM_{2.5}$ and ozone levels increased. In regions with lower pollution, associations between chronic exposure to $PM_{2.5}$ and ozone had stronger associations compared to the entire United States.

Results

From 2000 to 2012 in the Medicare cohort, there were 1,164,784 hospital admissions for ARDS from 2000 to 2012. The analyses included 37,167 zip codes for 13 years. On average there were about three hospital admissions for ARDS within a zip code per year. Annual average $PM_{2.5}$ and ozone concentrations were 11.0 µg/m^3 and 39.2 ppb, respectively. The

Image credit: American Thoracic Society

researchers found increases of 1 µg/m^3 in annual average $PM_{2.5}$ and of 1 ppb in annual average ozone were associated with increases in annual hospital admission rates for ARDS of 1% (0.97%, 95% CI: 0.88, 1.07) and 0.13% (95% CI: 0.06, 0.20), respectively.

In low pollution regions (annual average $PM_{2.5}$ level less than 12 µg/m^3), the same annual increases in $PM_{2.5}$ and ozone was associated with increases in annual hospital admission rates for ARDS of 1.71% (95% CI: 1.52, 1.91) and 0.30% (95% CI: 0.20, 0.39), respectively.

In a media release, lead author Jongeun Rhee, ScD, of the T. H. Chan School of Public Health, Harvard University, commented: "We highlighted the importance of air pollution as an environmental risk factor for ARDS, which has not been studied widely but contributed to a previous finding that was limited to ozone," said Dr. Rhee. She added: "Most importantly, we found increased hospital admission rates even when seniors were exposed to levels below current annual National Ambient Air Quality Standards (NAAQS) for $PM_{2.5}$ (12 µg/m^3).

Dr. David Christiani, the senior author, said: "These results add to the growing body of literature on various adverse health effects at current standards that demonstrate a need to lower our exposure limits." ■

European Society of Intensive Care Medicine Diversity Task Force

In March the European Society of Intensive Care Medicine (ESICM) (esicm.org) announced its Diversity Task Force (pictured), which will draft a policy paper and code of conduct related to gender, gender identity, age, sexual orientation, race, culture, socioeconomic status and multi professionalism. ESICM is the first major international medical society to publicly announce the formation of such a group.

In a press release the Society stated: "All members of ESICM, regardless of their gender, gender identity, age, sexual orientation, race, culture, socioeconomic status and multi professionalism should feel welcome and respected. Opportunities should be equal for every member within the society." More information will be made available at the ESICM LIVES 2018 annual congress in Paris in October. ■

Addressing the gender gap in critical care

A "persistent and pervasive" gender gap in academic critical care medicine is highlighted in a recent article in Critical Care Medicine by Geeta Mehta, MD, of the Department of Medicine and Interdepartmental Division of Critical Care Medicine, Sinai Health System, University of Toronto, Canada and colleagues from Canada and the UK (Mehta et al. 2018). The paper is the latest in a number of reports that highlight the disparity between the proportion of female intensivists in the healthcare workforce and their representation in conference faculty, editorial boards and critical care society leadership (Modra et al. 2016; Mehta et al. 2017).

Dr. Mehta and colleagues analysed women's participation as faculty in three international and two national critical care conferences held between 2010 and 2016. They found that in all the meetings reviewed male speakers outnumbered female speakers, with the gap more marked among physician speakers than speakers from nursing and allied health professions. The Society of Critical Care Medicine conference had the highest representation of women, and together with the UK Intensive Care Society State of the Art meeting showed a significant increase in proportion of female speakers over time.

The authors note: "We do not propose gender parity over excellence, nor do we propose arbitrary percentages of women… our proposals are based on representation of the gender demographic of our specialty and the provision of equal opportunities for equally meritorious women and men. We advocate for the invitation of women who are as qualified and accomplished as their male peers and who would enrich a program."

They propose four organisational strategies to increase women's participation as speakers at critical care conferences, including policies that have gender equity objectives based on merit, 30-40% females on programme committees, publication of metrics and an international speaker's directory. Dr. Mehta told ICU Management & Practice that the Critical Care Canada Forum is working to improve its gender balance at its next meeting. ■

References

Mehta S, Burns KEA, Machado FR et al. (2017) Gender Parity in Critical Care Medicine. Am J Respir Crit Care Med, 196(4): 425-9.

Mehta S, Rose L, Cook D et al. (2018) The speaker gender gap at critical care conferences. Crit Care Med, 28 Mar. doi: 10.1097/CCM.0000000000003114. [Epub ahead of print]

Modra L, Yong S, Austin D (2016) Women in leadership in intensive care medicine. ICU Management & Practice, 16(3): 174-6. Available from: https://iii.hm/jxi

Have you answered these surveys on intensive care medicine?

Three surveys seeking information from ICUs around the world are currently open for data collection.

ICU inter-professional rounding practices

This online survey, supported by the World Federation of Societies of Intensive and Critical Care Medicine, is led by Dr. Andre Amaral, Sunnybrook Research Institute, Toronto, Canada. It is open to intensivists, trainees and ICU nurses.

The purpose of the study is to:

- Provide an international perspective on current ICU inter-professional rounding practices
- Describe an international perspective on preferred ICU inter-professional rounding practices
- Describe an international perspective on the associations between ICU inter-professional rounding practices and end-user perceptions of quality of care
- Evaluate the degree of end-user satisfaction with ICU inter-professional rounding practices.

The steering committee comprises Dr Amaral, Dr. Jorge Salluh, Dr. JL Vincent, Dr. Steve Webb and Dr. Louise Rose.

The link to the survey is: **https://pt.surveymonkey.com/r/survey_icu**

International survey of the structure and organisation of ICUs (ISOREA)

Data on the structure and organisation of intensive care units (ICU) worldwide are scarce, especially in intermediate- and low-income countries. This lack of information is partly due to the high disparity in clinical care provided to critically ill people worldwide, to the diversity of the health systems models, and to the difficulty in reaching a consensus on the definition of what an ICU is.

The International survey of the structure and organisation of ICUs (ISOREA) [Enquête Internationale sur la Structure et l'Organisation des REAnimations], aims to evaluate the structures and organisation systems of ICUs in a big sample from high-, middle-, and low-income countries. Its exhaustive design should provide meaningful data in the field, says principal investigator, Prof. Armand Mekontso Dessap, Hôpitaux Universitaires Henri Mondor and Université Paris Est Créteil, Paris, France.

The survey includes questions about:

- The spatial characteristics of the ICU life support and monitoring techniques
- Human resources
- Clinical care administered to patients
- Research activities, and
- Training and quality improvement programmes.

Data will be collected over the first semester of 2018 and analysed during the second semester of 2018. Prof. Dessap says that this study may provide important insights to decision makers on the actions to undertake and the improvement projects to set up, especially in low- or middle-income countries.

The survey is endorsed by the European Society of Intensive Care Medicine (ESICM), the Société de Réanimation de Langue Française (SRLF) and the Société d'Anesthésie Réanimation d'Afrique Noire Francophone (SARANF).

The link to the survey is:

https://www.wepi.org/accounts/59efbfb6b142d/enquetes//1583567680/scripts/connect.php?t=1223669459&s=f

Survey: Models of critical care outreach systems

Critical care outreach teams (CCOTs) were introduced in an attempt to reduce morbidity and mortality through the earlier detection and resuscitation of acutely deteriorating patients. However, there are many different models of critical care outreach systems across the UK and internationally.

Dr. Duphal Patel, academic clinical fellow in anaesthetics and intensive care medicine at Cambridge University, UK, is leading an online survey that aims to take a cross-sectional view, collecting data looking at the staffing, availability, activities and governance of different critical care outreach systems (CCOS) across the world. Following this Dr. Patel will use a systems engineering approach to determine the optimal configuration(s) of a CCOS, and determine the most appropriate metrics to measure the success or impact of a CCOT. ■

The link to the survey is:

https://www.surveymonkey.co.uk/r/_criticalcareoutreach

The Accelerate Pheno™ system in clinical practice

Fast and accurate turnaround for critical results

Our clinical experiences of using the Accelerate Pheno™ system have greatly benefited patient care, providing earlier diagnostic certainty. Two complex sepsis cases are discussed, where the impact of rapid identification, with antibiotic sensitivities, of the causative organism from blood cultures is described.

Dr. Claire Thomas
Director of Infection Prevention and Control
Hampshire Hospitals NHS Foundation Trust
Basingstoke
UK

claire.thomas@hhft.nhs.uk

At Hampshire Hospitals NHS Foundation Trust, we endeavour to be ahead of the curve in diagnostics, being patient care focused, with a bedside to bench clinical approach. However, with our existing laboratory standard of care, our turnaround time for critical results like blood cultures was not optimal, and antibiotic initiation for sepsis is empirical. We evaluated the Accelerate Pheno™ system within our busy clinical microbiology laboratory during 2016/7.

We began using the Accelerate Pheno™ system as a lab evaluation in 2016, and as a full clinical evaluation with 100 assays in 2017, alongside our existing gold standard methodology. We developed a clinical algorithm for the use of the Accelerate PhenoTest BC, and could swiftly see that it was giving us what we wanted for our patients—rapid identification (ID) and a rapid antibiogram.

Antibiotics stewardship

We endeavour to have very tight control of antibiotic stewardship within our Trust. As rates of antibiotic resistance are rising in the community and in the hospital, we try to get the antibiotics right first time, giving our clinical teams guidance via local antibiotic policies (smartphone app), but this is not always accurate, and in rapidly deteriorating septic patients, there is a tendency to escalate up to 'end of the line', broad-spectrum antibiotics. We do not achieve diagnostic certainty until we get a positive blood culture, and then often only at day 3 of illness. So we were keen that the Accelerate Pheno™ system would play not only a huge role with improving how we treat sepsis and other infections, but also with antibiotic stewardship. This system would give us rapid timely results compared to our current system, which can take up to 3 days.

Clinical workflow

We hold a daily clinical microbiology/infection ward round that visits positive blood culture patients and septic patients. Each working day we see intensive care and high-dependency unit patients on our round with a laptop that has the latest results linked to the laboratory. We loaded signal-positive blood cultures on to the Accelerate Pheno™ system 7 days a week during normal working hours. We would stop taking blood cultures off the system at 22.00. We linked the results to an email that we could pick up wherever we were, on or off site. Our aim would ultimately be for the on-call doctors to have this result sent to them electronically at night, with an agreed clinical reporting system.

Significantly reduced identification and antibiogram times

The Accelerate Pheno™ system turnaround time was found to be extraordinary in terms of the ID, which was much appreciated by our users. The mean ID time was 1.35 hours, with the antibiogram coming through at a mean time of 6.65 hours.

Sensitivity and specificity

If we had a Gram-negative result, we would put it straight on the system. The sensitivity was 96.3% and the specificity was 99.8%. We had a categorical and MIC agreement with the standard of care. Its essential agreement was 97.9%, and the categorical was 97%.

We did use it for Gram-positives, but not as many found it useful for distinguishing *Staphylococcus aureus*, from *S epidermidis*, in selected cases.

Minimal training required

Training to use the system only takes around 30 minutes, and we hope to use it on the other sites, as we have 3 hospitals on different sites in our Trust, with 1 central microbiology laboratory. It takes 3-5 minutes to put each sample on. We are about to roll it out for full clinical use. Of note, it could be used by other trained scientific staff, not only by microbiologists.

Conclusion

The tool proved incredibly valuable towards significantly reducing the ID time to one and half hours, providing an antibiogram within 6-7 hours, and giving diagnostic certainty when managing septic cases, for us and the ward clinicans. We could access results remotely when on call, and as we have hospitals on three sites, it could be used for rapid diagnostics on one of the other sites as our laboratory is centralised.

CASE REPORTS

Case 1

A 31-year old male on the haematology unit with acute myeloid leukaemia had a recent *Clostridium difficile* infection and a central line enterococcal infection. He was on prophylactic posaconazole and the lines were removed. From rectal swabs he had been found to be colonised with a multidrug-resistant (MDR) *Pseudomonas*, suspected to be a carbapenemase producer. He deteriorated rapidly over the course of a few hours with shortness of breath, fevers, and clinical signs of sepsis. He was empirically started on piperacillin-tazobactam, with an aminoglycoside (amikacin). We took blood cultures at 11.00; his white cell count at this point was 0.3, so he was still essentially neutropaenic, with platelets of 38 and haemoglobin of 9.

The blood culture signal on the machine was positive at 16.31 with a Gram-negative organism on gram film. We processed the blood culture according to our normal standard of care, and also on the Accelerate Pheno™ system. The ID came through at 19.11 as *Pseudomonas aeruginosa*, which worried us because of what he was colonised with. We were already in the middle of an outbreak investigation, as the haematology unit had recently had a patient with MDR *Pseudomonas*, a GES-5 carbapenemase producer resistant to meropenem, ciprofloxacin, ceftazidime, gentamicin, sensitive to amikacin and colistin. The patient was stable, and we decided to keep him on the piperacillin-tazobactam and amikacin for the time being, but we asked to be called immediately if he deteriorated. We ensured we had colistin on the unit so that if he deteriorated we could give him that.

Six hours later we had the full antibiogram. It was an MDR organism that fitted with what he was colonised with. This allowed us to rationalise the antibiotic choice. We phoned the haematology doctors at 02.00 and changed the antibiotics to colistin and amikacin, with the information given. Using the Accelerate PhenoTest™ BC gave us clarity—we knew what we were dealing with, and it helped us to manage the patient as appropriately as possible with very targeted antibiotics. On review we realised he had a perineal tear. The patient recovered from his neutropaenia, and antibiotics were stopped at 2 weeks after the positive blood culture. With our standard system we would have had to wait for at least another 24-48 hours to identify the organism. In a very immunocompromised patient, it could have been extremely detrimental if we had not got this right.

Case 2

A 26-year-old female came in to the emergency department, after a collapse at home, with a queried septic arthritis. We were called in by the orthopaedic ward who said she was profoundly septic. On review, she was in respiratory failure with low blood pressure and acute kidney injury on a background of Noonan's syndrome. She was quite a complex patient with cardiac issues, secondary to her Noonan's. She was seen by the orthopaedic team at 11.00, and started on empirical treatment: intravenous meropenem. She had a background of penicillin allergy with a rash, so although meropenem is very broad-spectrum, that seemed reasonable at the time. The blood culture was signal positive at 11.00. The lab informed me at 11.15 that there was a Gram-negative bacillus coming through in the blood culture. They put this straight on to the Accelerate Pheno™ system. The patient was picked up by the high-dependency outreach team and transferred to intensive care. At 12.30, we got an ID and it was a *Serratia marcescens*, which we know to be a carrier of an AmpC resistance mechanism and therefore highly likely to be MDR. The antibiotic susceptibility testing (AST) then came through at 17.30, and it confirmed that we were doing the right thing with meropenem, but we felt we could also give gentamicin as she was on dialysis filtration, and still deteriorating.

We isolated her in a side room for optimal infection control, as this was a MDR organism, and she was subsequently found to have influenza A. She was subsequently found to have pneumonia, possibly secondary to having influenza A in the community. We were able to optimise her treatment over and above what we would normally do with our standard of care and have surety that we were using the right antibiotics. This knowledge also helped greatly with infection control actions. The patient made a recovery after a time in intensive care and the high-dependency unit (HDU).

Rapid response teams

This article reviews the RRT system concept and provides an update on the current state of such systems, their challenges, their performance, the evidence supporting their usefulness and their evolution.

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Rapid Response Teams (RRTs) are the key components of Rapid Response Systems. RRT-based rescue systems were developed in response to evidence that many deteriorating hospital patients experienced "failure to rescue" and went on to develop serious adverse events (SAEs), including death, cardiac arrest and unplanned ICU admission (DeVita et al. 2006). The RRT approach is based on several key concepts:

a) Identification of patients at risk

b) Early notification of responders (RRT)

c) Rapid intervention by the RRT, and

d) Audit of the system's performance

(DeVita et al. 2006).

RRT-based systems have now been implemented in the whole of Australia, and in many, if not most hospitals, in New Zealand, Denmark, The Netherlands, Sweden, the United Kingdom, Canada and the USA (Steel and Reynolds 2008; Winers et al. 2006). RRTs have been reported to operate in some hospitals in Brazil, Italy, Portugal, Germany, Iran, Finland, Saudi Arabia and Japan.

RRTs are not the same as cardiac arrest teams, and in many hospitals they exist in parallel with cardiac arrest teams. However, members of the RRT can also respond to cardiac arrests and act both as cardiac arrest team and RRT depending on the circumstances. A measure of success of the RRT system is that cardiac arrests decrease to the point of becoming rare events. The key distinguishing feature between RRTs and cardiac arrest teams is that they are intended to review patients at an earlier stage of clinical deterioration with the aim of preventing serious adverse events. The major function of RRTs is not to respond to cardiac arrests but rather to prevent cardiac arrests. Similarly, they function to prevent unexpected/preventable deaths and unplanned admissions to the intensive care unit. RRTs typically review, assess and treat patients with respiratory, neurological, and cardiac deterioration rather than patients who have already suffered a respiratory or cardiac arrest.

Multiple before-and-after studies in a few centres or in single centres (Chen et al. 2014; Bellomo et al. 2003; Jones et al. 2005; Sebat et al. 2007; Buist et al. 2007; Foraida et al. 2003; Sharek et al. 2007) have reported that the introduction of RRTs is associated with a significant reduction in cardiac arrests in ward patients. Such effectiveness appears greatest in hospitals where RRTs have operated for several years (so called mature systems) and deliver greater "RRT dose" (RRT assessments/1000 patients admissions) (Jones et al. 2009). Some meta-analyses have challenged the effectiveness of RRTs (Chan et al. 2010; McGaughey et al. 2007), but other more recent meta-analyses have reported that their implementation is associated with an overall reduction in mortality in both adult and paediatric studies ($P<0.001$) as well as a significant reduction in cardiopulmonary arrests in adult and paediatric patients ($P<0.001$) (Maharaj et al. 2015). Accordingly, there is continuing controversy regarding the overall effectiveness of RRTs. Importantly, RRTs do not appear to clearly lead to a decrease in hospital mortality. This is not surprising as most hospital deaths are neither preventable nor unexpected but represent the final event in a process called end-of-life care (EOLC).

Concept of failure to rescue

Patients in hospitals may develop a significant worsening of their condition and such change may herald the risk of a major adverse event. Despite such patients being in hospital, however, the doctors and nurses responsible for their care may fail to respond in a timely and/or appropriate manner. This failure to respond is termed "failure to rescue" (DeVita et al. 2006). Logical reasons for sudden critical illness and failure to rescue exist (**Table 1**), and explain why serious adverse events (SAEs) are surprisingly frequent even in major teaching hospitals.

Epidemiology of serious adverse events

Studies in the U.S. (Brennan et al. 1990; Thomas et al. 2000) and other countries (Wilson et al. 1995; Davis et al. 2002; McQuillan et al. 1998) demonstrate the following observations:

a) Unexpected SAEs are relatively common; and many

b) Are iatrogenic

c) Contribute to disability and mortality; and

d) Occur after failure to rescue (Wilson et al. 1999).

These studies also report that many serious adverse events are preceded by clinically detectable warning signs (Buist et al. 1999; Hodgetts et al. 2002; Bell et al. 2006). Many conditions have been reported to be associated with failure to rescue. These conditions include acute respiratory failure, acute changes in conscious state, hypotension, arrhythmias, pulmonary oedema and sepsis (Jones et al. 2006). The most

commonly measured serious adverse events of such deteriorations include cardiac arrest, unexpected death, and unplanned/emergency ICU admission (Hillman et al. 2005).

Warning signs

Abnormal vital signs are typically present for more than one hour and often more than one day in most patients who experience deterioration in the ward and go on to develop SAEs (Buist et al. 1999; Franklin and Mathew 1994). Logically, therefore, vital signs can be used to identify deteriorating patients from minutes to hours before a cardiac arrest or death or emergency ICU referral occurs. Thus, in most cases, there is a significant time-window to deliver intervention. Frequent and accurate measurement and reporting of vital signs is the key step in this process (DeVita 2005). Similarly, abnormalities in common laboratory tests can help identify patients at risk (Loekito et al. 2013).

Although the measurement of vital signs is risk-free and identifies most deteriorating patients, it does not occur predictably, accurately or completely (Leuvan and Mitchell 2008; Cretikos et al. 2008). Respiratory rate monitoring is particularly striking and the strongest predictor of a major clinical complication occurring within 24 hours (Cretikos et al. 2007). However, it is not optimally measured (Cretikos et al. 2008), contributing to the risk of "failure to rescue". Because of such limitations, there has been a growing call for hospital patients to have continuous or semi-continuous vital sign monitoring. As easily wearable noninvasive technology develops to at least measure respiratory rate, heart rate, oxygen saturation and becomes more widely and less expensively available, it is likely that a transition to such technology will start taking place in hospitals in developed counties (Bellomo et al. 2012; Subbe et al. 2017).

Responding to abnormal vital signs

When patients develop abnormal vital signs or abnormal laboratory tests, the traditional model of hospital response may be of limited quality and reliability. There may be triage errors (Chen and Hillman 2014), delayed doctor notification, failure by doctor to attend (Wilson et al. 1999), inadequate clinical assessment (Maharaj et al. 2015; McQuillan et al. 1998; Wilson et al. 1999; Hodgetts et al. 2002), suboptimal response to the urgency of the symptoms (Wilson et al. 1999), and failure to seek help or advice (Wilson et al. 1999). Having objective criteria, which clarify staff expectations, is thus seen as important in triggering a rapid response. In addition, rapid referral to personnel with appropriate expertise and equipment is likely beneficial. Deficiencies in identifying and responding to deteriorating patients provide an additional rationale for RRTs.

> "continuing controversy regarding the overall effectiveness of RRTs"

Key principles

An important principle underlying RRTs (and all critical illness) is that early intervention can improve patient outcome. In this regard, multiple studies reporting on delayed RRT activation have found that such delays lead to increased risk of serious adverse events (Chen et al. 2015). A key principle is the ICU without walls principle that delivers critical care expertise to the patient before (not after!) the development of adverse clinical outcomes.

Rapid response team-based system

The RRT is part of a system without which the team cannot deliver improved care. The system has an *afferent arm* whose task is to identify deteriorating patients and trigger a response. This arm includes having RRT calling criteria, their measurement and a mechanism of RRT activation. Its *efferent arm* is the RRT. A third arm is the *performance review arm*, which collects and analyses data from events and continuously seeks to improve prevention and response. Finally, there is the *administrative arm* (DeVita et al. 2006), which coordinates resources and implements policy changes.

Table 1. Possible reasons for failure to rescue

- Lack of continuous or near continuous or even frequent vital signs monitoring in the general ward
- Lack of automated alarm or alert systems in association with vital signs which are independent of human factors
- Incomplete measurement of vital signs (esp. of respiratory rate)
- Lack of explicit criteria or policies for activating higher level interventions
- Infrequent physical presence and visual review by a ward nurse
- Infrequent assessment and attendance by a ward doctor
- In surgical wards, lack of presence by doctors because of their need to be in an operating room
- Judgment by variable members of staff regarding whether escalation is necessary
- Judgment by staff members varies according to training, experience, professional attitude, working environment and position
- Slow response to a crisis or deterioration because of a multi-step response chain (bedside nurse to charge nurse to junior doctor to registrar/fellow to consultant/attending)
- Increasing patient complexity in modern hospital wards with more frequent episodes of deterioration

The key characteristic of the response teams is that they are activated when a patient fulfils pre-defined criteria. Many organisations print mnemonic cards or posters to promote use. RRT activation is rapid and usually bypasses traditional unit-based approaches to care. The team responds rapidly (within minutes) to the call and delivers critical care equipment and expertise to the patient's bedside (DeVita et al. 2006).

Triggering criteria

The efferent arm is triggered in response to so-called "calling criteria" based on derangements in vital signs. However, many hospitals include "I am worried" type criteria to allow staff to escalate treatment if they perceive there is a serious problem even in the absence of such criteria. In some hospitals family members can also activate the RRT if they are worried about the condition of their hospitalised family member. Criteria can be used to trigger intervention in at least two major different ways. One uses them to calculate an Early Warning Score (McGauhey et al. 2007; Gao et al. 2007), where components are summed to obtain a score, and if the score achieves a certain value a response is triggered. In other centres, the presence of any one abnormality is sufficient for activation of the RRT. No studies have compared RRT performance under such different triggering systems.

RRT composition

Typically, in larger hospitals, at least one RRT member is a dedicated critical care fellow or trainee (so called Medical Emergency Team or MET), who is accompanied by a nurse with a dedicated set of drugs and equipment (England and Bion 2008). In some hospitals, however, the team may simply be based on an ICU nurse or respiratory therapist or both, who are "first responders" and then themselves decide whether to activate the full response involving ICU doctors. In Australia (Bellomo et al. 2003), New Zealand and Scandinavia, the typical model is the MET. Most studies demonstrating improved patient outcomes have involved a MET (Jones et al. 2009). The RRT must bring with it the necessary medications and tools to deliver the ICU without walls to the patient's bedside (**Figure 1**).

Interventions and outcomes

Some interventions performed by the response team are simple (oxygen, intravenous fluid, diuretics, bronchodilators and diagnostic blood or radiology tests). However, a significant proportion of patients require critical care level interventions (Bellomo et al. 2003). Evidence from several studies indicates that the system can also help address end-of-life care planning (Hillman et al. 2005).

The only cluster-randomised multicentre controlled trial of RRTs was termed MERIT (Medical Emergency Response and Intervention Trial) (Hillman et al. 2005). On primary analysis, MERIT failed to show an outcome benefit, although both trial arms showed an outcome benefit compared to baseline. However, more detailed analysis of the results found evidence of benefit. For example, a post hoc analysis of the MERIT study showed a significant outcome improvement (death, cardiac arrest) when the data was analysed in an *as treated* rather than an *intention to treat* (as assigned) model. In this analysis, there was a significant and linear decrease in poor outcome as RRT responses increased (Chen et al. 2009). Other studies have revealed a significant reduction in all-cause hospital mortality, particularly in surgical patients (Bellomo et al. 2003; Jones et al. 2007).

Several single-centre before-and-after trials supported the contention that RRTs improve outcome (Bellomo et al. 2003; Jones et al. 2003; Sebat et al. 2007; Buist et al. 2007; Foraida et al. 2003; Sharek et al. 2007), and recent meta-analysis strongly supported such an effect (Maharaj et al. 2015). The limited evidence available for such RRT-based systems is in great part due to the fact that individual randomisation trials or blinding of the intervention are simply not possible. The highest-level approach to obtain randomised controlled evidence would require cluster randomisation trials and such trials would require up to 200 clusters (hospitals) to have sufficient statistical power to detect a realistic effect on SAEs. Moreover, as these systems require time to "mature" (to make staff change behaviour from the traditional model to the new model), simply randomising to a RRT intervention or no-RRT Is not representative of the true effect of the team once the new model has been accepted. Another way to assess such RRT systems is to study the impact of national programmes. The introduction of RRTs in The Netherlands offered such an opportunity and demonstrated a clear effect on cardiac arrests (Ludikhuize et al. 2015).

In another before-and-after study, the reduction in cardiac arrests was estimated to save approximately 2,000 post-cardiac arrest bed days annually (Bellomo et al. 2003). The RRT can also deliver education of nursing and medical staff (Buist and Bellomo 2004), and teach them how to better manage acutely ill patients

Figure 1. Typical rapid response system cart containing the necessary tools and medications to create an intensive care unit like system at the patient's bedside

(Jones et al. 2006). Finally, as RRT systems mature and encounter more and more out of ICU critical illness, they begin to significantly contribute to end-of-life care decisions and management (Chen et al. 2008; Brown et al. 2017; Tan and Delaney 2014).

How to make a RRT work

The introduction of a RRT is sociologically complex because it subverts a traditional model of care. Thus, a coordinated strategy is needed to prevent poor implementation (DeVita and Hillman 2006), and support from hospital medical, nursing and administrative

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leaders is needed to achieve success. Time, patience, education and collegially constructive interactions are also needed (Bellomo et al. 2003). It should be made clear that the role of the RRT is to provide a safety net rather than taking over patient care. The team should be adequately resourced to enable appropriate management of any critical care event.

The afferent arm requires sustained education of nursing and medical ward staff. Without this effort the RRT system will underperform. Accordingly, repeated education of all existing and new hospital ward staff is crucial. Inclusion of a physician team leader is key because it can expedite transfer to the ICU, and/or facilitate end-of-life care when needed (Jones et al. 2009).

Successful RRTs in teaching hospitals deliver a "dose" of least 40 triggers/1000 patient admissions (Jones et al. 2009). Increasing response "dose" is key to reducing cardiac arrests (Jones et al. 2005; Buist et al. 2007; Foraida et al. 2003).

Simulation training improves team performance and allows a structured approach to managing the deteriorating patient. Regular audits are needed to assess performance (DeVita et al. 2006).

Controversies

The preponderance of evidence supporting RRT-based systems comes from short–term before-and-after studies. Meta-analyses of studies assessing such systems have reported inconsistent findings. However, it is extremely unlikely that a "definitive" trial will ever be conducted. Thus, the decision to introduce RRT-based systems or not in healthcare jurisdictions and/or a single institution is based on judgement and considerations of risks, costs and likely benefits. As stated at the outset, several healthcare systems (USA, UK, Australia, New Zealand, The Netherlands, Denmark, Canada, Sweden) have taken the view that RRT-based system should be a standard of care.

Implementation of a RRS may theoretically de-skill ward staff. However, surveyed nurses in both Canada and Australia disagree (Bagshaw et al. 2010). Inappropriate patient management or conflict with the primary team is a concern but, in fact, uncommon. The optimal team composition remains unknown, but a medical team leader seems desirable (Jones et al. 2009).

Implementation of a RRT-based system may divert resources away from ICU patients (Winters et al. 2006). No evidence of this, however, exists. RRT systems may divert the focus away from other effective patient safety initiatives (Winters et al. 2006) (e.g. hospitalists, nurse practitioners, or increased number of ICU beds). However, the opposite may be true. Implementation of a RRT-system is potentially expensive. However, no cost analyses have been undertaken to assess its monetary value.

Finally, an unexpected problem has recently been noted in very mature systems that have operated for >20 years, as is the case in several Australian centres: "RRT addiction". In such hospitals the number of RRT activations has reached the several thousand calls/year value with a dose of >100 calls/1000 admissions and wards have become dependent on the RRT for all kinds of "episodes" with the threshold for activating the team becoming lower and lower. In this setting, concerns have developed that ward staff deskilling and disengagement may be a serious problem. However, such hospitals also report persistent major reductions in cardiac arrest rates, making it uncertain whether such high rates of RRT activation are desirable or undesirable.

Conclusions

RRT-based systems are now an established part of medical and nursing practice in many hospitals and countries. Their goal is to make hospitals safer and to prevent cardiac arrests, emergency late ICU admission and unexpected death. Even though conclusive evidence is not available (as is the case for ICUs or cardiac arrest teams or coronary care units), the logic behind their development is compelling. Hospitals or healthcare jurisdictions that adopt such RRT systems typically never look back and ask themselves why they had not implemented such a system earlier. In some ways, even though the evidence of benefit is not conclusive, RRTs represent a key component of an overall shift in culture and thinking toward greater and more predictable safety and quality in acute healthcare. In this regard, it is surprising that the adoption of RRTs has not spread more widely beyond English-speaking and Nordic/Scandinavian healthcare systems. Accordingly, it is likely that the future will see the slow but steady spread of such systems or similar systems to other developed countries. ■

Conflict of interest

Rinaldo Bellomo declares that he has no conflict of interest.

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Is pre-hospital coagulation management in trauma feasible?

Coagulation management remains a formidable challenge in severely bleeding trauma patients. A strong rationale suggests starting treatment of trauma-induced coagulopathy in the pre-hospital phase.

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The burden of trauma is increasing worldwide, particularly in less well-resourced nations. There are an estimated 5 million deaths per year, more than TB, malaria and HIV combined. Trauma particularly affects young adult males, seeing a disproportionate long-term morbidity and loss of income (Hay et al. 2017). Despite advances in trauma care, haemorrhage remains the leading cause of trauma-associated preventable death in mature trauma systems in developed countries (Tien et al. 2007). About half of these deaths occur in the first hour, with many occurring pre-hospital (Oyeniyi et al. 2017). To aim for and achieve earliest haemorrhage control is literally vital for bleeding patients in any context.

Trauma-induced coagulopathy (TIC) (Johansson et al. 2017) consists of acute trauma coagulopathy (ATC) and resuscitation coagulopathy (RC). ATC occurs in around 1 in 4 patients with major trauma and is a consequence of injury and occurs within minutes of the event (Floccard et al. 2012). Shock seems to exacerbate TIC (Kushimoto et al. 2017). TIC RC is a consequence of resuscitation fluids, acidosis and hypothermia and is near universal in trauma requiring blood transfusion.

The currently most comprehensive pathophysiological model of ATC is conceptualised as systemic endothelial damage or *endotheliopathy* (Johansson et al. 2017). This concept credits the destruction of the proteoglycan layer (glycocalyx), covering all endothelial surfaces in the body, with a pivotal role in mechanism of TIC. Among the main drivers of this endotheliopathy are inflammatory cascades and sympathoadrenal activation. The degradation products of this endotheliopathy, such as syndecan-1, can be measured in the pre-hospital phase and are correlated with mortality (Ostrowski et al. 2017). The treatment of this endotheliophathy may become a new therapeutic target.

Conventional TIC management starts on admission to the resuscitation room and consists of intravenous tranexamic acid, the only current specific treatment for ATC, and blood product resuscitation. The latter includes fresh frozen plasma, platelets and fibrinogen, usually given in a 1:1:1:1 ratio (Holcomb et al. 2015; Harris et al. 2018) but targeted therapy may be an alternative (Gonzalez et al. 2016). The rapid deterioration and mortality associated with trauma haemorrhage sees the early treatment of TIC in the pre-hospital environment to be of paramount importance (Spinella and Cap 2017). The pre-hospital use of blood products in this context is the focus of this mini-review.

Detecting pre-hospital trauma-induced coagulopathy

The first challenge for pre-hospital TIC Management is to detect it. **Clinical scores** have been described and could be applied to pre-hospital use to predict TIC (**Table 1**). The first generation of scores predicted massive transfusion (Brockamp et al. 2012). However, massive transfusion is not consistently associated with TIC, concerns only a minority of patients and became less frequently required (Cantle and Cotton 2017). Other scores use specific pre-hospital parameters to predict TIC (**Table 1**). Scores may offer the advantage of easily identifying patients that will not require blood products. Overall, scores appear to be used infrequently (Hamada et al. 2015) and their impact on management has not been prospectively evaluated. Clinical gestalt remains probably equivalent to the aforementioned scores to detect TIC (Pommerening et al. 2015).

Deployment of **point-of-care (POC)** devices (Gauss et al. 2014; Mistral et al. 2017) in the pre-hospital setting theoretically offers an objective alternative for TIC detection. Their level of agreement compared to laboratory-based results is variable and the value of POC-measured variables remains a matter of debate (Hagemo 2013). Furthermore, most POC devices measure international normalised ratio (INR), probably not a reliable indicator of TIC. Determination of their role and potential benefit, in particular in comparison to clinical judgment, requires more research.

Managing pre-hospital trauma-induced coagulopathy

Current pre-hospital TIC management relies on blood component therapy. However, the recombination via transfusion results in a coagulopathic product with an estimated INR of 1.5. Whole blood is favoured by some pre- and in-hospital providers and may be less coagulopatic and more simple to administer (Spinella et al. 2016). The strategy has not been assessed in a randomised trial. For the time being pre-hospital TIC management relies on currently available component therapy which shall be considered.

Tranexamic acid (TXA) remains a fundamental element of any TIC strategy based on the results of the Crash-II trial (CRASH-2 trial collaborators et al. 2010). Some groups question standard and routine administration without prior documentation of hyperfibrinolysis, because of a potential negative influence in patients with physiological fibrinolysis

Table 1. Clinical scores to predict massive transfusion (MT) and trauma-induced coagulopathy (TIC)

Score	Variables	Predictive performance
Prediction of massive transfusion scores (selection)		
ABC [Nunez et al. 2009] Acute Blood Consumption	Penetrating trauma, HR >120 b/min, systolic pressure <90 mmHg, FAST positive	AUC 0.76 Sensitivity 76.1% Specificity 70.3% LHR+ 2.5 LHR- 0.34
TASH [Yücel et al. 2006] Trauma-Associated Severe Haemorrhage	Unstable pelvis, open femur, FAST positive, HR >120 b/min, systolic pressure < 100mmHg, Hb <12, BE < -2	AUC 0.89 Sensitivity 84.4% Specificity 78.4% LHR+ 3.8 LHR- 0.21
Clinical gestalt to predict massive transfusion and bleeding		
GESTALT [Pommerening et al. 2015]	At discretion of physician in charge	AUC 0.66 Sensitivity 66% Specificity 64% LHR+ 1.53 LHR- 0.53
Prehospital prediction of coagulopathy		
COAST [Mitra et al. 2011] Coagulopathy of Severe Trauma INR >1.5	Entrapment, systolic pressure 90-100 mmHg, likely pelvic or abdominal injury, thoracic decompression, temperature <35	AUC 0.83 Sensitivity 60.0% Specificity 96.6% LHR+ 15 LHR- 0.42
TICCS [Tonglet et al. 2017] Trauma-Induced Coagulopathy Clinical Score Viscoelastic parameters, INR >1.3, Fib <1.5 g/dl	Critical, systolic pressure <90 mmHg, extent of injury (torso, abdomen, pelvis)	AUC 0.70 Positive predictive value 48% Negative predictive value 89%
PACT [Peltan et al. 2016] Prediction of Acute Coagulopathy of Trauma INR >1.5	Pre-hospital: age, GCS, shock index, intubation, traumatic arrest, mechanism	AUC 0.80 Sensitivity 69% Specificity 74% Score >/= 5 factors: LHR+ 23, LHR- 0.55
Prediction of coagulopathy components		
FIbAT [Gauss et al. 2017] Fibrinogen on Admission in Trauma Fibrinogen <1.5g/dl	Age <33y, pre-hospital HR >100, pre-hospital systolic pressure <100 mmHg, FAST positive, lactate >2.5mmol/l, temperature <36, delta Hb >2 g/dl, admission Hb <12 g/dl	AUC 0.87 Sensitivity 46.0% Specificity 96.6% Score >/= 5 factors: LHR+ 23, LHR- 0.55

AUC area under curve BE base excess FAST focused assessment with sonography in trauma GCS Glasgow Coma Scale Hb haemoglobin HR heart rate INR international normalised ratio LHR +/- likelihood ratio positive and negative

(Moore et al. 2016). Its beneficial effect on overall and 24-hour mortality seems reproducible after pre-hospital administration in patients with bleeding or a high likelihood of transfusion (Wafaisade et al. 2016; Morrison et al. 2012). The earlier TXA is administered the safer and more effective it is (Gayet-Ageron et al. 2018).

> "knowledge and familiarity of use required for pre-hospital TIC-targeted resuscitation suggest it may require delivery by enhanced care teams"

Red blood cells (RBC) are a crucial element of TIC management, mainly because RBC improve the rheological properties of blood-facilitating clot formation. The Mayo Clinic helicopter emergency medical service in the USA and French physician-staffed emergency medical systems have practised pre-hospital RBC transfusion since the 1980s. Various and heterogenous reports shared observational data on the clinical impact of pre-hospital RBC use (Lockey et al. 2013; Lyon et al. 2017), some with promising results (Brown et al. 2015). A meta-analysis of these studies did not indicate a benefit (Smith et al. 2016), but did not include a recent publication (Rehn et al. 2018) that indicates increased survival to hospital.

Fresh frozen plasma (FFP) is available and carried by pre-hospital providers as cooled thawed plasma, useable for up to 3 days. Lyophilised plasma was widely used in the 1950s and has regained interest recently (Martinaud et al. 2012) (**Table 2**). Lyophilised plasma solves logistical issues associated with thawed FFP. Plasma may attenuate TIC-associated endotheliopathy, maybe by restoring the proteoglycan layer (Kozar et al. 2011). Lyophilised plasma contains higher fibrinogen concentrations and is associated with quicker correction of coagulopathy compared to FFP (Garrigue et al. 2018). Lyophilised plasma is an ideal pre-hospital component of TIC management, easy to carry and administer, and its use is feasible in the pre-hospital context (Jenkins et al. 2014).

Fibrinogen concentrate (FC) is the key substrate of the coagulation cascade (Maegele et al. 2015), and low levels are associated with increased mortality (Inaba et al. 2013; McQuilten et al. 2017). Low plasma fibrinogen

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Table 2. Lyophilised plasma types

Type of Plasma	Properties	Current use
German lyophilised Plasma (LyoPlas N-w) *(DRK Blutspendedienst West, Germany)*	Single donor AB-Plasma, no pathogen inactivation, delivered after 4 months, lyophilised in glass bottle, storage 25 months 12–25 °C, use in sterile aqua	RePHILL trial, some civil units and Israeli Special Forces
French lyophilised plasma (FLyP®) *(Centre de Transfusion Sanguine des Armées, France)*	Pool of > 10 donors, different ABO groups, pathogen inactivation (Amotosalen-UV- irradiation), inactivated leucocytes, storage two years at 14–25°C, use in sterile aqua	French and US special forces, French military, some French civilian centres
Bioplasma FDP® *(National Bioproducts Institute, Pinetown, South Africa)*	Pooled ABO-Universal-Plasma pathogen inactivation (S/D-method) and lyophilised	No data

Table 3. Lists of ongoing trials, investigating the components of pre-hospital TIC Management or their combination

Trial	Intervention	Outcome
COMBAT Control of Major Bleeding After Trauma **ClinicalTrials.gov NCT01838863**	Randomised administration of 2 units of AB-plasma vs. normal saline	Primary: 28-day mortality Secondary: Multi-organ failure
FinTIC ClinicalTrials.gov **NCT01818427**	Randomised high-dose fibrinogen concentrate administration vs standard care	Primary: Fibrinogen polymerisation on viscoelastic test Secondary: Viscoelastic test and laboratory parameters, thromboembolic events
PAMPer Pre-hospital Air Medical Plasma **ClinicalTrials.gov NCT01818427**	Randomised pre-hospital air ambulance 2 units plasma administration of 2 units of plasma vs standard care	Primary: 28-day mortality Secondary: transfusion organ failure
PATCH Pre-hospital Antifibrinolytics for Traumatic Coagulopathy and Haemorrhage **ClinicalTrials.gov NCT02187120**	Randomised pre-hospital administration of TXA vs placebo	Primary: Glasgow Extended Outcome Scale at 6 months Secondary: transfusion, coagulopathy, mortality, etc,
PREHO-PLYO Pre-hospital Plasma lyophilised **ClinicalTrials.gov NCT02736812**	Randomised pre-hospital administration of lyophilised Plasma vs normal saline	Primary: change in Prothrombin level Secondary: INR, ROTEM
PRO-COAG Prothrombin Concentrate Complex Trauma Hemorrhage **ClinicalTrials.gov NCT03218722**	Randomised intra-hospital PCC administration vs placebo	Primary: transfusion requirements Secondary: INR, ROTEM parameters
RePHILL Resuscitation with Pre-Hospital blood products **IRAS ID: 179484**	Randomised pre-hospital administration of 2U blood and FFP vs normal saline	Primary: Survival Secondary: organ perfusion, lactate levels,

ROTEM rotational thromboelastometry

leads to reduced clot firmness (Ostrowski et al. 2011) and is the first coagulation factor to reach critically low levels (Schöchl et al. 2014). The fibrinogen-to-RBC ratio was independently associated with improved survival (Stinger et al. 2008), and only high-dose fibrinogen substitution appears to correct TIC (Khan et al. 2014). FC presents the advantage of easy carry, use and low-volume administration. Currently there are no randomised trials demonstrating efficacy or improvements in mortality.

Prothrombin complex concentrate (PCC) can consist of either three- or four-factor preparations. The composition can vary substantially and contain pro-coagulant factors, mainly factors II, IX, and X, with or without factor VII, and anti-coagulant factors such as Protein S and C and Antithrombin III (Grottke and Levy 2015). Preclinical studies suggest an appealing pathophysiological rationale (Hansson et al. 2017). Small clinical studies suggest PCC used in combination with FC to be associated with lower mortality and reduced blood product use (Schöchl et al. 2010; Innerhofer et al. 2013); the main risk is associated thromboembolic events (Grottke and Levy 2015). PCCs are easy to carry, use and allow low-volume administration. A prospective trial (PRO-COAG) is currently ongoing in France (**Table 3**).

There are no published pre-hospital trials, which assess the efficacy of TIC-targeted resuscitation strategies that include blood product delivery. The pre-hospital environment carries specific organisational, logistical and physiological constraints. The time window to identify TIC and administer treatment such as blood products is limited in the pre-hospital environment and increasing scene time may increase mortality. The level of knowledge and familiarity of use required for pre-hospital TIC-targeted resuscitation suggest it may require delivery by enhanced care teams. There may be insufficient time for clinicians to assess for TIC and deliver the large volumes of component blood therapy (2-4 RBC, 2-4 FFP, 4g of Fibrinogen). This will require the teams to identify the key interventions for pre-hospital care delivery in terms of efficacy, cost and ease of delivery.

Pre-hospital TIC strategy

Grounded upon the preceding observations and concepts a pre-hospital TIC strategy could comprise the first-line administration of tranexamic acid,

lyophilised plasma and FC. All three are easy to use, carry and store; combined they represent a reasonable volume load that is feasible to administer within the pre-hospital time frame. Pre- and in-hospital treatment should be integrated and seamless as part of a unified pathway. This should include agreed triggers, algorithms and treatment at a network or preferably national level. Examples include so-called 'code red' protocols (Weaver et al. 2012; Hamada et al 2018). An integrated, interrelated pathway would reduce still-existing barriers to timely blood product administration (Stanworth et al. 2016). A synergy between clinical judgement and machine learning algorithms embedded into patient monitors might improve detection of TIC in the near future.

In summary, initiation of pre-hospital TIC management is feasible and ongoing prospective trials will define the most appropriate treatment strategies.

Conflict of interest

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Abbreviations

ATC acute trauma coagulopathy
FC fibrinogen concentrate
FFP fresh frozen plasma
INR international normalised ratio
PCC prothrombin complex concentrate
POC point-of-care
RBC red blood cells
RC resuscitation coagulopathy
TIC trauma-induced coagulopathy
TXA tranexamic acid

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Pre-ICU health organisation in Norway

Presents the main principles of the Norwegian acute healthcare system.

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Norway is a rather small country with a population of about 5.3 million. More than half of these inhabitants are located in and around the larger cities, with about a million in the capital region of Oslo. Hence, significant parts of the country are rural, with fjords and high mountains, combined with winter darkness and harsh weather conditions (**Figure 1**). However, the country is 2500 km long and has approximately 50 hospitals, all part of the national health system. Some of these hospitals are serving large and sparsely populated areas. These hospitals may have rather small post-anaesthesia care units (PACUs) caring for intensive care unit (ICU) patients, but ICU patients in need of more specialised care will in most cases be transferred to the larger hospitals with more complete ICUs by ground or air ambulance. This has had a great influence on how the Norwegian acute healthcare system is organised.

Our country has been blessed with a solid economy based on export of oil, gas and fish, giving the politicians financial resources for reaching their goal of providing the same level of health services for everyone regardless of place of residence. Given the challenging nature of this aim, one may argue that they have succeeded since Norway scores high on parameters like life expectancy and other health-related indicators.

The Norwegian acute healthcare system is based on two key factors:

1. A well-developed emergency care system organised in the municipality, and
2. A nationally distributed and complete emergency medical system (EMS), with a nationwide medical emergency communication system connecting the emergency communication centres, ground and boat ambulances, in addition to numerous air ambulances (both fixed-wing and rotor-wing). The latter resources are staffed by specially trained nurses and anaesthesiologists.

> "it is rather uncommon that a patient presents at a hospital emergency department without being seen by a physician on beforehand"

Norwegian emergency healthcare organisation

According to national regulations, every Norwegian municipality must have a system in place for providing emergency medical care for their residents and also others, e.g. visitors and tourists. This means that the more than 300 municipalities are responsible for the primary healthcare service, including the primary care general practitioners (GPs), and GPs on call 24-7. In addition, they are also responsible for providing out-of-hours services and there are approximately 100 local emergency medical communication centres (LEMC) and 180 local casualty clinics. Because of this system, it is rather uncommon that a patient presents at a hospital emergency department (ED) without being seen by a physician on beforehand. The exception is in some of the emergencies, where ambulances transport severely ill and injured patients directly to the ED. The four regional health authorities are responsible for the secondary and specialised healthcare service through the local hospital trusts. This includes hospitals, ground, boat and air ambulance services, and the emergency medical communication centres (EMCC) (Official Norwegian Reports 2015; Ministry of Health and Care Services 2015) (**Figure 1**).

Care for acutely ill or traumatised patients is based on a two-tiered system where the municipalities are responsible for the first part and the hospital trusts responsible for the more specialised part of the system. GPs, ambulance personnel and sometimes the anaesthesiologists in the air ambulance system, cooperate in acute pre-hospital responses. Other countries organise their emergency healthcare system differently, many without the involvement of GPs or the primary healthcare services. GPs have an important role in the Norwegian primary care services. One function is the work as a "gatekeeper", and patients must be admitted to hospital by a doctor. Exceptions are made when ambulance personnel consider the patient to have a life-threatening medical condition, and the patient is transported directly to hospital.

Persons in need of emergency medical care are supposed to call the national emergency telephone number 113, reaching the nearest EMCC (Norwegian Medical Association 2009). The Norwegian EMCCs are staffed with medically trained personnel (nurses and ambulance personnel with emergency medicine experience). They will provide counselling, and alert the appropriate emergency health resources if needed, including dispatch of ambulances, on-call GPs and air ambulance.

The EMCCs use a national priority dispatch system as a decision tool (the Norwegian Index for Medical Emergencies) to classify medical problems into three different levels of responses represented by colour codes (Norwegian Medical Association 2009). Health authorities regulations require 90% of all emergency phone calls to EMCCs to be answered within 10 seconds (Ministry of Health and Care Services 2015). If inhabitants suspect an acute (but not life-threatening) condition in need of medical care they are supposed to call the nearest LEMC via the national number 116117. Like the EMCC, the LEMC are staffed with nurses. National regulations require that LEMC should answer 80% of phone calls within 2

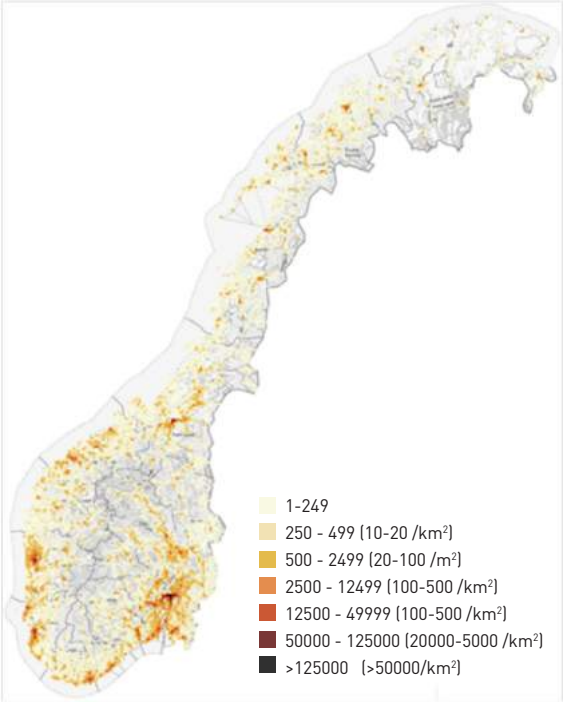

Figure 1. Graphical display of the population density in Norway

Source: Statistics Norway **kart.ssb.no**

minutes (Ministry of Health and Care Services 2015). A digital and restricted nationwide medical communication network is used for communication between the LEMCs, EMCCs and the other cooperating resources*.

The medical emergency responses are divided into three levels:

- Acute or red responses in presumably life-threatening situations, where the GP on call and ambulance is immediately dispatched (Official Norwegian Reports 2015). Approximately 25% of all contacts with EMCCs are due to acute responses, while only 3% of the contacts to LEMCs lead to an acute response (Haaheim et al. 2014; Morken et al. 2016).
- **Urgent** or yellow responses in potentially life-threatening situations, where an ambulance may be dispatched or the patient referred to a local GP (Official Norwegian Reports 2015). Approximately 36% of the contacts with EMCC lead to an urgent response, while 27% of the contacts to LEMC lead to an urgent response (Haaheim et al. 2014; Morken et al. 2016). Usually the EMCC transfer these calls to a LEMC if the medical problem does not require an ambulance (Norwegian Medical Association 2009).
- **Non-urgent** or green response is when it is presumed that time is of little medical importance and the patient can wait to be examined until a doctor eventually is available (Norwegian Medical Association 2009). Usually, these patients are evaluated by their GP during office hours. Approximately 36% of the contacts with EMCC are due to non-urgent responses, while 70% of the contacts with LEMC are due to non-urgent responses (Haaheim et al. 2014; Morken et al. 2016).

Every year, the more than 500 ambulances perform close to 700,000 missions (130 per 1,000 inhabitants), of which approximately 30% are acute, 40% urgent and 30% non-urgent missions (Statistics Norway 2015). Response time varies, and in 2016, the rural ambulance services reached the patient within 25 minutes in 81% of the missions, while in urban areas, the ambulance reached the patient within 12 minutes in 72% of the missions. The national goal is 90% in both described cases (Helsedirektoratet 2016). In rural parts of Norway, there is a relatively low volume of severely injured or ill patients, and therefore both GPs and ambulance personnel need frequent training to maintain their skills (Official Norwegian Reports 2015; Myklestad et al. 2014; Norwegian National Advisory Unit on Trauma 2015). This type of training is seen as cost-effective skill improvement and is required by regulations (Ministry of Health and Care Services 2015; Utsi et al. 2008).

The Norwegian Intensive Care Registry (**intensivregister.no**) receives data from about 36 hospitals. In 2016 a total of 13,679 ICU patients, accounting for 15,403 ICU-stays and 62,311 ICU-days were registered. Close to 60% of the stays were at local and central hospitals, while the rest were at the four university hospitals. The median length of stay was 2.0 days (95% CI=2.0-2.2), and the overall 30-day mortality was 23%.

As can be expected with many rural hospitals, a number of patients in need for specialised ICU treatment must be transported to the larger ICUs. Hence, there is need for a system for transporting such patients between hospitals, and in Norway this is solved by a national air ambulance system.

The national air ambulance service consists of 13 physician-staffed ambulance helicopters (on 12 bases), equipped to offer advanced emergency medical treatment outside the hospital and to transport patients directly to a hospital if needed (Norwegian National Air Ambulance Service n.d). In addition, there are seven search and rescue (SAR) helicopters and nine fixed-wing aeroplane air ambulances, which also are part of the national air ambulance system (**Figure 2**). This service provides an important part of the pre-ICU system, and also has the capability to transport patients on ECMO and intra-aortic balloon pump, and incubators with babies on nitric oxide. In 2016, this service treated approximately 20,000 patients, of whom about 6,000 were transfers between hospitals (Statistics Norway **ssb.no**).

As one can understand from the above, in a long and sparsely populated country, with challenging geography and weather, the pre-ICU system in Norway is comprehensive and well developed. Nevertheless, there is a constant need for identifying patients in need of ICU care, and also to maintain

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quality of care at smaller hospitals, which don't treat seriously ill or injured patients on a regular basis. Team training and simulation has become an important way of compensating for this (Wisborg et al. 2008). ■

Conflict of interest

Guttorm Brattebø declares that he has no conflict of interest. Øyvind Østerås declares that he has no conflict of interest.

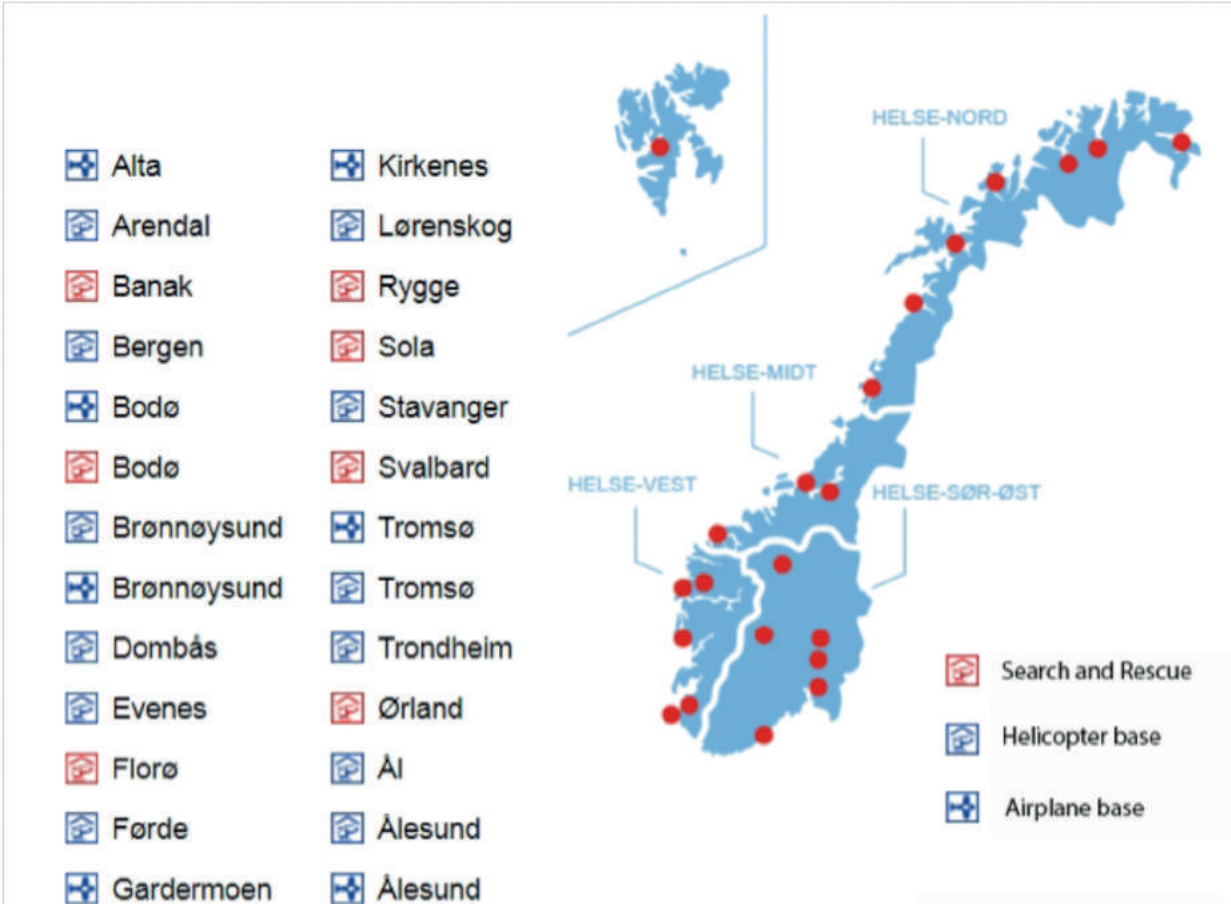

Figure 2. Location of various air ambulance resources in Norway (including Spitsbergen)

Source: Luftambulansetjenesten **luftambulanse.no**

* Nødnett – the Norwegian Emergency Public Safety Network is a separate radio network, built specifically for rescue and emergency users.

Abbreviations

EMCC emergency medical communication centre

GP general practitioner

LEMC local emergency medical communication centre

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Emergency pre-hospital care challenges: Greece

The ongoing economic crisis in Greece and inflow of refugees has led to changes to the pre-hospital emergency medicine services.

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Greece is a country of 10.1 million inhabitants, half of whom live in six cities: Athens, Thessaloniki, Heraklion, Patra, Larissa and Ioannina. In recent years the country drew media attention because of the financial crisis and the inflow of refugees, which often pushed state services and infrastructure to the limit. Nevertheless, along with problems, new chances emerged.

Healthcare system

The Greek healthcare system is a mixed system, combining Social Health Insurance (SHI) and central financing of the National Health System (NHS). The country is divided into seven administrative health districts. There is an uneven distribution of public facilities and staff across the country, with most of them sited in urban areas (OECD/European Observatory on Health Systems and Policies 2017). Each region has several hospitals and smaller health units under its jurisdiction, but the pre-hospital emergency care services (PEMS) are an independent public institution. Until 2013 hospitals had separate limited ambulance services for non-emergency cases (transport of hospitalised patients and, when needed, biomedical material). An administrative reform in late 2013 discontinued hospitals' ambulances services and transferred all patient transportation under the umbrella of PEMS.

Pre-hospital emergency care services structure

PEMS were developed during the mid-1980s with the foundation of the National Center of Emergency Care (NCEC or "EKAB"); which is entirely funded from the state budget. NCEC central is located in Athens, and the country is divided into 12 independent departments. Each has its own dispatch centre (DC) and is responsible for providing PEMS in a certain geographical area (ekab.gr/chorotaxiki-katanomi) (**Figure 1**). The NCEC phone number is 166; indirect calls can also be realised via the 112 phone number (European Commission Communications Committee 2017). The working model is a mixture of the classical European and American model (Al-Shaqsi 2010). Ambulances and DCs are staffed by emergency medical technicians (EMTs) with advanced training, while emergency medical service (EMS) physicians are also engaged in pre-hospital acute care as DC coordinators or mobile intensive care unit physicians at the scene. Education of PEMS staff apart from doctors is unified, but there are no official levels of PEMS training. Moreover, emergency medicine has not yet been formed as a separate subspecialty or specialty. Physicians participating in the system are exclusively employed by NCEC and come from different background specialties (mostly anaesthesiology, general surgery, and cardiology) (World Health Organization. Regional Office for Europe & European Union 2008). The only official postgraduate programme offered for medical doctors is the 12-month PEMS postgraduate educational programme in pre-hospital emergency medicine.

> "managing medical emergencies for refugees' camps appeared to affect PEMS workload"

The numbers and data of this article come from the Thessaloniki DC in northern Greece, which is the second largest in the country. It answers an average of 32,000 phone calls and manages about 7000 emergencies every month (Aslanidis et al. 2016). For the same time interval, the biggest DC in Greece (Athens DC) answered 160,000 phone calls and managed about 30,000 emergencies.

The crises

The Greek healthcare system was not well prepared to cope with the challenges imposed by the deep and lasting economic crisis (Economou et al. 2014). A profound impact on almost every aspect of healthcare emerged (Laliotis et al. 2016). It is no surprise that over 200 articles are dealing with the subject *Financial crisis and health in Greece* after 2009 (Pubmed Search 2018).

Within this framework of constantly increasing population needs, underfunding of the public sector, uneven distribution of health resources, medical understaffing and a 'brain drain' phenomenon, the refugee crisis in the last years exacerbated an already very difficult situation. Only for the period January 2015- June 2016 the system had to deal with an inflow equal to almost 10% of the country's population (United Nations High Commissioner for Refugees Bureau for Europe 2016).

Most published studies deal with the consequences of the aforementioned at hospital emergency department (ED) level. Higher use of public ED services, public hospital dental and obstetric services (Economou et al. 2014), neurological services (Bougea et al. 2016), higher incidence of physical abuse (Kontos et al. 2017a) and soft tissue infections are some of the findings reported (Kontos et al. 2017a). Still, the overall impact assessment of the economic and refugee crisis is biased by the lack of a standard quality of acute hospital care network system. There is no widespread periodical public reporting based on a standard set of quality indicators (e.g. hospital case-fatality rates for acute myocardial infarction [OECD/European Observatory on Health Systems and Policies 2017]).

At the same time, PEMS usage has increased over the years (Aslanidis et al. 2016) (**Figure 2**). The more interesting fact is the change of type of PEMS cases.

Figure 1. Location of Dispatch Centres

The only optimistic feature has been the decreasing trend of car accident-related trauma (OECD/European Observatory on Health Systems and Policies 2017; Aslanidis et al. 2016). On the contrary, suicides, violence-related trauma and acute alcohol intoxications cases steadily increased (Aslanidis et al. 2016). An increase in complications and exacerbations of chronic conditions (e.g. hypoglycaemias in diabetic patients, COPD exacerbations) managed by PEMS seem to confirm the high rate of unmet health needs reported in other studies (OECD/European Observatory on Health Systems and Policies 2017; Kotsiou et al. 2018).

In addition, managing medical emergencies for refugees' camps appeared to affect PEMS workload, more in terms of quality than in quantity. The only study dealing with the subject comes from Northern Greece. During a 6-month period in 2016, medical emergencies from 15 refugees' camps that were handled by PEMS contributed to an increase of 'only' 3-5% in the total number of emergency cases. However, the geographical distribution of the camps and, mainly, the character of the cases tell a different story. Most of the camps were located several kilometres away from the main city; thus, time engagement of PEMS for those cases often created dispatching problems. More than 70% of the cases concerned people up to 45 years old. In comparison with the general population, a high incidence of paediatric and obstetric emergencies were recorded. Trauma cases were also high (35%), with equally high rates of crime-related injuries (Nikolaidou et al. 2017).

Response and reforms

It became obvious that both organisational and structural changes were needed in order to cope with the challenges posed by the aforementioned factors. Major efficiency-oriented and infrastructural reforms were initiated after 2010, all based on three priority axes: universal health access, transparent, modern and efficient health system administration; and fair and sustainable financing (OECD/European Observatory on Health Systems and Policies 2017). PEMS was not an exception.

Organisation and administration

During 2017 a primary care health plan was launched in order to prioritise primary care. Launching of fully autonomous emergency departments, mainly with staffing in hospitals is also part of that reform (OECD Health profile Greece 2017). The latter two are expected to have a great effect on PEMS usage.PEMS DCs' information systems have also been modified, in order to enhance management of emergencies and interconnectivity among different DCs in the country. Linkage of those systems with the existing hospital information systems is expected.

Also, an attempt to modernise ambulance vehicles, medical equipment, expand helicopter PEMS and launch naval PEMS has been initiated. Collaboration with other public services, both civilian and

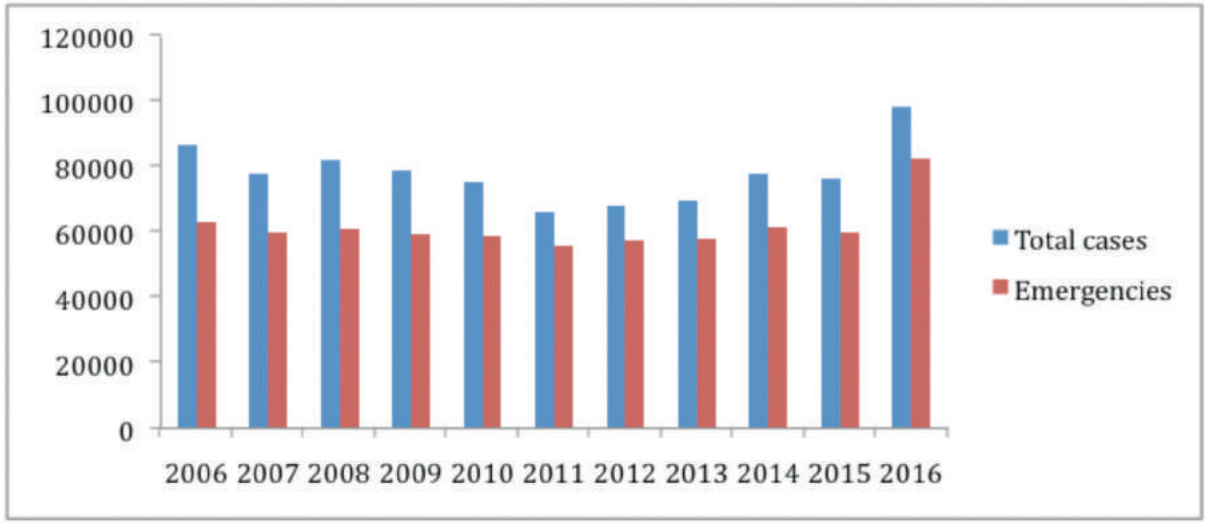

Figure 2. Annual distribution of PEMS cases (total and emergencies) in Thessaloniki Department

military, and with the private sector, which mainly contributed to the system with donations, is essential to this effort.

> "emergency medicine has been recognised as an official subspecialty"

Education

The termination of hospital ambulance services in late 2013 increased PEMS workload (Aslanidis et al. 2017). This triggered a discussion about the future official formation of different level of EMS.

The PEMS Public Vocational Institute curriculum has been modified. Future EMS staff must complete an extended curriculum of 1500 hours theory and 960 hours of ambulance practice before sitting for the National Accreditation Examination (Ministry of Health 2018). The change is tremendous, especially in practice, compared to the old syllabus that contained only 120 hours of ambulance practice. Programmes of continuing professional development for PEMS staff, alongside public educational programmes were also intensified.

Emergency medicine has been recognised as an official subspecialty and a national committee formed in order to suggest the minimum educational requirements, in accordance with the European Society of Emergency Medicine (EuSEM) curriculum (Härtel et al. 2017).

Efficiency assessment underway

The information systems deployed during recent years (OECD/European Observatory on Health Systems and Policies 2017) have created a huge national data-gathering network. Data analysis to fully evaluate all these changes that took place as a PEMS response to the challenges posed by economic crises and inflow of refugees is underway. ■

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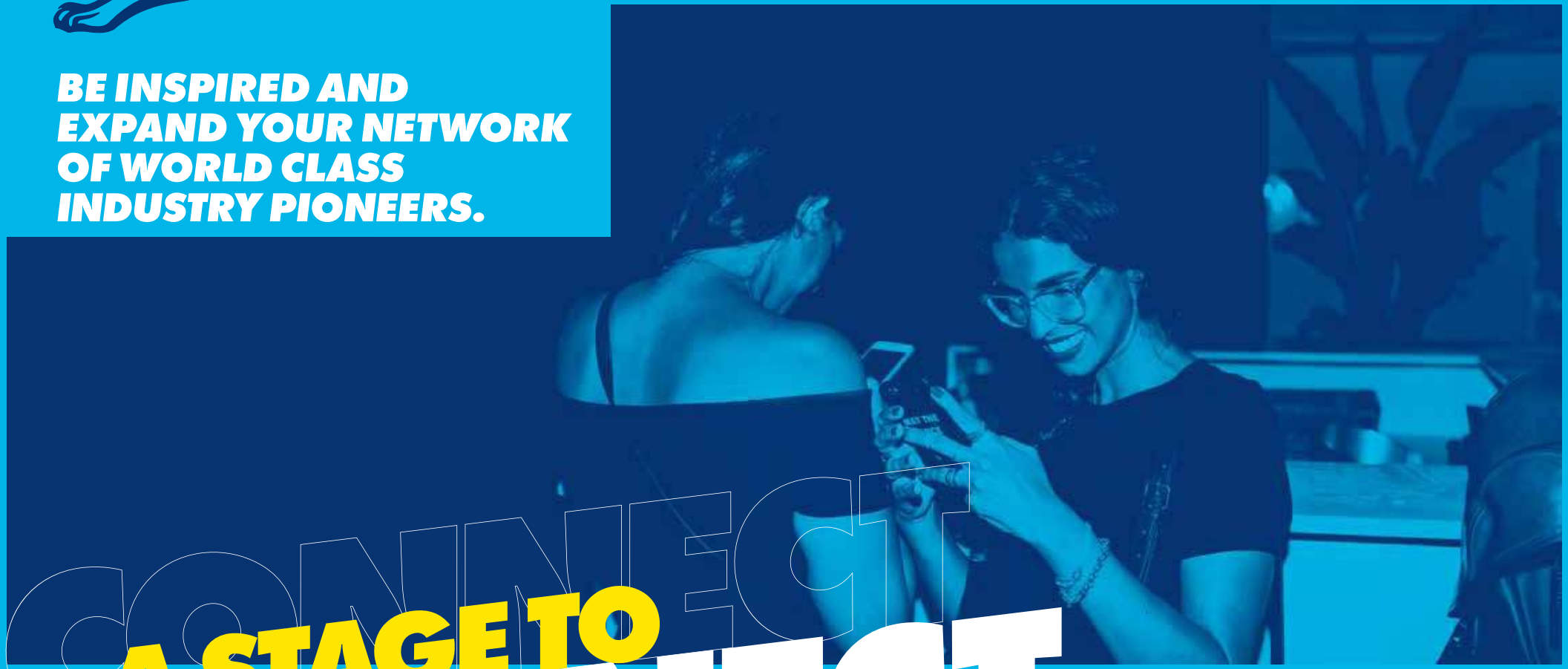

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Point-of-care ultrasonography in critical care

A brief overview of point-of-care ultrasound (POCUS) in the ICU: for the already converted, a reminder of how POCUS has changed ICU practice; for the ultrasound naïve, an aperitif to leave the reader with interest in this evolving paradigm shift of patient care.

As intensivists, we have all faced this scenario: a 28-year-old woman, 35 weeks pregnant, presenting to the emergency department with respiratory failure, acute kidney failure and a non-diagnostic chest radiograph. Regardless of the clinical history and physical exam, the diagnosis may remain ambiguous without further testing. How would you proceed with the workup for this patient?

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Using the traditional compartmentalised approach, numerous tests may be ordered, including a CT of the chest with contrast, ultrasound studies of the abdomen and lower extremities, and an echocardiogram. This approach leads to the inherent clinical and time dissociation implicit with consultative radiology and echocardiography. Alternatively, a critical care physician may perform a point-of-care ultrasound (POCUS) exam at the bedside, integrating the results to establish a diagnosis and guide patient management.

Physicians have used ultrasonography for more than half a century to aid diagnosis and guide procedures. With technological advancement, ultrasound equipment became more compact and led to the advent of POCUS, which is defined as ultrasonography brought to the patient and performed by the provider in real time (Moore and Copel 2011). The realisation that physicians can see and assess physiological function in real time has been a tipping point in critical care medicine and has revolutionised the care of patients in the intensive care unit (ICU). This dynamic imaging is a complete paradigm shift from the traditional consultative approach where technologists and physicians not intimately involved in patient care are responsible for image acquisition and interpretation. This eliminates clinical and time dissociation in patient care, allows a timely diagnosis without potentially dangerous patient transport and reduces radiation exposure (Moore and Copel 2011). The critical care literature is replete with studies supporting the use of POCUS, and as an increasing number of providers acquire critical care ultrasonography training, POCUS is becoming the standard of care in the ICU (Moore and Copel 2011; Killu et al. 2014).

Thoracic ultrasonography

While the differential diagnosis of respiratory failure may be broad, thoracic ultrasound allows the intensivist to characterise the abnormality by determining the predominant pathophysiologic process present. Thoracic ultrasound may determine if the patient has predominately wet lungs (cardiogenic or non-cardiogenic pulmonary oedema), an alveolar consolidation pattern (acute respiratory distress syndrome [ARDS], pneumonia, or atelectasis), a pneumothorax, a pleural effusion, or any combination. The accuracy, sensitivity, and specificity of thoracic ultrasound are similar to chest CT in patients who present with respiratory failure. Pioneering work by the intensivist Daniel Lichtenstein led to the development of the basic lung ultrasound findings used in the ICU.

> "POCUS is becoming the standard of care in the ICU"

Lung sliding with an A line pattern indicates that the visceral pleural surface is moving freely with respiration against the parietal pleura, and defines a normal aeration pattern. When observed in multiple places on the thorax this indicates that major pleural or parenchymal abnormality is unlikely to exist. Lung sliding also rules out a pneumothorax with a negative predictive value of 100% at the site of the ultrasound probe (Lichtenstein and Menu 1995). A *lung point* is the point where normal pleural interface contacts the boundary of the pneumothorax and when observed is 100% specific for a pneumothorax (Lichtenstein et al. 2005). A recent meta-analysis concluded that ultrasound was superior to chest radiography in detecting a pneumothorax (Arajhi et al. 2012). Trained providers can easily use POCUS for immediate diagnosis of this condition instead of waiting for a formal radiograph.

Thoracic ultrasonography may help in identification of the cause of respiratory failure. *A-lines* are horizontal repetitions of the pleural line, and indicate a normal aeration pattern of the lung. However, when the sub pleural interlobular septa are oedematous, hyperechoic comet tail artifacts called *B-lines* arise, which indicate the presence of an *alveolar interstitial syndrome*. When bilateral, multiple B-lines can signify cardiogenic or non-cardiogenic pulmonary oedema; when unilateral they likely represent infection, or rarely unilateral pulmonary oedema (re-expansion oedema or mitral regurgitation) (Lichtenstein and Mezière 2008). Since B-lines are dynamic and disappear as the underlying process improves, repeat ultrasound exams can be used to monitor a patient's response to treatment. A-line versus B-line patterns on lung ultrasonography also allow the differentiation of exacerbations of chronic obstructive pulmonary disease (COPD) and pulmonary oedema secondary to decompensated heart failure (Lichtenstein and Mezière 1998). Thoracic ultrasonography also has 90% sensitivity and 98% specificity in detecting alveolar consolidations, which have a sonographic appearance similar to that of the liver, a pattern referred to as *hepatisation of the lung*. Ultrasound is arguably the best radiographic modality for the diagnosis and characterisation of a pleural effusion, and allows safe and accurate placement of various chest tubes if clinically indicated. Diaphragmatic function is also accurately assessed with ultrasound and may help in deciding when to liberate patients from mechanical

ventilation (Ferrari et al. 2014). In the BLUE-protocol described by Lichtenstein, profiles have been designed to allow rapid diagnosis of the common causes of acute respiratory failure with an accuracy > 90% (Lichtenstein and Mezière 1998).

Critical care echocardiography

The categorisation of shock state with goal-directed echocardiography has logical benefit for patients in cardiorespiratory failure. Using limited echocardiographic views, the intensivist can rapidly determine whether the shock state is distributive, obstructive (massive pulmonary embolus or tamponade), cardiogenic or hypovolaemic. Life-threatening processes are identified immediately (massive pericardial effusion) and allow coordination of emergent procedures (pericardiocentesis or thrombolysis) Key findings, such as right ventricular pressure overload from heart-mechanical ventilator interactions, or preload sensitivity in undifferentiated shock, is readily identified by the intensivist with basic goal-directed echocardiography.

Echocardiography also allows rapid assessment of the causes of respiratory failure that derive from cardiac dysfunction. Goal-directed echocardiogram performed during cardiopulmonary resuscitation may identify a large pericardial effusion, a flail mitral leaflet, an intracavitary thrombus, or a dilated hypokinetic right ventricle (RV) with apical sparing (McConnell's sign). These findings may guide the team in performing emergency interventions. Echocardiography may also identify patients where continued cardiopulmonary resuscitation will not be successful (Varriale and Maldonado 1997; Blaivas and Fox 2001).

Echocardiography also allows the intensivist to monitor the evolution of disease, observe the response to potentially therapeutic interventions, such as inotropic drugs, and to search for new problems that arise during the course of a critical illness.

Goal-directed vascular ultrasonography

As an ever-threatening nemesis to the intensivist, the overt or covert presence of deep vein thrombosis (DVT) and pulmonary embolism are a frequent cause of morbidity and mortality in the ICU. Fortunately, numerous studies have confirmed that non-radiologists can become competent at diagnosing a DVT with an accuracy comparable to radiologists, and only compression ultrasonography is required to make a diagnosis of a DVT (colour and spectral Doppler are unnecessary) (Lensing et al. 1997).

The ultrasonographic appearance of a typical thrombus is a vein with an intraluminal echogenic focus with non-compressible walls. However, fresh, immature thrombi may not be echogenic, and therefore the primary diagnostic criterion is a lack of vessel compressibility and not visualisation of the thrombus.

A limited compression ultrasound study, with five compression points, has a sensitivity and specificity similar to that of a complete examination in detecting a lower extremity DVT (Lensing et al. 1989; Crisp et al. 2010), and is particularly useful when combined with goal-directed lung and cardiac ultrasound in a haemodynamically unstable patient.

Abdominal goal-directed exams

While the abdominal space is complex and the mastery of abdominal ultrasonography is time-consuming, goal-directed abdominal ultrasound is easy to perform and has numerous applications in the ICU. These include the detection of ascites, assessment for hydronephrosis, distension of the bladder, assessment of the aorta and gross organ abnormalities.

Abdominal ultrasound is an optimal first-line imaging modality for the evaluation of peritoneal free fluid. The "focused assessment with sonography for trauma" (FAST) protocol is used in evaluating the patient for free peritoneal fluid from haemorrhage (American Institute of Ultrasound in Medicine 2014). Ultrasound has been shown to be very sensitive and specific for haemoperitoneum, but can be used for evaluation of free peritoneal fluid from any cause.

While the hepatobiliary and pelvic structures are amenable to imaging with bedside ultrasound, the intensivist must use caution in making diagnoses out of their comfort zone, as there are numerous

Returning to our original case

We met our patient in the emergency department; a chest CT with contrast was ordered to rule out a pulmonary embolus, an abdominal CT was ordered to rule out hydronephrosis, and an echocardiogram was ordered to rule out acute cor pulmonale and a pregnancy-related cardiomyopathy. The patient was intubated, hypotensive and severely hypoxaemic. What did we do?

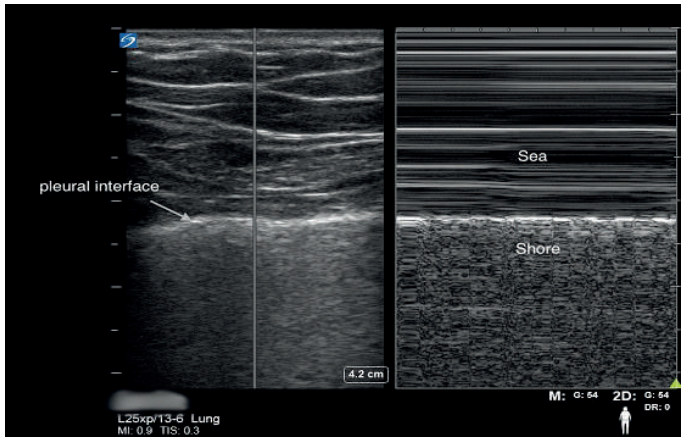
Time 0:
A thoracic ultrasound revealed bilateral B-lines consistent with pulmonary oedema of unclear aetiology: no alveolar consolidation or pleural effusion was present.

Time 1.5 minutes:
Goal-directed echocardiography revealed normal LV function, normal RV size and function, no pericardial effusion, grossly normal valvular function, and a large inferior vena cava without respiratory variation.

Time 2.5–5 minutes:
A goal-directed abdominal ultrasound did not reveal significant hydronephrosis and DVT compression ultrasound was normal.

Time 5 minutes:
Based on the lab results and findings of the POCUS exam, it was determined that the patient had preeclampsia with ARDS. This diagnosis was rendered in just 5 minutes by an intensivist with basic training in critical care ultrasonography, saving this very unstable patient from a dangerous delay in diagnosis as well as unnecessary transport and radiation exposure.

normal variants that may be confused for pathology. A focused US of the kidney and the bladder should be incorporated into the exam for any patient presenting with renal failure, haematuria, urinary retention, abdominal/flank pain or renal trauma. Goal-directed abdominal ultrasound can be used to detect hydronephrosis and urinary obstruction as a cause of acute renal failure. Hydronephrosis is diagnosed when an anechoic area is noted within the renal sinus, which is not vascular in origin (Wang and Chen 2007).



The intensivist can also use ultrasonography in patients with acute abdominal conditions to rule out free air, observe peristalsis, and assess the abdominal aorta to detect abdominal aortic aneurysm rupture or abdominal aortic dissection.

Whole-body ultrasonography?

The benefit of goal-directed ultrasonography is that it relies on the clinician. Since POCUS is used as an extension of the physical exam it is naturally applicable in a 'head-to-toe' fashion to augment the diagnostic process. However, this is not practical, just as a daily fundoscopic exam in a patient with status asthmaticus seems like a waste of time. We perform goal-directed ultrasound as the name implies, where it is needed. All patients in respiratory failure have a thoracic ultrasound, DVT study, and echocardiography. A negative DVT study in a patient with ARDS allows for a baseline to compare should the clinical situation change, as regularly occurs with critically ill patients. Rapid changes in cardiac contractility are seen frequently with normal to hyperdynamic left ventricular (LV) function reduced to either severe global dysfunction or with increasing frequency apical ballooning disease. Patients in renal failure have abdominal ultrasonography to rule out hydronephrosis and to evaluate the bladder; and so on.

Conclusion

We do not deny the life-saving contribution of medical advancement. However, evidence-based medicine through controlled clinical trials has not confirmed the benefit of mechanical ventilators, CAT scans or routine blood analysis. Yet we hold these truths to be self-evident and all intensivists must have intimate knowledge of these tools. POCUS should be no different; a tool used by all intensivists because the logic and evidence of its utility is overwhelming and self-evident. Excuses, such as "I do not need it", "How can I learn it?", "It is too time consuming" etc., have all been overcome by thousands of intensivists worldwide through successful training programmes and mentorship. Old dogs can learn new tricks! As illustrated by this case, POCUS is an extremely valuable tool, which should be used by all intensivists in the evaluation of critically ill patients. It is now difficult to find a critical care journal that does not have articles supporting the use of POCUS and intensivists who use it regularly feel as though they could never go back to practising without it. POCUS signals an era of time-saving and cost-efficient "visual" medicine and once you start using ultrasonography there is definitely no going back. ■

Conflict of interest

Gulrukh Zaidi declares that she has no conflict of interest. Seth Koenig declares that he has no conflict of interest.

Abbreviations

ARDS acute respiratory distress syndrome
DVT deep vein thrombosis
ICU intensive care unit
POCUS point-of-care ultrasound

References

For full references, please email editorial@icu-management.org or visit https://iii.hm/k6u

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Liver support in the intensive care unit

Mechanism of action and science

The idea of liver assist is extremely attractive for patients with liver failure, as the liver possesses huge capacity to regenerate. The hypothesis behind the use of extracorporeal liver assist is to enhance the regenerative environment by removing or replacing toxic molecules while the liver can regenerate. Extracorporeal liver assist devices are either based on the principles of blood purification or attempt to provide some synthetic function. The devices based on the principles of blood purification include albumin dialysis, plasma separation and filtration or therapeutic plasma exchange. The alternative is the bioartificial liver, which incorporates hepatocytes in the extracorporeal circuit. Attempts to develop effective extracorporeal liver assist devices continue. With better device design, understanding of the pathophysiological basis of liver failure and emergence of tools to stratify patients, it is likely that an effective liver assist device will emerge.

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The liver has a huge capacity to regenerate. The hypothesis behind the use of extracorporeal liver assist is to enhance the regenerative environment by removing or replacing toxic molecules while the liver can regenerate. The two principal indications for the use of these devices are in patients with acute liver failure (ALF) and those with acute-on-chronic liver failure (ACLF). The predominant difference between these syndromes is that in ALF the native liver is normal whereas in ACLF the liver is cirrhotic. Extracorporeal liver assist devices are either based on the principles of blood purification or attempt to provide some synthetic function. The devices based on the principles of blood purification include albumin dialysis, plasma separation and filtration or therapeutic plasma exchange (TPE). The alternative is the bioartificial liver, which incorporates hepatocytes in the extracorporeal circuit. The available devices and emerging technologies are described below (**Figure 1**).

Albumin dialysis

Two main types are currently available.

Molecular Adsorbents Recirculating System (MARS®, Gambro AB) *(Stange et al. 1993a; 1993b)*

Albumin dialysis is achieved by dialysis of blood across an albumin-impermeable membrane (membrane pore size has a cut-off of approximately 50-60 kDa) against 20% human serum albumin (HSA). The HSA solution is continuously stripped of protein-bound and water-soluble substances by passage through a secondary circuit containing a charcoal column, an anion exchange resin column and a low-flux dialyser.

The earliest randomised trial of MARS in ACLF was performed 20 years ago in 13 patients (n=8 MARS vs 5 controls) with type 1 hepatorenal syndrome and demonstrated a survival advantage with MARS, with no survivors in the control group (standard medical therapy [SMT]) versus 37.5% in the MARS group at day 7 (Mitzner et al. 2000). Subsequent randomised controlled trials (RCTs) of MARS versus SMT have yielded mixed results, with some studies showing a survival benefit (Heemann et al. 2002) and others no benefit (Sen et al. 2004; Banares et al. 2013). The largest study of MARS in ACLF (RELIEF study) (Banares et al. 2013) (**Table 1**) involved 189 patients (n=95 MARS vs 94 SMT) with there being no difference observed in 28-day survival on an intention-to-treat analysis (60.7% [MARS] versus 58.9% [SMT]). However, MARS treatment was associated with a significant reduction in serum bilirubin (26.4% vs 8.9%, $p < 0.001$), serum creatinine (20.0% vs 6.4%, $p=0.022$) and some improvement in the degree of hepatic encephalopathy (HE) (from grade II-IV to grade 0-I) (OR 0.37; 95% CI 0.12-1.09; $p = 0.07$). A meta-analysis of MARS in liver failure, which included 6 RCTs totalling 453 ACLF patients, showed no improvement in survival with MARS (OR 0.88; 95% CI 0.74-1.06; $p = 0.16$) (He et al. 2015). Another meta-analysis included 10 studies (7 ACLF and 3 ALF), of which 9 were RCTs and 1 non-RCT. No beneficial effect of MARS on mortality was observed (OR 0.91; 95% CI 0.64-1.31; $p = 0.62$) (Vaid et al. 2012). However, a significant reduction in serum bilirubin (net change -7.0mg/dl; 95% CI -10.4, -3.7; $p <0.001$) and an improvement in the grade of HE (OR 3.0; 95% CI 1.9 - 5.0; $p<0.001$) were noted with MARS (Vaid et al. 2012). The failure to observe a beneficial effect with MARS in ACLF may be due to heterogeneity of studies, both due to varying patient populations and a variance in defining ACLF; all the studies pre-date the seminal definition of ACLF as per the European Foundation for the Study of Chronic Liver Failure (EF-CLIF) (Moreau et al. 2013). Gerth et al. (2017) performed a retrospective analysis using the EF-CLIF ACLF definition. Of 101 ACLF patients (n=47 MARS vs 54 SMT) included at a single centre, higher survival was seen at 14 days with MARS (91.5% vs 50% SMT), which only remained significant when extended to 28 days in those with ACLF grade 2 or 3 ($p = 0.022$) (Gerth et al. 2017). In the re-analysis of the RELIEF cohort those with ACLF grade 2 or above benefitted most with MARS but only in the short term (14-day survival, 77.4% vs 66.1% SMT), whereas those with ACLF grade 1 treated with MARS had an increased mortality (14-day survival 20% vs 10% SMT) (Gerth et al. 2017). Overall in ACLF patients current evidence supports a limited role for MARS, in carefully selected patients with higher grades of ACLF or in those with advanced HE.

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The largest RCT of MARS in ALF included 102 patients (n=53 MARS vs 49 SMT) from 16 French transplant centres and showed no survival benefit of MARS at 6 months (84.9% vs 74.4% SMT, p = 0.28) (Saliba et al. 2013). A significant criticism of this study was the short time from randomisation to liver transplantation (median 16.2 hours), which may have limited any demonstrable effect from albumin dialysis.

Fractionated Plasma Separation, Adsorption and Dialysis device (Prometheus®, Fresenius Medical Care AG & Co. KGaA) *(Falkenhagen et al. 2013; Rifai et al. 2003)*

Plasma separation from blood is achieved by passage of blood across an approximately 300 kDa cut-off membrane. Plasma is cleansed by direct passage through two cartridges containing different adsorbents. Plasma is then returned to the blood circuit for clearance of water-soluble substances by a high-flux dialyser. A modification of this device, which excludes the high flux dialyser, known as double plasma molecular absorption system (DPMAS, Fresenius Medical Care) is also under investigation, as a plasma-sparing alternative to TPE (Wan et al. 2017).

There are few controlled studies of Prometheus® in liver failure (Rifai et al. 2003; Laleman et al. 2006). The largest RCT included 145 ACLF patients (n=77 vs 68 SMT) and demonstrated no survival advantage at 28 days (66% vs 63% in the SMT group, p = 0.70) (Kribben et al. 2012). A retrospective case series of 23 ALF patients supports a potential role for Prometheus® as a bridge to transplantation or recovery (Senturk et al. 2010), but further data are needed for validation before any recommendation.

Therapeutic plasma exchange

Therapeutic plasma exchange (TPE) requires use of an extracorporeal blood cell separator for removal of plasma from blood. Patient plasma is then discarded, whilst blood cells are mixed with a replacement fluid and returned to the patient. Fresh frozen plasma (FFP) is the typical replacement fluid, but HSA has also been reported. TPE aims to achieve removal of toxins plus harmful inflammatory mediators and replacement of beneficial plasma proteins normally synthesised by the liver.

There have been no RCTs of TPE in ACLF, but evidence from prospective studies supports evidence for an improvement in Model for End-Stage Liver Disease (MELD) score and survival (Yue-Men et al. 2016; Ling et al. 2012; Zhou et al. 2015). Early case series of TPE improving outcomes in ALF (Nakamura et al. 2000; Kondrup et al. 1992; Larsen et al. 1995) have been supported by a multicentre RCT of high-volume plasma exchange (HVP) (15% of body weight [8-12L FFP]), which included 182 patients (92 HVP vs 90 SMT), and showed an improved hospital survival; 58.7% versus 47.8% (SMT) hazard ratio (HR) 0.56; 95% CI 0.36-0.86; p = 0.0083) (Larsen et al. 2016). In those patients that did not receive emergency liver transplantation, HVP improved survival compared to SMT (p=0.03), but in those who received a transplant prior use of HVP did not improve outcome compared to SMT (Larsen et al. 2016).

Bioartificial liver support devices

The rationale of bioartificial devices is to augment any residual liver function and support the failing liver by incorporating functional hepatocytes in combination with blood detoxification or additional mechanisms to attenuate liver injury.

Extracorporeal Liver Assist Device (ELAD™, Vital Therapies Inc.)

The key component of ELAD™ is a quartet of hollow fibre dialysis cartridges containing HepG2/C3A cells, a human hepatoblastoma cell line, within the extra-fibre spaces. ELAD has been trialled in a small number of ALF patients with limited efficacy (Millis et al. 2002; Sussman et al. 1992; Ellis et al. 1996), but the larger phase 2 VTI-212 trial of ELAD in ALF was terminated. An RCT of ELAD therapy in severe alcoholic hepatitis (VTI-208), which included 203 patients (96 ELAD and 107 SMT), did not demonstrate any survival benefit of ELAD therapy at 91 days (51.0% vs 49.5% SMT), thus failing

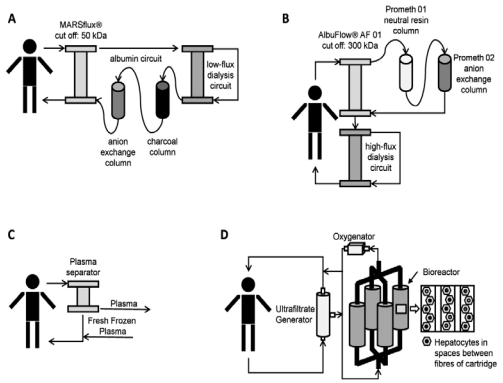

Figure 1. Schematic representations of currently available liver assist devices. A) MARS B) Prometheus C) Therapeutic plasma exchange D) ELAD

its primary endpoint (Thompson et al. 2018). Although not pre-specified, survival in patients with a combination of both MELD <28 and age <46.9 years (n=59) was significantly better in the ELAD group compared to SMT (100% vs 73%, p = 0.006) at 91 days (Thompson et al. 2018), which is the basis for the current VTI-308 trial of ELAD in alcoholic hepatitis (**clinicaltrials.gov/ct2/show/NCT02612428**).

Emerging technologies in extracorporeal artificial liver support devices

ADVanced Organ Support (ADVOS previously known as Hepa Wash, Hepa Wash GmbH)

ADVOS® detoxifies blood by albumin dialysis against a 2% albumin dialysate (Al-Chalabi et al. 2013). The albumin dialysate is recirculated via the ADVOS circuit, which contains two parallel conventional haemofilters, in which albumin-bound toxins are released through exposure to an alkaline or acid environment and subsequently removed by filtration. This design aims to maintain clearances of protein bound toxins through the treatment period (Al-Chalabi et al. 2013).

Table 1. Randomised controlled trials for liver support devices in liver failure and outcomes

Device	Study	Trial type	n	Primary outcome
ACLF				
MARS	RELIEF[Banares et al. 2013]	multicentre RCT	189 MARS 95 SMT 94	28-day survival MARS 61% vs SMT 59%
MARS	Hassanein et al. [2007]	multicentre RCT	70 MARS 39 SMT 31	improvement of HE MARS 34% vs SMT 18.9% (p = 0.044)
Prometheus	HELIOS [Kribben et al. 2012]	multicentre RCT	145 Prometheus 77 SMT 68	28-day survival Prometheus 66% vs SMT 63% (ns) 90-day survival Prometheus 47% vs SMT 38% (ns)
ELAD	VTI 208 [Thompson et al. 2018]	multicentre RCT	203 ELAD 96 SMT 107	91-day survival ELAD 51.0% vs SMT 49.5% (ns)
ALF				
MARS	FULMAR [Saliba et al. 2013]	multicentre RCT	110 MARS 57 SMT 53	6-month survival MARS 85% vs SMT 76% (ns)
HVP	Larsen et al. [2016]	multicentre RCT	183 HVP 92 SMT 91	Survival to hospital discharge HVP 59% vs SMT 48% (p = 0.008)

SMT standard medical therapy; ns no significance, p >0.05

In a pig liver failure model ADVOS® resulted in improvement in survival, cerebral perfusion pressure, haemodynamic status and kidney function (Al-Chalabi et al. 2013; 2017). A retrospective report of the first fourteen patients treated with ADVOS (mean treatment session 575 minutes) showed that there was significant reduction in serum bilirubin and creatinine (Huber et al. 2017).

Li-Artificial Liver Support (Li-ALS)

Li-ALS combines a low-volume TPE (exchange of approximately 2.5% body weight of plasma) circuit with a modified MARS secondary circuit, in which high-flux haemofiltration replaces low-flux haemodialysis (Zhou et al. 2015). This approach seeks to benefit from the more comprehensive detoxification achieved by TPE compared to MARS, without need for a supply of exogenous fresh frozen plasma, as patient plasma is returned post-detoxification to the patient. In a D-galactosamine pig model of ALF, Li-ALS resulted in an improvement in survival compared to treatment with low-volume TPE alone and to treatment with the modified MARS circuit alone (Zhou et al. 2015).

University College London-Liver Dialysis Device (DIALIVE)

In DIALIVE blood is filtered across two filters; one a high-cut off membrane (nominal cut-off of 60kDa) through which albumin passes, the second is a selective endotoxin adsorption membrane. Albumin lost during filtration is replaced by HSA infusion (Lee et al. 2015), thus this effective albumin exchange addresses the irreversible loss of detoxifying function of albumin in liver failure. Targeted removal of endotoxin aims to reduce innate immune response, which is a key pathophysiological component driving ACLF. In a pig model of paracetamol-induced ALF, DIALIVE improved survival and cardiovascular and respiratory function and reduced circulating dysfunctional albumin, endotoxaemia and immune system activation (Lee et al. 2015). DIALIVE is currently being evaluated in a multi-centre RCT to assess its performance and safety (clinicaltrials.gov/ct2/show/NCT03065699).

> "extracorporeal liver assist enhances the regenerative environment by removing or replacing toxic molecules while the liver can regenerate"

Academic Medical Centre Bioartificial Liver (AMC-BAL)

The bioreactor features of AMC-BAL are a non-woven matrix for 3D hepatocyte cultures; spiralling of this 3D matrix around oxygen carrying capillaries; and direct exposure of hepatocytes to patient plasma (van de Kerkhove et al. 2005). The first trial of this device in 12 ALF patients used primary porcine hepatocytes; however, the risk of zoonoses has tempered further development as porcine DNA was found in patient plasma (van de Kerkhove et al. 2005).

Spheroid reservoir bioartificial liver (SRBAL)

The bioreactor of SRBAL contains primary porcine hepatocytes in suspension, which when exposed to an oscillation frequency of 0.25Hz cluster into spheroids with stable cell viability (Nyberg et al. 2005; McIntosh et al. 2009). Hepatocyte spheroids demonstrate good hepatocyte function in terms of: phase I and phase II drug

metabolism; ammonia conversion to urea via the urea cycle; and albumin synthesis (Nyberg et al. 2005). A trial using a pig ALF model has shown improved survival, but further development is required (Glorioso et al. 2015).

Conclusions

The idea of liver assist is extremely attractive for patients with liver failure, as the liver possesses huge capacity to regenerate. If the patient can be kept alive long enough, it may be possible for the liver to regenerate and return the patient to the state of health they were in prior to developing liver failure. Although many of the devices available have been shown to improve the clinical condition, only plasma exchange was able to improve transplant-free survival of patients with ALF. Attempts to develop effective extracorporeal liver assist devices continue. With better device design, understanding of the pathophysiological basis of liver failure and emergence of tools to stratify patients, it is likely that an effective liver assist device will emerge.

Conflict of interest

Rajiv Jalan has research collaborations with Takeda, Ocera, and Yaqrit, and consults with Yaqrit. Rajiv Jalan is the founder of Yaqrit Limited, which is developing UCL inventions for treatment of patients with cirrhosis. Rajiv Jalan is an inventor of ornithine phenylacetate, which was licensed by UCL to Mallinkrodt Pharma. He is also the inventor of Yaq-001, DIALIVE and Yaq-005, the patents for which have been licensed by his university into a UCL spinout company, Yaqrit Ltd. No other authors declared conflicts of interest. ■

Abbreviations

ADVOS ADVanced Organ Support
ALF acute liver failure
ACLF acute-on-chronic liver failure
CI confidence interval
DPMAS double plasma molecular absorption system
EF-CLIF European Foundation for the Study of Chronic Liver Failure
FFP fresh frozen plasma
HE hepatic encephalopathy
HSA human serum albumin
HR hazard ratio
HVP high-volume plasma exchange
kDA kilodalton
MELD Model for End-Stage Liver Disease
OR odds ratio
RCT randomised controlled trial
SRBAL Spheroid Reservoir Bioartificial Liver
SMT standard medical therapy
TPE therapeutic plasma exchange

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For full references, please email editorial@icu-management.org or visit https://iii.hm/k6v

Management of bleeding in visceral surgery and liver transplantation

The implementation of patient blood management programmes led to reduced blood product usage. However, haemorrhage secondary to major surgery remains a major cause of potentially preventable death. Considering the heterogeneity of procedures and technical approaches, it is not surprising that the bleeding risk stratification for visceral surgery is not clearly defined. However, there is agreement on the high bleeding risk of major hepatic surgery and liver transplantation. Massive bleeding protocols are also variable depending on local conditions: in some centres, the use of blood products in a fixed ratio is recommended, while in others a targeted approach using point-of-care guidance is favoured. In patients with liver dysfunction a restrictive fluid strategy and a targeted approach using factor concentrates guided by viscoelastic tests is recommended. We present a practical view on different aspects related to the management of bleeding in visceral and liver surgery.

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I. Bleeding management in visceral and liver resection surgery

Preoperative assessment of bleeding risk is essential for adequate management of surgical patients. Bleeding risk depends both on the patient and the planned procedure. Regarding patient-related risk factors, congenital bleeding disorders are less common in the general population compared to acquired bleeding disorders such as antithrombotic therapy or associated pathology (liver or renal diseases, cancer, haematologic diseases). The bleeding risk stratification of visceral surgical procedures is not well established; except for cholecystectomy, hysterectomy and very short procedures, the other types of visceral surgical interventions are considered as high bleeding risk procedures similar to cardiac and orthopaedic surgery, based on definitions derived from anticoagulant bridging management studies (Spyropoulos and Douketis 2012). However, the high bleeding risk of major hepatic surgery and liver transplantation is recognised. In a study of more than 2000 patients with intraoperative bleeding exceeding 5 litres, the percentage of liver resection patients included was higher than liver transplant or heart surgery patients (Irita 2011).

When preparing for high bleeding risk surgery, preoperative workup is essential. According to the European Society of Anaesthesiology (ESA) guidelines, the bleeding questionnaire is the best tool for assessing perioperative bleeding risk (Kozek-Langenecker et al. 2017). If preoperative anaemia exists, the causes must be identified and addressed, if possible (Kozek-Langenecker et al. 2017). Preoperative autologous donation is a technique useful in patients with extremely rare blood groups or with multiple antibodies (Vassallo et al. 2015). It decreases the incidence of allogenic blood transfusion, but actually increases the overall incidence of transfusion because of the lower preoperative haemoglobin levels compared to patients who did not pre-donate blood (Vassallo et al. 2015; Henry et al. 2002).

In order to decrease intraoperative blood loss, the prevention of hypothermia, hypocalcaemia and acidosis is extremely important (Martini 2009; Kozek-Langenecker et al. 2017). Deliberate induced hypotension was associated with a significant reduction in operative blood loss in patients undergoing orthopaedic or neurosurgical procedures (Soghomonyan et al. 2017; McNeill et al. 1974). However, this strategy needs an individualised approach to balance the risks of blood loss with the preservation of vital organ perfusion. Other autologous blood conservation techniques used in visceral surgery include acute normovolaemic haemodilution (ANH) and cell salvage. ESA guidelines recommend against the use of controlled hypotension combined with ANH and caution when using ANH in patients with preexistent coagulopathy (Kozek-Langenecker et al. 2017). Intraoperative cell salvage reduces the need for allogenic blood transfusions and it is often used in cardiac and orthopaedic procedures. In abdominal surgery, the use of intraoperative cell salvage is lower due to concerns about the risks of reinfusing malignant cells (in oncologic patients) or infection risk (in bowel surgery). However, the use of cell salvage is not contraindicated in oncologic patients or in bowel surgery, provided adequate precautions are undertaken (Kozek-Langenecker et al. 2017).

Visceral surgery

In some situations, the occurrence of life-threatening bleeding during visceral surgery cannot be avoided and adequate measures are essential for a successful outcome. In the event of a massive bleeding situation, the three key elements of blood volume replacement, optimisation of tissue oxygenation and coagulopathy prevention must be remembered. The activation of a massive bleeding protocol with intervention algorithms adapted to local conditions is highly recommended (Kozek-Langenecker et al. 2017). There are several types of massive transfusion protocols. In some centres the massive transfusion protocol recommends administration of red blood cells (RBC), fresh frozen plasma (FFP) and platelet concentrate in a specified ratio according to local guidelines. The use of ratio-based resuscitation was extended beyond the trauma setting, but we still lack studies demonstrating its benefits

in non-trauma patients(Mesar et al. 2017). Additional studies are required to define the optimal ratios in different types of surgical patients (Mesar et al. 2017). In some centres the massive transfusion protocol recommends a targeted approach for bleeding patients using point-of-care-based algorithms. Another option to address massive bleeding is a combination of massive transfusion protocols: initiation of a ratio-driven transfusion protocol from start of haemorrhage with an early shift towards a targeted approach when the situation allows timely results of point-of-care or standard coagulation tests (Johansson et al. 2014; Ghadimi et al. 2016). Recently a further option for treating massive bleeding based on the essential role of fibrinogen in the coagulation process was described in trauma patients, recommending the administration of fibrinogen concentrate and RBC in a manner similar to the 1:1 ratio (Rossaint et al. 2016).

Regardless of the massive bleeding protocol used, the final goal is to decrease patient morbidity and mortality. In a study aiming to identify a haemoglobin target associated with the least odds of death after resuscitation has been completed and the patient's vascular space has equilibrated, it was demonstrated that both over-transfusion and under-transfusion were associated with increased mortality (Zielinski et al. 2016).

"reducing blood loss and blood transfusions in liver surgery is mandatory for improving patients' outcome"

Liver resections

Liver resections have been associated with high mortality and morbidity rates. In a review published in 2007, de Boer et al. underlined the effect of blood loss and blood transfusions in liver surgery and the relevant association between blood transfusion and postoperative morbidity, especially infectious complications (de Boer et al. 2007). A decade on, blood transfusion continues to be an independent predictor of mortality and morbidity in patients undergoing major or minor hepatectomy, both for benign and malignant pathology.

Reducing blood loss and blood transfusions in liver surgery is mandatory for improving patients' outcome. As bleeding usually occurs during liver parenchymal transection, the control methods used by surgeons include vessel occlusion techniques and the use of different instruments for resection (Romano et al. 2012). There are several techniques of hepatic vascular control methods, but the main ones are the inflow vascular occlusion of the liver (known as Pringle's manoeuvre with the occlusion of the triad within the hepatoduodenal ligament) and total hepatic vascular exclusion (THVE) (the combined inflow and outflow vascular occlusion) (Romano et al. 2012; Huntington et al. 2014). Anaesthetic management is adapted to the technique used for the reduction of operative bleeding. When inflow vascular occlusion of the liver is applied, maintenance of a low central venous pressure (CVP) is recommended in order to decrease blood loss (Li et al. 2014; Huntington et al. 2014; Kozek-Langenecker et al. 2017; Moggia et al. 2016). Potential risks of this technique are inadequate vital organ perfusion, air embolism and loss of volaemic reserve in case of bleeding (Huntington et al. 2014). The methods for maintaining a low CVP include intravenous fluid restriction, systemic nitroglycerin, furosemide, intravenous morphine and even intraoperative whole blood phlebotomy, but an individualised strategy is recommended for obtaining a low CVP while minimising the associated risks (Huntington et al. 2014; Rekman et al. 2017; Tympa et al. 2012). The use of the low CVP approach is not associated with intraoperative blood loss reduction during hepatic resections in healthy donors for living related liver transplantation (Kim et al. 2009; Choi et al. 2015). The low CVP technique is abandoned in the case of massive bleeding or in cases when the inflow vascular occlusion technique is converted to THVE (Romano et al. 2012).

While Pringle's manoeuvre is generally associated with haemodynamic stability, with a small decrease in cardiac output, and increase in systemic vascular resistance and mean arterial pressure, in THVE rapid haemodynamic changes are expected due to caval clamping, blood loss or hepatic reperfusion (Tympa et al. 2012). Selective hepatic vascular exclusion has a haemodynamic profile similar to inflow vascular occlusion techniques. It provides a bloodless surgical field and it is indicated when CVP cannot be lowered despite adequate management. It is tolerated by most patients and it is more effective than Pringle's alone in controlling bleeding (Tympa et al. 2012).

II. Bleeding management in liver surgery for patients with chronic liver disease

An increasing number of patients with chronic liver diseases are scheduled for non-transplant surgery. For abdominal surgery, the perioperative mortality of cirrhotic patients is correlated with the severity of the liver disease as assessed by the Child-Pugh or Model for End-Stage Liver Disease (MELD) scores (Lopez-Delgado et al. 2016). Historically, patients with liver cirrhosis were considered to be at risk of bleeding due to coagulation defects; however, according to more recent research, bleeding in cirrhosis is due mainly to vascular abnormalities (Tripodi and Mannucci 2011). In health, there is a balance between pro- and anti-haemostatic factors. In compensated cirrhosis, this balance is maintained, the anti-haemostatic factors being counterbalanced by pro-haemostatic factors (Tripodi and Mannucci 2011). The prolongation of standard coagulation tests (Activated Partial Thromboplastin Time [aPTT], Prothrombin Time [PT], International Normalised Ratio [INR]) in cirrhotic patients reflects only the deficit in pro-coagulant factors, being insensitive to the concomitant decrease in anticoagulants (Tripodi and Mannucci 2011). In vitro studies demonstrated similar amounts of thrombin generated in cirrhotic patients as in healthy controls when using a thrombin generation assay modified to reflect the action of both pro-coagulants and anticoagulants (Tripodi et al. 2005). Not only is the plasmatic coagulation rebalanced in cirrhosis, but also the primary haemostasis where the low number of platelets is compensated by the increased plasmatic levels of von Willebrand factor leading to increased platelet adhesion capacity (Lisman et al. 2006). The balance of fibrinolysis is also maintained by concomitant alterations of pro- and anti-fibrinolytic factors and by clot structure changes associated with decreased clot permeability and increased resistance to lysis (Hugenholtz et al. 2016; Lisman et al. 2001). However, this rebalanced haemostatic system in cirrhosis is not as stable as in health and can be easily disturbed by different precipitating events (Tapper et al. 2013; Saner et al. 2013). As a result, bleeding management in

cirrhotic patients undergoing surgery has to preserve this fragile balance for as long as possible. As prolonged standard coagulation tests are not useful to reflect the rebalanced haemostasis in cirrhosis, it is not recommended to correct them before invasive procedures, but rather to limit haemostatic interventions to bleeding patients (Saner et al. 2013). The administration of FFP determines volume loading, with increased portal and venous pressure correlated with increased surgical bleeding. Therefore a restrictive fluid approach and targeted therapy with factor concentrates guided by viscoelastic point-of-care tests in bleeding patients are recommended (Saner et al. 2013; Kozek-Langenecker et al. 2017). In cirrhotic patients undergoing liver resections the use of antifibrinolytic drugs should also be considered (Kozek-Langenecker et al. 2017).

Liver transplantation

The same principles are applied in cirrhotic patients undergoing liver transplantation (LT). During liver transplant surgery, there are specific recommendations for the different surgical phases:

i) In the first stage of LT the dissection and mobilisation of the liver may lead to significant surgical bleeding, especially in patients with abdominal adhesions or increased portal pressure (Görlinger et al. 2016). The use of cell salvage techniques, a low CVP strategy and a targeted approach guided by viscoelastic tests for bleeding management are recommended (Görlinger et al. 2016; Kozek-Langenecker et al. 2017).

ii) During the anhepatic phase, surgical bleeding is uncommon as all the major vessels are clamped and bleeding is usually due to coagulopathy. Due to the increased release of tissue plasminogen activator (tPA) from endothelial cells and the absence of hepatic clearance function, hyperfibrinolysis can occur in this phase (Görlinger et al. 2016).

iii) The last phase of the LT procedure, the neohepatic phase, begins with the reperfusion of the graft and is characterised by profound haemostatic abnormalities leading in some cases to clinically important bleeding. Hypothermia, acidosis and hypocalcaemia are frequently encountered after reperfusion contributing to the worsening coagulopathy (Görlinger et al. 2016). Thrombocytopaenia is aggravated as platelets get trapped in the graft; due to the tPA release from the graft, hyperfibrinolysis is common after reperfusion. However, in most cases it is self-limited (Görlinger et al. 2016). A heparin effect can occur in the neohepatic phase due to the release from the graft of the exogenous heparin administered to the donor before aortic cross-clamping and of the endogenous heparin-like substances from endothelial cells (Görlinger et al. 2016). With a functional liver graft, the hyperfibrinolysis and the heparin effect are self-limited and treatment is not necessary in the absence of diffuse bleeding (Görlinger et al. 2016).

The algorithms for bleeding management in liver transplant surgery include predefined trigger and target values usually based on viscoelastic testing and recommend haemostatic interventions only in bleeding patients and not for correction of abnormal test results. A sequential approach is recommended, addressing first hyperfibrinolysis, then clot firmness, followed by the correction of enzymatic factors deficiency (Görlinger et al. 2016). Due to the antithrombin deficiency in cirrhosis and the low antithrombin content of prothrombin complex concentrates (PCC), it seems that a lower dose of PCC compared to the dose required for warfarin reversal is enough for restoring reduced thrombin generation in cirrhotic patients undergoing liver transplant surgery (Abuelkasem et al. 2017).

Caution is recommended when procoagulant therapy is administered in cirrhotic patients, as the balance of haemostasis can easily tip toward thrombosis. Bleeding is a major concern during LT, but the overzealous replacement of deficient procoagulant factors should be avoided, as intraoperative thrombotic events such as intracardiac thrombosis or pulmonary embolism are often fatal (Feltracco et al. 2015; Warnaar et al. 2008). In the early postoperative period, hepatic vessel thrombosis is a threat to both patient and graft survival and prophylactic antithrombotic treatment must be considered despite hypocoagulable routine laboratory tests (Arshad et al. 2013).

Conclusion

Bleeding management in visceral surgery and liver transplantation is extremely complex and requires a comprehensive perioperative coagulation treatment algorithm adapted to the local conditions of each institution as a backbone for the construction of an individualised treatment plan adapted to each patient.

Conflict of interest

Ecaterina Scarlatescu declares that she has no conflict of interest. Dana R. Tomescu declares that she has no conflict of interest. ■

Abbreviations

ANH acute normovolaemic haemodilution
CVP Central venous pressure
FFP fresh frozen plasma
LT liver transplantation
RBC red blood cells
THVE Total hepatic vascular exclusion

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For full references, please email editorial@icu-management.org or visit https://iii.hm/k6w

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Immediate-type hypersensitivity reactions in the ICU

Incidence and impact on patients' outcome unknown

For the ICU patient, correct and timely diagnosis of drug hypersensitivity is required to administer emergency epinephrine treatment, and retrospective allergological investigation is needed to identify the culprit drug and safe alternatives. For ICU departments, epidemiological data regarding the incidence of drug-induced immediate-type hypersensitivity are scarce and the impact on patientsí outcome in terms of morbidity and mortality, as well as on healthcare-associated costs, is difficult to quantify.

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Patients admitted to the intensive care unit (ICU) may have a known previous drug hypersensitivity or may present the first episode during their ICU stay. Drug-induced immediate-type hypersensitivity reactions are characterised by acute onset of illness with multisystem involvement due to histamine and other mediators' release from mast cells and basophils (Ozcan et al. 2016). Acute events generated by potential triggers that induce cell degranulation can lead to severe reactions, sometimes with permanent disability due to brain hypoperfusion or hypoxia, and even death.

For the patient, correct and timely diagnosis of drug hypersensitivity is required to administer emergency epinephrine treatment. Early recognition allows timely intervention. Delayed administration of epinephrine is generally accepted as a cause of mortality (Reitter et al. 2014). With appropriate and aggressive treatment, the prognosis of anaphylaxis per se is good. Retrospective identification of the culprit drug is required in order to avoid further administration.

For ICU departments, epidemiological data regarding the incidence of drug-induced immediate-type hypersensitivity are scarce and the impact on patients' outcome in terms of morbidity and mortality, as well as on health-care associated costs, is difficult to quantify. Immediate-type hypersensitivity reactions to drugs may be more common than reported in critically ill patients admitted to the ICU (Green and Potter 2007; Kanji et al. 2010). Due to limitations in correct diagnosis in the ICU, these reactions might be managed poorly (Green and Potter 2007).

Epidemiology of drug-induced immediate-type hypersensitivity

ICU patients receive several drugs simultaneously, being prescribed drug regimes that include many chemicals from different classes. Almost all drugs commonly prescribed in the ICU have been reported as potential triggers for anaphylaxis (**Table 1**) (Ozcan et al. 2016).

Is the frequency with which each drug or drug class induces hypersensitivity reactions in the ICU known?

Immediate-type hypersensitivity to drugs is an issue of concern for ICU physicians even though most reports address intra-anaesthetic anaphylaxis retrospectively. In a UK-wide survey approximately 76% of anaesthetists had attended a case of perioperative anaphylaxis and 4% had encountered a lethal event, (Kemp et al. 2017). There are several published guidelines regarding intraoperative anaphylaxis, but further investigation and referral to national registries is inconsistent (Kemp et al. 2017). The reported OR incidence varies widely from 1:1.556 (Kemp et al. 2017) to 1:10-20.000 (Mertes et al. 2009; Gibbs et al. 2013). Antibiotics in the U.S. and neuromuscular blocking agents in Europe seem to be the leading drug class responsible for immediate type hypersensitivity (**Table 1**).

Many anaesthetists across Europe work simultaneously in the OR and ICU, thus transfer of knowledge is to be expected.

Do epidemiological data regarding incidence and frequency distribution vary considerably in the ICU?

Epidemiology and reaction patterns differ in accordance with consumption trends (Fernandez et al. 2017).

ICU patients with self-reported previous drug-induced immediate-type hypersensitivity reactions

A history of drug allergies needs to be documented in each hospitalised patient. Approximately 10-25% of patients admitted to hospital declare that they have had an allergic reaction, especially to antibiotics and non-steroidal anti-inflammatory drugs (Torda and Chan).

For ICU patients, drug allergy labelling might be translated to avoidance of certain drugs, use of broader-spectrum antibiotics and thus, increased antimicrobial resistance thereafter, as well as higher costs. Antibiotic selection is important for critically ill patients who require antibiotics for their diseases, in a setting where drug-resistant infections are becoming more common. Inappropriate antimicrobial selection is an important issue for antibiotic stewardship in ICU departments. Effective antibiotic allergy management is essential for antibiotic stewardship programmes (Macy et al. 2017).

Table 1. Potential triggers for anaphylaxis in the intensive care unit (ICU) and frequency of each drug/class of drugs for induction of anaphylaxis in retrospective studies in the surgical population undergoing general anaesthesia in the operating room (OR)

Drugs commonly used in the ICU, which may trigger anaphylaxis	USA (OR) (Iammatteo et al. 2017) n=34	UK (OR) (Meng et al. 2017) n=31	France (OR) (Taquard et al. 2017) n=714	Spain (OR) (Lobera et al. 2008) n=48
Antibiotics (Green and Potter 2007) Non-steroidal anti-inflammatory drugs Neuromuscular blocking agents (NMBAs) Colloids Hypnotics (including ketamine) (Ozcan et al. 2016) Opioids (Tomar et al. 2012) Clorhexidine, including impregnated central venous catheters (Egner et al. 2017; Khoo et al. 2011) Proton pump inhibitors or anti-H_2 medication (Gonzalez et al. 2002) Latex Blood transfusions	Induction agents 36% Cefazolin 32% Odansetron 12%	Antibiotics 52.3% NMBAs 38.1% Morphine 4.8% Gelofusine 4.8% No cause identified 19.4%	NMBAs 60.6% Antibiotics 18.2% Dyes 5.4% Latex 5.2% Hypnotics 2.2% Opioids 1.4%	Antibiotics 44% NMBAs 37%

ICU intensive care unit NMBA neuromuscular blocking agents OR operating room

The majority of patients with self-reported drug allergies can be tested, and in most cases the results of the tests are negative and patients can safely receive the drugs. More than 95% of patients who report penicillin allergy tolerate beta-lactams (Blumenthal et al. 2017). The gold standard for de-labelling patients is to perform skin tests, followed by drug challenge tests if the skin tests are negative. Antibiotic allergy is often misdiagnosed and testing is infrequently performed in the hospital setting, even though feasible (Chen et al. 2017). In the ICU the pool of healthcare providers who can perform antibiotic skin testing might need to be expanded (Rimawi et al. 2014). It has also been suggested that in ICU patients with confirmed hypersensitivity, de-sensitisation protocols can be used to achieve acute tolerance, (Macy et al. 2017; Blumenthal et al. 2017).

Do we know the clinical impact of applying these algorithms in patients with haemodynamic instability? Are patients with ileus suitable to undergo oral de-sensitisation regimes? Do we know the efficacy of desensitisation regimes to achieve acute tolerance in this patient population?

The diagnosis of immediate-type hypersensitivity reactions may be difficult both during the acute event, when early and aggressive treatment is required, and after the acute phase reaction, when identification of the culprit drug is required to prevent further exposure.

Why could immediate-type hypersensitivity reactions not be recognised and/or under-reported in critically ill patients?

Diagnostic difficulties for the acute event in the ICU

Establishing the diagnosis of acute immediate-type hypersensitivity is hampered by the complexity of organ dysfunction/insufficiency encountered in the ICU population and the multitude of drugs that are simultaneously administered. Clinical judgement is essential for the interpretation of acute clinical status deterioration superimposed on serious underlying pathology. Hypersensitivity reactions may be severe and manifestations may be similar to other disease states more commonly encountered in the ICU. The most frequent manifestations of drug hypersensitivity are cutaneous, cardiovascular and pulmonary. Due to vasodilator cytokines acute release, the most common anaphylaxis may present as distributive shock, similar to septic shock. Anaphylaxis might also be a cause for coronary artery vasospasm.

"epidemiological data on drug-induced hypersensitivity reactions in the ICU are scarce"

Is the clinical profile of drug hypersensitivity reactions occurring in the critically ill similar to those in non-ICU patients? Could the clinical profile be blunted in patients with immune suppression due to underlying disease and possibly, medication (steroids, antihistamines)?

Retrospective diagnosis and identification of culprit agent

Retrospective diagnosis of drug-induced immediate-type hypersensitivity is complex, and systematic studies in the critically ill population are lacking. In vivo and in vitro tests can only be performed 4 to 6 weeks after the acute event, as each hypersensitivity manifestation leads to mediators' consumption, including histamine, leukotrienes, tryptase and others. In this timeframe, results may be false-negative, and thus patients in the ICU are unable to be tested even though they might require the drugs which are suspected to have caused the reaction.

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Table 2. Retrospective diagnostic tests for suspected drug-induced immediate-type hypersensitivity reactions

Investigation	Description of the examination	Problems for the critically ill
Tryptase	• Mediator released from mast cells and basophils • Serum levels increase 1-2 hours after an anaphylaxis event and remain elevated 4-6 hours (Laguna et al. 2018) • Operating room guidelines suggest serial measurements, including a baseline value • Increased tryptase in both IgE and non-IgE-mediated hypersensitivity	• No consensus regarding thresholds for tryptase (Meng et al. 2017) • High number of false-negatives and a low predictive value in non-ICU population, with moderate sensitivity (Baretto et al. 2017). In the critically ill, false-positives are likely to be encountered as mast cells and basophils degranulate in conditions of severe hypoxia
Skin tests	• Skin prick tests and intradermal tests with potential culprit drugs and cross-reactive substances • Positive and negative controls are absolutely required Normal saline is used as negative control and histamine as positive control	• Important in vivo diagnostic tools • Skin tests can be performed for patients who require a drug that they report to have had a reaction to. If skin tests and basophil activation tests are negative, then a drug challenge test is necessary to exclude hypersensitivity. Skin tests are used before the challenge tests as a safety measure • No study on ICU skin tests' reactivity has been published
Drug challenge tests	• Controlled administration of increasing doses at intervals of 15-30 min, starting with 1/1000 of the therapeutic dose (Kemp et al. 2017)	• Gold standard for drug hypersensitivity diagnosis, generally performed in drug allergy units under strict monitoring • Procedures complex and not standardised for all drugs • Not validated for critically ill patients in systematic studies
Specific IgE antibodies	• Drug-specific antibodies can be found in the serum using either radio-immunoassay techniques (used in the past) or ELISA methods (currently in use)	• Sensitivity and specificity varies among studies, dosing can only be performed for some drug classes • Drug-specific IgE antibody dosing can confirm hypersensitivity if the immunological reaction is IgE-mediated, but cannot confirm non-IgE mediated events. Thus sensitivity is only moderate and a negative result does not exclude anaphylaxis
Basophil activation tests	• Imply the in vitro exposure of the patients' basophils (isolated using flowcytometry) to different drugs • Require fresh blood	• Can be performed only 4-6 weeks after the acute event. In the critically ill, isolation of basophils is difficult (personal experience, results not published) • Can be performed for all drug classes, but not clorhexidine • Availability restricted to drug allergy investigation centres
Histamine and leukotriene release tests	• Not sufficiently standardised for diagnostic use (Laguna et al. 2018)	• Limited utility for clinical practice

ELISA enzyme-linked immunosorbent assay

Identification of the patients at risk is most important. The history of drug-induced hypersensitivity reactions has to be documented and the clinical manifestations have to be analysed, as some manifestations are not true hypersensitivity.

Identification of the culprit agent is hampered by the lack of diagnostic studies with optimal sensitivity and specificity (**Table 2**).

Are these diagnostic studies validated for the critically ill patients?

Retrospective diagnosis algorithms are still not harmonised across Europe and vary considerably, especially if the patient has access or not to a drug allergy investigation centre. Moreover, the performance of each retrospective diagnostic test is not perfect and sensitivities are only moderate, as shown in non-ICU patients. *How could all these diagnostic possibilities be applied and interpreted in the critically ill? Systematic studies are lacking.*

Conclusions

We have many questions and few answers regarding drug hypersensitivity in the ICU. *Are systematic studies necessary?* Definitely, yes. The true incidence of anaphylaxis in the ICU is difficult to estimate. The incidence of immediate-type hypersensitivity reactions to drugs has not been reported in the ICU population, even though in this setting, patients receive concomitantly many potential triggers for anaphylaxis. It is possible that these reactions are underreported due to difficulties in establishing the diagnosis and drawbacks in performing diagnostic studies. The impact on patients' outcome, morbidity, mortality, and healthcare-associated costs are as yet unknown.

In the future, raising awareness regarding immediate-type hypersensitivity reactions might be reflected in epidemiological studies and might improve knowledge regarding these (possibly) not so rare adverse drug reactions in the critically ill.

Each department needs to have guidelines for acute immediate-type hypersensitivity reactions (recognition and management) and for the retrospective investigation of previous reactions. Immediate access to guidelines for anaphylaxis treatment and established referral pathways for investigation are required to confer optimum care in the ICU, and to ensure departmental preparedness to manage such patients. ■

Conflict of interest

Cristina Petrișor declares that she has no conflict of interest. Natalia Hagău declares that she has no conflict of interest. Nadia Onițiu-Gherman declares that she has no conflict of interest.

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For full references, please email editorial@icu-management.org or visit https://iii.hm/k6x

Results of an antimicrobial stewardship programme implementation in a multidisciplinary hospital

The interventional single-centre with historical control study was conducted in a 600-bed multidisciplinary hospital to evaluate 4 yearsí results of an antimicrobial stewardship programme. We found a significant reduction in average duration of courses of antimicrobial therapy, length of stay of patients with infection in ICU, mortality in patients with bacteraemia, the rate of extended-spectrum beta-lactamases (ESBL) and Carbapenem-resistant production of Gram-negative bacteria, and the role of the ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter species*) group in nosocomial infections with bacteraemia.

Nosocomial infections are caused by a variety of organisms; most of them are multidrug-resistant (MDR) isolates, which refer to a group of ESKAPE pathogens (Shevchenko and Onishchenko 2001; Boucher et al. 2009). The multicentre epidemiologic study Extended Prevalence of Infection in Intensive Care (EPIC) II demonstrated the structure of nosocomial infection pathogens: *Enterobacteriaceae* was shown as the cause of 35.7% of all infections, *Ps.aeruginosa* – 19.9%, *Ac.baumannii/haemolyticus* – 8.8%, *St. aureus* – 20.5%, *E.* spp. – 10.9%, and *Candida* spp. – 17.0% (Vincent et al. 2009). Antimicrobial resistance directly affects the results of treatment, due to the difficulties in choosing antibiotics for starting therapy and even after identification of the pathogen (Ferrer et al. 2014; Blot et al. 2007; Kumar et al. 2006; Gelfand et al. 2016; Surgical infections of skin and soft tissues 2009; Abdominal surgical infection 2011; Dellinger et al. 2013; Kwon et al. 2007; Marchaim et al. 2008). An inappropriate course of antimicrobial therapy (AMT) leads to further emergence, spread of resistance and the vicious circle closes. The hospital becomes a comfortable environment for MDR infection and a high-risk place for patients. The main way to change this situation is the implementation of an integrative strategy including control of the prescription of antibiotics in combination with a comprehensive infection control programme. Numerous international and national antimicrobial stewardship programme (ASP) recommendations have been developed, but only limited data demonstrate positive results in real life clinical practice.

Aim

Our purpose was to analyse the effectiveness of the local ASP within 3 years after implementation.

Study design

The interventional single-centre with historical control study was conducted in the Federal State Public Institution "National Medical and Surgical Center named after N.I. Pirogov", a 600-bed multidisciplinary hospital (35,000 inpatients, 22,000 surgical procedures per year).

The intervention

We started the ASP in early 2013, when according to guidelines (Savelyeva et al. 2012) a multidisciplinary team was formed with the main task of analysing the results of microbiological monitoring and to prepare the first edition of protocols of perioperative antibiotic prophylaxis and empirical AMT (Protocol – in this article). The team included specialists who could make decisions about the use of antibiotics. In June 2013 the protocols were ready. From this point protocols are updated annually, based on the local antibiotic resistance data (more than 20,000 strains), and include different schemes of AMT regarding the patient's risk factors for antibiotic-resistant pathogens, such as age, previous stay in an acute or chronic care facility, invasive procedures, antibiotic exposure etc. The ASP also includes infection control measures, the development plan for the bacteriological laboratory (real-time PCR, full-genomic new generation sequencing), educational programmes and internal audit.

Statistical analysis

We compared a historical control period (2012) and intervention period (2014–2016). To determine the statistical reliability of the differences in absolute values in the case of a normal distribution, the Student's t-test was used, with the Mann-Whitney criterion different from the normal one. To determine the statistical significance of the differences in relative values, the Pearson's chi-squared test with Yates continuity correction or, where appropriate, Fisher's exact test were used. A 95% confidence interval was additionally indicated in describing the resistance indicators due to a large data set. Descriptive variables are represented as n (%) or mean value m (standard deviation σ) and median M (first and third quartiles Q1-Q3).

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Table 1. Characteristics of patients with infection in ICU

Parameter	2012	2014	2015	2016	p*
Number of patients, n	502	558	415	580	-
• patients with infection, n (%)	250 (49.8)	249 (44.6)	204 (49.2)	223 (38.4)	<0.001
• number of infections incidence, n (%)	320 (63.8)	293 (52.5)	254 (61.2)	255 (43.9)	<0.001
APACHE II, m (σ)	14.7 (7.2)	14.6 (6.6)	13.7 (6.0)	13.6 (6.9)	0.091
Infection-related mortality in ICU, n (%)	34 (13.6)	25 (10)	21 (10.3)	29 (13.0)	0.892
Length of stay in ICU patients with infections, days. M (Q1-Q3)	4 (1-9)	3 (1-10)	4 (1-10)	2 (1-8)	0.011
Localisation of infection					
Lower respiratory tract, n (%)	104 (32.5)	88 (30.0)	68 (26.8)	73 (28.6)	0.363
Intra-abdominal, n (%)	83 (30.0)	78 (26.6)	65 (25.6)	51 (20.0)	0.112
Skin and soft tissues, n (%)	89 (27.8)	69 (23.6)	65 (25.6)	79 (31.0)	0.46
Urinary tract, n (%)	19 (5.9)	32 (10.9)	28 (11.0)	40 (15.7)	<0.001
Central line-associated bloodstream infection (CLABSI), n %)	2 (0.6)	12 (4.1)	7 (2.7)	8 (3.1)	0.026
Central nervous system (CNS), n (%)	6 (1.9)	7 (2.4)	6 (2.4)	0	0.036
Paranasal sinuses, n (%)	17 (5.3)	7 (2.4)	8 (3.2)	3 (1.2)	<0.01
Other, n (%)	0	0	7 (2.7)	1 (0.4)	0.443

* in comparison 2012 and 2016
m mean value M median σ standard deviation

Table 2. Change in the number and duration of AMT in the ICU

Parameter	2012	2014	2015	2016	p*
Number of AMT courses in ICU for 1 patient, m (σ)	0.53 (0.6)	0.52 (0.67)	0.54 (0.6)	0.42 (0.6)	0.041
Duration of AMT, medium (ICU + profile Dept), days; m (σ)	15.7 (13.1)	12.6 (10.8)	10.2 (7.8)	8.4 (7.1)	<0,001
Days of AMT for 1 patient (ICU + profile unit), days; m (σ)	7.7 (12.1)	5.6 (9.5)	5.0 (7.5)	3.5 (7.8)	<0.0001

* in comparison 2012 with 2016
m mean value σ standard deviation

Results and discussion

ICU patient characteristics are presented in **Table 1**. This 12-bed ICU is specially for patients with different complications developed during the treatment.

Table 1 shows that for all periods nosocomial infections are the main reason, among all complications, for being in ICU, with a reduction in number after 3 years of ASP implementation. Therefore ASP may help to reduce the infection rate but not as fast wins. The infection control system begins to bring real results only when, as the result of ASP, specialists changed the emphasis from the question of choosing an antibiotic to the questions of pathogen identification and transmission.

The severity and mortality in this group of patients remained the same, probably because it depends on many factors, including underlying disease and co-morbidity. The length of ICU stays of patients with infection also varied significantly. In 2012 the duration of such patient treatment in the intensive care unit (ICU) was 1 to 126 days, and in 2016 from 1 to 112. However, the median duration of ICU stays in 2016 decreased and this was statistically significant.

The localisation of infections has not changed: lower respiratory tract infections accounted for about 1/3 of the total infections in the ICU, the remaining 2/3 were intra-abdominal, skin and soft tissue, urinary tract infections and other localisation. Morever, on the first steps of the ASP, the level of infections may rise and the structure can vary, because it largely depends on the quality of diagnostics and internal audit. Thus, in our hospital in 2014 (in comparison with the pre-interventional period) the frequency of CLABSI and urinary tract infections increased due to the introduction of unified criteria for diagnosing these complications in 2013 (in the first version of the Protocol).

> "a permanent instrument for improving the quality of medical care"

The decrease of infection rate in ICU patients during the intervention period respectively reduced the number of AMT courses (**Table 2**). However, a significant reduction in AMT duration is an obvious consequence of ASP implementation. It is important to note that we compared the average duration of courses of AMT, including the period of post-ICU treatment. We consider this approach to be of high importance, since ASP can be effective only when implemented in the whole hospital, and not just in the ICU.

After ASP implementation the frequency of bacteraemia caused by MDR organisms, as well as the incidence of *Candida* spp. changed significantly (**Table 3**). The level of Gram-positive microorganisms bacteraemia remained the same: only single strains of MRSA were detected annually. Vancomycin-resistant *E. faecium* strains were recorded last in 2011. After the ASP implementation, the incidence of bacteraemia of *Enterobacteriaceae* spp. ESBL+, *K. pneumoniae* CPR reduced significantly. Moreover, in the intervention period the production of ESBL in strains of *K. pneumoniae* and *E. coli* significantly decreased from 61.8%; 95% CI 58.9-64.7% to 40.0%; 95% CI 43.3-36.7%, p <0.0001, and the analysis of CPR Gram-negative bacteria noted a significant decrease in the resistance to this group of antibiotics from 32.4%; 95% CI 34.4-30.4% to 23.7%; 95% CI 26.0-23.7%, p <0.0001.

Table 3. Structure of bacteraemia caused by ESKAPE pathogens and Candida spp.

Pathogen	2011	2012	2013	2014	2015	2016	p*
Number of blood cultures taken	1165	1140	1159	1059	1124	1252	
Patients with positive blood cultures	94	74	87	100	86	82	
Positive blood cultures, n (%)	203 (17.4)	167 (14.6)	175 (15.1)	188 (17.8)	185 (16.4)	181 (14.5)	
Positive blood cultures in ICU, n (%)	145 (71.4)	128 (76.6)	126 (72.0)	119 (63.3)	130 (70.3)	129 (71.3)	
MRSA, n (%)	2 (1.0)	2 (1.2)	2 (1.1)	1 (0.5)	3 (1.6)	3 (1.7)	0.326
E. faecium VR, n (%)	10 (4.9)	0	0	0	0	0	0.999
Enterobacteriaceae spp. ESBL, n (%)	34 (16.7)	60 (35.9)	56 (32)	40 (21.3)	48 (25.9)	21 (11.6)	<0.001
K. pneumoniae CPR, n (%)	5 (2.5)	25 (15.0)	31 (17.7)	13 (6.9)	15 (8.1)	10 (5.5)	<0.01
A. baumannii + *P. aeruginosa* MDR, n (%)	35 (17.2)	17 (10.2)	5 (2.9)	12 (6.4)	6 (3.2)	12 (6.6)	0.249
Candida spp., n (%)	20 (9.6)	7 (4.2)	5 (2.9)	6 (3.2)	4 (2.2)	2 (1.1)	0.093
Patients with candidaemia, n (%)	8 (8.6)	5 (6.8)	4 (4.6)	5 (5.1)	1 (1.2)	1 (1.3)	0.102
Non-ESKAPE/non-*Candida* bacteraemia, (%)	48.1	33.5	43.4	61.7	59.0	73.5	<0.0001
Mortality of patients with bacteraemia in ICU, n (%)	28 (50.9)	19 (38.8)	22 (36.7)	14 (23.3)	16 (31.4)	13 (28.9)	0.04
Length of ICU stay, days M (Q1-Q3)	31 (22-61)	37 (23-65)	41 (24-62.5)	39 (17.75-58.25)	27 (15-61.5)	24 (11-35)	0.001

* in comparison 2012 with 2016

CPR carbapenem-resistant ESBL extended-spectrum beta-lactamase MDR multidrug-resistant

MRSA methicillin-resistant S. aureus VR vancomycin-resistant

As a result, the role of the ESKAPE group decreased from 66.5% to 26.5% (i.e. 2.5 times, $p < 0.0001$) and, importantly, these changes correlated with a decrease in the mortality of patients with bacteraemia.

Conclusion

Usually, the main goals of ASP are considered as reducing the costs of antimicrobial therapy, consumption of antibiotics, the number of errors in prescribing AMT, the incidence of infectious complications and mortality. All these goals are certainly important, but they cannot unite in one team different specialists from attending physicians to the CEO, because each of them has its own priorities. Obvious or hidden conflict of interests ultimately lead to the transformation of the ASP into a one-off action, where the results are negative or questionable. The CEO does not receive the expected savings; doctors,s waiting for new possibilities in drug choice, really receive only tightening control, but not the right to prescribe needed drugs.

We chose another ASP goal—reducing the level of antibiotic resistance in the hospital. This goal is often underestimated by practising physicians and especially by the hospital administration, but the choice of such goals does not cause a negative attitude. This is enough to start reforms, and only later does it become clear for all that reducing the incidence of infections caused by MDR pathogens is beneficial to everyone. It helps to simplify the selection of starting and empirical therapy, reduce the length of hospital stay and mortality in patients with infection, and reduce costs. Step by step, the level of antimicrobial resistance in hospital turns into a common goal, unites specialists into a team, becomes the most important criterion for assessing the effectiveness of ASP and turns this programme into a permanent instrument for improving the quality of medical care. ■

Conflict of interest

The authors declare that they have no conflict of interest.

Abbreviations

AMT antimicrobial therapy

ASP antimicrobial stewardship program

CPR carbapenem-resistant

ESBL+ Extended-spectrum beta-lactamase

ESKAPE *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter species*

ICU intensive care unit

MDR multidrug-resistant

MRSA methicillin-resistant *Staphylococcus aureus*

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The role of speech and language therapy in critical care

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The role of speech and language therapists (SLTs) in critical care can be unclear so this article sets out the scope of practice to increase awareness of the value of SLTs as part of the wider multidisciplinary team.

Speech and language therapists (SLT) are trained to deliver specialist clinical services to adults with a broad range of disorders, including hearing impairment, motor speech disorders (dysarthria, dyspraxia), acquired language disorders (dysphasia), voice problems (dysphonia), and swallowing problems (oropharyngeal dysphagia [OD]). These are often linked to an acquired neurological disorder, such as stroke, traumatic brain injury, Parkinson's disease and dementia, although other acute conditions may affect these functions, especially when linked to respiratory dysfunction requiring tracheostomy and ventilation. The role of SLT within critical care has increased as patients with complex impairments are sedated less and experience communication and swallowing impairments. These functions are frequently seen as a return to normality during the process of recovery and a measure of quality of life (Segaran 2006; Carroll 2007; Karlsson et al. 2012; Engstrom et al. 2013). There are few UK-based studies evaluating SLT interventions in critical care; however, as the number of National Institute for Health Research fellowships for Allied Health Professionals (AHP) increases it is hoped that this will generate the research needed to provide evidenced-based therapy.

Normal swallowing and speech functions

Swallowing employs the same range of muscles and nerves as those required for breathing and speaking, namely the pharynx, larynx, tongue and lips. The swallow is described in three phases (Groher and Crary 2015), although these are interlinked and dependent on each other to be effective (**Figure 1**). The oral phase requires volitional control of a bolus, either food or fluid, in preparation for swallowing; this includes chewing food using the full range of tongue and jaw movements and holding the food within the oral cavity using lip closure. The tongue then pushes this bolus posteriorly into the pharynx, triggering a series of reflexive movements to move the laryngeal structure vertically and anteriorly. These biomechanical movements are essential for a three-way closure of the glottis, to protect the airway from penetration—true and false vocal cords adduct and the epiglottis provides additional cover and redirection of the bolus towards the oesophageal entrance, which opens biomechanically with vertical and anterior laryngeal movement. It is for this reason that you may see an SLT assessing swallowing through midline palpation of the larynx to determine swallow timing and range of hyolaryngeal movement to indicate swallow completion. The adjacency of the airway next to the oesophageal entrance means that any mistiming or obstruction of the swallow movement can result in the entrance of food or fluid directly into the airway. The cough reflex is a strong airway-protective mechanism designed to expectorate foreign bodies. However, in patients who are intubated, these reflexes are often absent (Kallesen et al. 2016), increasing the risk of aspiration. If overt signs of coughing are absent, this is described as silent aspiration. To fully understand the breakdown and remediate the problem requires early recognition of risk factors and assessments sensitive to dysphagia. Bedside evaluation cannot always determine the effectiveness of pharyngeal clearance or airway protection.

Dysphagia management

Oropharyngeal dysphagia is often the primary reason for SLT referral in ICU, with its recognised link to increased risk of aspiration pneumonia and subsequent mortality (Altman et al. 2010). At the acute stage this is mainly related to effective oral secretion management, as patients who swallow infrequently or ineffectively risk aspirating saliva with a high bacterial load. This increases the risk of ventilator-associated pneumonia, so SLTs often deal with optimising oral hygiene and hydration in the early stages before fluid and food trials can be evaluated. Although early identification and management of dysphagia is recommended to reduce risk, access to SLT can be limited due to low staffing and lack of specialist skills. SLTs are often viewed as peripatetic services to ICU with referrals made by the medical team following a process of screening for swallowing difficulties by nursing staff (Cichero et al. 2009). A swallow screen should include an evaluation of oral motor functions, such as lip and tongue movements, voice, cough and swallow trials with varied consistencies to evaluate timing of swallowing and abnormal responses to food and drink. Currently there are no validated swallow screening tools for ICU patients; existing tools have been developed for use with stroke patients (Trapl et al. 2007; Martino et al. 2009; Edmiaston et al. 2010) and may be unreliable.

For patients requiring tracheostomy and ventilation both motor and sensory laryngeal function can be altered following intubation (Skoretz et al. 2010; Macht et al.

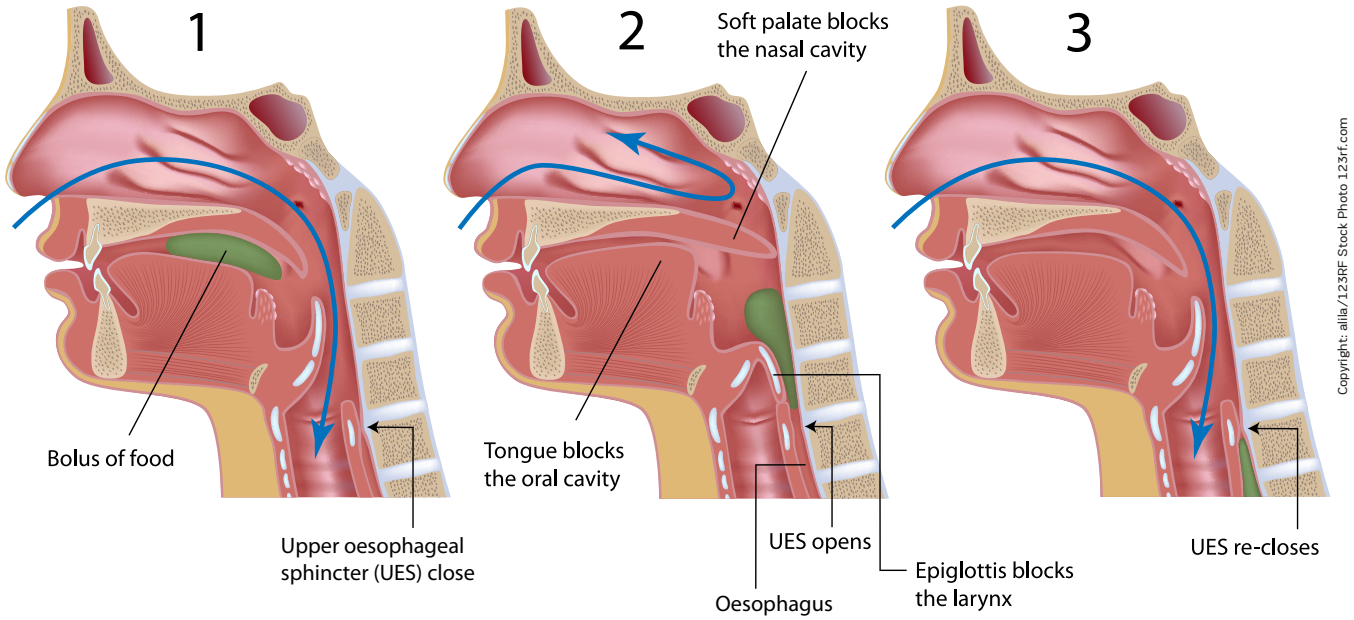

Figure 1. Three stages of swallowing 1. Oral stage involves the manipulation of the bolus whilst normal breathing continues; 2. Pharyngeal stage - the swallow triggers a series of movements to protect the airway whilst the bolus passes through the pharynx; 3. Oesophageal stage - the bolus travels through the oesophagus and normal breathing resumes.

2011; Moraes et al. 2013), and disruption to normal breath-swallow synchrony can affect timing of swallowing (Martin-Harris et al. 2005; Terzi et al. 2007; Nishino 2012), leading to an increased risk of silent aspiration. A number of studies have reported OD as a feature of non-neurological patient subgroups, such as sepsis (Zielske et al. 2014), acute lung injury (Brodsky et al. 2014), ARDS (Brodsky et al. 2016), cardiac surgery (Daly et al. 2016), critical illness polyneuropathy (Ponfick et al. 2015) and spinal cord injury (Shem et al. 2012), suggesting a respiratory link. These impairments cannot be easily detected by screening tools so instrumental assessments of swallowing are recommended, namely videofluoroscopy (VFS) and fibreoptic endoscopic evaluation of swallowing (FEES). These are employed by SLTs with specialist competency training (Royal College of Speech and Language Therapists 2013; 2015) and provide different information on swallowing functions.

"the role of SLT within critical care has increased as patients with complex impairments are sedated less and experience communication and swallowing impairments"

The VFS examination takes place in a radiology department and requires transfer of the medically stable patient. During the examination, a patient is sat upright and required to eat and drink a range of food textures coated with barium sulphate contrast that are video x-rayed to identify timing, efficiency and safety of swallowing across all phases (Logemann 1993). Aspiration of this material can cause harm, so this examination may need to be modified for patients requiring ventilation and is not suitable for those who need to remain supine or are haemodynamically unstable. FEES is a more accessible assessment (Langmore 2001) that can be undertaken at the bedside within the ICU using a video-nasendoscope. It provides a direct view of the pharynx and larynx only and helps to identify structural impairments and physiological responses to secretions and food trials, in terms of swallow timing, pharyngeal clearance and airway protection. Although aspiration is the key indicator of swallow safety, the role of the SLT is to identify the cause of breakdown and to trial strategies aimed at reducing risk of aspiration in order to facilitate safe oral intake. A number of studies have employed FEES to identify OD in post-extubation patients (Leder et al. 1998; Hafner et al. 2008; Scheel et al. 2015). For scenarios where swallow safety is at high risk and airway protection is limited, a decision may be made to keep a patient nil by mouth and optimise nutrition through non-oral routes, after discussion with the wider team.

"voice work can be employed to increase laryngeal lift and vocal cord adduction"

SLTs are trained to plan and deliver a number of therapeutic interventions to manage the impairments that cause OD (Martino and McCulloch 2016). These can target an identified impairment, such as reduced hyolaryngeal elevation, through strengthening exercises or strategies. Treatment approaches include exercises to increase range and strength of lip and tongue movements, including resistance exercises. Voice work can be employed to increase laryngeal lift and vocal cord adduction and a number of swallow strategies have been developed to target specific impairments (Logemann 2006), such as the Shaker, Masako and Mendelsohn manoeuvres, Effortful swallow and Facial Oral Tract

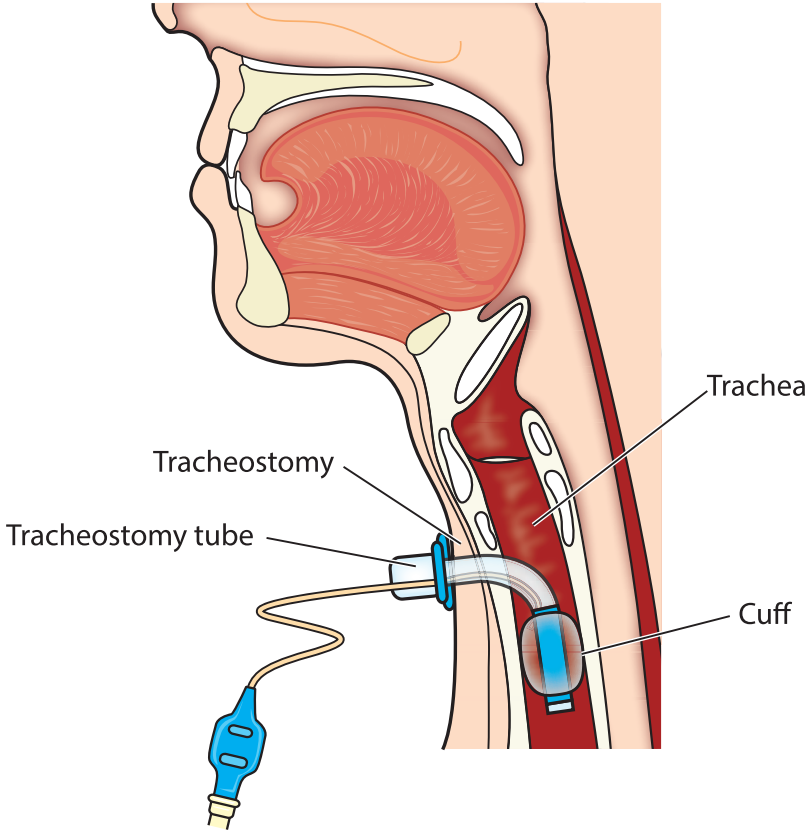

Figure 2. Cuffed tracheostomy within trachea directs airflow away from larynx and upper airway

Therapy (Hansen and Jakobsen 2010). Alternatively, the risk of aspiration can be reduced through compensatory approaches that do not remediate the swallow problem. This approach is suitable for patients with cognitive or language problems who are unable to comply with exercises. The use of thickened fluids can be employed for patients who are unable to control fluids in the mouth or have a delayed swallow initiation. These impairments have to be verified on instrumental assessment as inappropriate use of thickener can have negative consequences (Cichero 2013). Similarly, diet modifications, such as purée or soft mashed food have to be used in relation to the oral and pharyngeal swallow impairment and their use monitored.

Communication

The ability to communicate and interact with their environment is a key concern for many patients in critical care, especially during intubation and ventilation whilst awake (Karlsson et al. 2012; Guttormson et al. 2015). This poses challenges for staff interaction and the verification of capacity (Wojnicki-Johansson 2001). A number of alternative methods are available, which range from low-technology aids, such as picture or alphabet charts (Radtke et al. 2011) to high-technology systems such as eye-gaze systems, although individual assessment is required as one device may not be suitable for all patients (ten Hoorn et al. 2016). The most effective method of communication is speech, and for those being ventilated via a tracheostomy this can only be achieved when the cuff is deflated (**Figure 2**). This can be done gradually as part of a ventilator weaning process termed laryngeal weaning, using collaborative team-working to include SLTs and respiratory physiotherapists to evaluate respiratory and laryngeal functions. This differs from respiratory weaning whereby the cuff remains inflated whilst the patient is trained to self-ventilate. A short-term alternative is a method termed above-cuff vocalisation (ACV) (McGrath et al. 2015), which uses an external air source through a subglottic suction port to achieve phonation whilst the tracheostomy cuff remains inflated. This has also been found to benefit laryngeal functions for swallowing (McGrath et al. 2018).

> "SLTs contribute to team decision-making and rehabilitation goals throughout the patient's pathway"

Supporting tracheostomy weaning

Guidance set out by the Royal College of Speech and Language Therapists (2014) identified SLTs as being integral to the multidisciplinary environment of critical care and involved in the weaning process for tracheostomy and ventilator-dependent patients in addition to the rehabilitation of swallowing and communication difficulties. These needs were highlighted in the National Institute for Health and Care Excellence (NICE) guidance for rehabilitation after critical illness (2009), although a national audit of tracheostomy care (National Confidential Enquiry into Patient Outcomes and Death 2014) found delays to SLT referral for tracheostomy patients and a lack of access to FEES procedures to support clinical decision-making.

Conclusion

SLTs are considered a key member of many teams, linking up with physiotherapy, occupational therapy, nursing care, pharmacy

Table 1. SLT involvement along the critical care pathway

SLT role	SLT action
Early interventions: Patient intubated or tracheostomy in situ	• Monitor oral mucosa for change and support regular oral hygiene and moisturisation • Maintain range of oral-motor and swallow movements • Review secretion control for either dry mouth or excess saliva • Consider early communication options
Patient starts weaning from ventilator	• Evaluate laryngeal function to anticipate barriers to weaning (using flexible nasendoscopy) • Support laryngeal wean through facilitation of cuff deflation • Monitor swallow for effective secretion management, consider swallow trials following FEES evaluation • Review communication and encourage use of voice with increased translaryngeal airflow
Post-decannulation	• Facilitate progress to full oral diet • Review voice, communication skills and intelligibility

and dietetics to deliver early therapeutic interventions for speech and swallowing. Early interventions will translate to prevention of complications and potential reduction in length of stay (**Table 1**). SLTs also add professional value by contributing to team decision-making and rehabilitation goals throughout the patient's pathway, in line with Quality Standard 158 (National Institute for Health and Care Excellence 2017), especially as they often work across wards and may follow the patient through their rehabilitation and into the community. A current challenge is the lack of directly-funded SLT services in ICU despite support from the guidelines for the provision of intensive care services (GPICS) (Faculty of Intensive Care Medicine and Intensive Care Society 2015). This limits both clinical involvement and professional development within teams that contribute to changing culture and practice.

There is currently no post-registration training programme for critical care skills so SLTs require clinical experience alongside other team members to develop their competencies, with a minimum banding level of band 7 with senior support or band 8a if sole clinician (nhsemployers.org/your-workforce/pay-and-reward/agenda-for-change/pay-scales). As this is a small professional group an online forum has been set up to provide support, share practice and problem-solve about situations specific to critical care. Education is provided through Clinical Excellence Networks (CEN) for tracheostomy, dysphagia and FEES/VFS. A new Twitter group, @CriticalCareSLTs links SLTs to the wider critical care world with responsive interactions, strategic discussions and an opportunity to share examples of practice which raise awareness of our role. ■

Conflict of interest

Jackie McRae declares that she has no conflict of interest.

Abbreviations

FEES fibreoptic endoscopic evaluation of swallowing
ICU intensive care unit
OD oropharyngeal dysphagia
SLT speech and language therapists
VFS videofluoroscopy

References

For full references, please email editorial@icu-management.org or visithttps://iii.hm/k6y

Making the case for social work practice in the care of critically ill ICU patients

The role of the ICU social worker

End-of-life issues occur frequently in the intensive care unit (ICU). The specific training and skills received by social workers provides them with the necessary tools to collaborate with the interdisciplinary team and provide holistic care to the patient and family. Research has shown that there is great variation in the level of participation of the social worker, often because they do not have a formal role. We examine the stressors impacting patients, family members and staff in the ICU, the various roles that social workers can play and provide a construct for how the ICU social worker can be an integral member of the critical care team.

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Social work's role in end-of-life care in the intensive care unit (ICU) varies widely across and within hospitals. Social workers can be a valuable asset in the provision of end-of-life care. They are trained to provide support to patients and families, improve communication between medical providers and patient/family, advocate for their wishes as well as being attuned to cultural needs (Eicholz Heller and Jimenez-Bautista 2015; Saunders et al. 2015). Where the ICU team is generally busy and time constrained, the social worker can take the necessary time to listen, educate and advocate for the patient and family as well as serve as a bridge between the patients, families and medical team. Yet, despite all of these advantages, social workers in many institutions do not have a formal role in the ICU (Gonzalez 2013).

Demographics and the 'cost' of ICU care at end of life

"Approximately 10% of patients admitted to the ICU will die in or shortly after they leave the ICU" (McCormick 2011, p. 54). Statistically, 20% of all deaths in the United States occur in ICUs (Curtis 2005; Gries et al. 2008). Between 11.5% and 30% of U.S. hospital cost is in the ICU, and roughly half of the patients who have a length of stay longer than 14 days in the ICU eventually die (Rose and Shelton 2006). In the ICU as many as 95% of the patients are incapacitated due to illness or sedation (McCormick et al. 2007; Truog et al. 2008), which results in the family making treatment decisions and participating in goals of care discussions with the critical care clinicians (Curtis and Vincent 2010; Rose and Shelton 2006). Due to biomedical advances and technical skills, patients' lives are often extended, which can lead to prolonged suffering (Christ and Sormanti 1999).

ICU environment stressors

Admissions to the ICU are often decided by non-critical care physicians and many times are unexpected and emergent (Delva et al. 2002). Additionally, end-of-life care is frequently not discussed with patients or families prior to the decision to admit to intensive care (Rady and Johnson 2004). This can create a level of tension between the ICU team and the family, patient and prior medical team. Critical care physicians are often unfamiliar with a patient's prior medical history, do not have an existing relationship with the patient and family and hence are not fully prepared to discuss end-of-life decisions. This can lead to a medical treatment plan that is incongruent with the patient's wishes.

In the ICU, there are many providers involved in each patient's care. This can lead to conflicting and confusing information being relayed to the patient and family. Additionally, because the ICU is a complex environment, levels of stress, anxiety and depression increase. Additionally, death is a deeply personal experience and each individual interprets the event very differently depending on their cultural and religious backgrounds and life experiences. For, example, someone with strong Catholic beliefs may be unable to accept the futility of ongoing life support, despite no chance of survival.

Also contributing to stress, families must balance managing their life outside of the ICU, including such responsibilities as: caring for children, paying bills, going to work, and at the same time caring for and supporting their dying loved one (Abbott et al. 2001). This results in caregiver burden, and can impact their ability to understand and interpret medical information provided, the decline of their loved one, and can escalate conflicts with the medical team. Families often feel stress, confusion, depression and helplessness. Many suffer from symptoms of acute stress disorder, post-traumatic stress disorder (PTSD), or posttraumatic stress reaction (Carlet et al. 2003; McAdam and Puntillo 2009; McAdam et al. 2010). Family members in ICUs are usually in a state of crisis (Delva et al. 2002; Mann et al. 1977) and feel unprepared to act as the patient's decision maker (Rose and Shelton 2006). These factors can affect their

treatment decisions for the patient as well as their satisfaction with the quality of care received in the ICU (Abbot et al. 2001).

Role of ICU social worker with patient and family

ICU social workers play a key role in end-of-life care, acting as case managers, counsellors, teachers, mediators and advocates (Bomba et al. 2010; Csikai 2006). They are trained to work with the whole person, and understand diverse cultural, ethnic and socioeconomic backgrounds (Heyman and Gutheil 2006; Saunders et al. 2015). Master-level social workers receive training in the foundational skills needed to engage, assess and intervene through the use of critical thinking, active listening and strong communication skills. They are also trained in more advanced skills such as crisis intervention, strengths perspective, cognitive restructuring, person-in-environment as well as individual and family therapy (Hartman-Shea et al. 2011; Kondrat 2013).

> "formal inclusion of social work on the ICU team provides invaluable additions to the holistic care of critically ill patients and their families"

Social workers can help families navigate the ICU environment through understanding how it functions and the roles of the staff involved in the care of the patient (McCormick et al. 2010; Rose and Shelton 2006). "Families require accurate, clear, and timely information presented in a language that invites a beginning integration not only of the issues at hand but also of the potential outcomes" (McCormick 2011, p. 54). Social workers develop coping skills with families to deal with the stressful environment, clarify medical information regarding prognosis, decision-making options (e.g. do not resuscitate, artificial hydration/nutrition, mechanical ventilation, antibio-tics, renal dialysis, etc.), and the difference between supportive/comfort care and life-maintaining care (Heyman & Gutheil 2006; McCormick et al. 2010). Hartman-Shea et al. (2011) found that psychosocial counselling and support was one of the most frequent social work activities most linked to family satisfaction and the reduction of anxiety. The social worker has the ability to assist with those needs through spending time with families to review the medical information and process their emotions. Assessments are crucial in the ICU team's ability to partner and work with families. The ICU social worker is able to assess how the family responds to crisis situations, the family dynamics and their communication patterns, which aids the medical team in providing a more empathic, compassionate and effective means to communicate with the family (Hartman-Shea et al. 2011). It is imperative that families of ICU patients understand and are aware of the different end-of-life care options; including how and where the patient's death can occur and the process surrounding the death in order to make decisions congruent with the patients' wishes (McCormick et al. 2007). Hartman-Shea et al. (2011) identified twenty-four medical social work interventions (**Table 1**).

Table 1.

Family support	End-of-life decisions	Procedural items
Identify proxy decision maker	Organ donation	Facilitate support groups
Crisis intervention	Staff support	Discharge planning
Assess perceptions of illness	Anticipatory grief work	Practical assistance
Cultural assessment	Advance directives	Funeral assistance
Psychosocial assessment and counselling	Medical team collaboration	Hospitality services
Arrange/ attend family conferences	Spiritual needs	Transfer to another social worker
Education	End-of-life care	Post discharge follow-up
Identify support system		
Facilitate family communication		

Social workers are often the most knowledgeable and comfortable discussing end-of-life care and hospice choices. They can guide the family and patient in understanding and making meaning of the different end-of-life options appropriate and available, as well as what each of those options means to the patient and family through an examination of the potential benefits or burdens (Csikai 2006, p. 1307). The social worker fills in the gaps that ICU medical providers may leave for families, working as 'context interpreters' for family members (Cagle and Kovacs 2009). The ICU social worker is able to help the families take the most important and relevant information and put it into context while also working through the feelings and reactions families have from this information (Cagle and Kovacs 2009). Due to their work with families, social workers decrease family members' feelings of helplessness in the ICU (Miller et al. 2007) as well as their acute stress.

Role of social worker on interdisciplinary team

Cagle and Kovacs (2009) and McCormick and colleagues (2010) stress the significant impact social workers have on improved communication between patients, families and healthcare providers. Social workers spend time speaking with families directly, discussing the family's perspective on the patient's condition, clarifying information, organising and attending family conferences and providing relevant psychosocial information to the ICU medical team (Rose and Shelton 2006). ICU clinicians are trained to assess and treat critically ill patients. Their bias is to treat and support, which can, in some instances, lead to futile treatment, prolonged

ICU stays and patient and family suffering. The social worker can advocate for the patient and, as the palliative care literature clearly demonstrates, improve adherence to patient/family wishes and outcomes (May et al. 2015; Cassel et al. 2010). Social workers "can encourage health professionals to understand and clarify their own role in the decision-making process, promote communication and problem solving, and identify and improve systems that may interfere with optimal communication and problem solving regarding such sensitive problems as end-of-life decisions" (Werner et al. 2004, p. 34).

Family conferences are an effective strategy for medical providers to discuss end-of-life care and have been linked to the reduction of the family's symptoms of PTSD, anxiety and depression (Browning 2008; McAdam and Puntillo 2009). The social worker plays a key role in family conferences, from arranging the meeting to ensuring that the key family members are present and available for the meeting, as well as acting as a context interpreter and clarifier during the meeting. The social worker can provide support to the family after the meeting.

Conclusion

"Social work in the ICU has become a subspecialty of medical social work just as the ICUs themselves have become more specialized" (McCormick 2011, p. 55). Presently, there is great variability in the way social work is included on the care team across ICUs and hospitals. The formal inclusion of social work on the ICU team provides invaluable additions to the holistic care of critically ill patients and their families. Through the application of skills in stress management, cultural competency, identifying caregiver burden, as well as employing their training in addressing critical decisions and end-of-life care, social workers improve patient/family experience, decision making and outcomes of care. ■

Conflict of interest

Allison Gonzalez declares that she has no conflict of interest. Robert Klugman declares that he has no conflict of interest.

Abbreviations

ICU Intensive care unit

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Emirates Critical Care conference

Where east meets west

Professor Hussain Al Rahma is Head of the Emergency and Critical Care Services Directorate at Al Zahra Hospital in Dubai, UAE. He is Chairman of the Emirates Critical Care Conference, President of the International Pan-Arab Critical Care Medicine Society and President of the Emirates Intensive Care Society. Dr. Al Rahma studied medicine at King Edward Medical Centre in Lahore, Pakistan and completed the German Board certificate in Internal Medicine at the University Klinikum-Essen 1997. He joined Rashid Hospital for 10 years and later Dubai hospital for 10 years as HOD for critical care on his return to the UAE before taking up his current position at Al Zahra Hospital.

What do you enjoy most at the Emirates Critical Care Conference?

The Emirates Critical Care Conference (ECCC) just completed its 14th event. It is an event where you learn, teach, meet old and make new friends, a place where people from all over the globe get together to share their experience and knowledge.

What makes Dubai the leader for critical care provision and education in the region?

ECCC-Dubai became a benchmark for critical care physicians, nurses and technicians to build their networks, and many federations, alliances and societies founded and collaborated together to initiate much research.

Dubai became a hub where the west meets the east, low-income country meets high-income country to exchange ideas and improvements for developing countries to cope with the obstacles and challenges they might face.

In your invitation video for the conference, you say that "Critical care is a right and not a privilege." How does this motivate all your many activities in critical care and emergency medicine?

Critical care and emergency medicine is a speciality which when needed should be available for all, in a wink of an eye; for us time is limited and life is precious.

You are a leader in intensive care in the UAE - setting up the first multidisciplinary independent ICU with fully trained intensivist in UAE and founding a department of emergency and critical care. How did you achieve this success?

> "building up critical care and emergency medicine is my life journey"

Building up critical care and emergency medicine is my life journey. For me it started by identifying the obstacles and challenges. My plan started with building up the team that will make things possible, a team that has the power, tolerance, dedication and commitment; then it was by convincing people and gaining the support and resources; Dubai is the land of miracles where everybody can live his dream.

There is global interest in "event medicine". How did you achieve success with setting up sports events emergency teams for major sporting events in Dubai?

Achieving success is down to teamwork. It is never a one man show; as a leader you need to delegate to the right person so they deliver their best at the right time; results build themselves. Aim for your target without distraction and you will reach it, the difference is only when you will reach it and it depends on the energy you give. In teamwork I believe in "trust everybody and check everything".

What are your key areas of interest and research?

My interests are multidisciplinary; I believe in critical care.

Psychology and human behaviour is a major determinant if you love something. I am also interested in emotional intelligence and leadership.

What are your top management tips?

- Human resources: delegate to the right person

14th Emirates Critical Care Conference

- There is no stupid person; there might be an ignorant team mate that needs to be educated and motivated (trust everybody check everything)

What would you single out as a career highlight?

14 years of sharing knowledge and exchanging experience from all over the world at the Emirates Critical Care Conference.

If you had not chosen this career path you would have become a…?

My dream always was to be a man who helps people during their pain.

What are your personal interests outside of work?

Calligraphy is my hobby; I still am trying to fly an airplane since childhood.

Your favourite quotes?

- No pain, no gain
- If you will not endure, you will never know what life is all about ■

Distributing a life source in Africa

Lifebank has developed crucial infrastructure in Nigeria, enabling the efficient transportation and storage of blood, saving thousands of lives. HealthManagement editor Marianna Keen spoke to CEO and founder Temie Giwa-Tubosun about her journey.

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To what degree has the blood shortage in Nigeria been tackled so far, due to the work of LifeBank?

It's a very small degree to be perfectly honest. It's such an endemic problem that it would be such a difficult thing to say that we solved the problem in two years. We've saved about 4,000 people from dying. I don't think we've solved the problem significantly, but we're on our way to solving it. We have the determination that can solve it. And now we need to figure out the skills set in Nigeria, and get the investment we need to do that.

Have you reached your goal so far?

Absolutely. We set out to prove that you could build a business that is valuable, that solves this problem. We feel very confident that we've met our goals.

How does the LifeBank process work? How have you made use of innovative technology?

It starts with the people who have the blood—the blood banks. When they get to work in the morning, they list their products with us, so that gives us an inventory of how many units of blood are available in parts of our community. We have a map and database that has a list of all the blood that is available in the parts of our community—very simple. Then we deploy this information into the hands of the hospitals who need the blood. Whenever any hospital needs blood, they contact LifeBank, and we get them the blood they need. They can contact us, either via a phone call—we have a 24/7 call centre—or they can use our web app. It is a very simple app; it just requests certain things from the person requesting the blood. As from the beginning of March, hospitals are now also able to connect with us using an Unstructured Supplementary Service Data (USSD) platform. This USSD platform allows people who don't have an internet connection to still communicate with one another, using the mobile phone network. So hospitals and clinics can still make purchases using USSD.

After the hospital has made its order, we deliver the blood to the hospital in 45 minutes or less, and we maintain the condition of the products we move by using a WHO recommended cold chain. Our hospitals pay about 8 dollars for our services. Some hospitals pay a little more, and some hospitals pay a little bit less, but it averages out to about 8 dollars per unit of product.

How vital is LifeBank in providing an effective supply chain?

We're essentially a distribution company that distributes these products to the people who need it, in the right conditions and on time. The first thing we do is we connect blood banks to blood donors. People who are interested in becoming blood donors can register on a different app that we run, and it connects them to blood banks. Then, after blood banks have collected, stored and tested the blood, we connect them to the hospitals. So we are basically the conduit that was missing before, we connect everybody in this blood chain and make sure that patients, at the end of the day, get the blood they need.

> "we're essentially a distribution company that distributes these products to the people who need it, in the right conditions and on time"

In what other healthcare areas do you think technology, smart logistics, and big data can be applied to deliver a seamless health supply-chain system across Africa?

I think it could be very useful in various sectors of healthcare. I think this kind of distribution could be helpful with vaccines, organs, oxygen and medical samples. I think it could be really interesting with things like drugs and supplies, such as insulin, anti-venom, anti-rabies, basically anything that patients need and anything that hospitals generally don't like to stock in the hospital. I think our innovation can be absolutely useful for things like that.

Will LifeBank branch out from the distribution of blood to organs and other essentials for hospitals?

We're already working on it! We are going to launch new operations in a few months. We want to move vaccines, organs and oxygen, and basically anything that hospitals need that they cannot find.

Is the goal for the LifeBank enterprise to be eventually deployed across Africa?

We would like to. Our big, ambitious goal is to be in every village and every last mile in Africa, and to be able to distribute these essential medical products to every single hospital on the continent. That's our big goal and we're working towards it.

Why do you believe social enterprises such as LifeBank are so important to healthcare in Nigeria and in other countries?

That's a very good question. I have a strong belief in businesses. I think businesses can help to solve unique and major problems in Africa, and in the developing world in general. I think the businesses that have a social niche can be absolutely the best way to solve a lot of these problems that we've been dealing with for so long. I think that having a business model ensures longevity. It allows you to continue solving this problem over time. It allows you to completely focus on the problem and deliver value to the people who need the value the most. And the reward you get for delivering value is money, and that money allows you to be sustainable, to sustain your ambition. I feel very strongly that businesses with social impact can be a significant way of solving an endemic and entrenched problem, especially problems around infrastructure, and that includes infrastructure within healthcare.

How have you and your team encouraged people to donate blood, and what methods will you use to continue to do so in the future?

I don't think we have actually encouraged people to do this, as I think people always wanted to give blood, but they just didn't know how. If you talk to most people in Nigeria, and you tell them how many people are dying in Nigeria every year because they have no blood, and you tell them they have the power to change that, I think most people are really interested to solve the problem. The problem in the past has been giving them the right tools, the right places, so they can go and actually give the blood. I think that's what we've been able to do very well.

What are the biggest organisational and managerial challenges you have faced within LifeBank?

Building infrastructure in a community that has no infrastructure and no history of infrastructure. I think it's actually very difficult.

One story I found interesting was from Jeff Bezos, Amazon CEO. He recently spoke about when he started Amazon.com and said that when he got his first order, he just took it to his local post office and his local post office was able to get it to where it was needed. I just thought that was so fascinating. There's such a thing in Nigeria where if you want to open a bookshop, if you want to distribute blood, if you want to distribute anything—in fact it's the same across the continent and in any developing country—you basically have to create your own infrastructure, your own distribution system. When we launched, we originally wanted to be just an app, and not a distribution company or a logistics company, but we realised we just couldn't move away from a distribution and supply chain. And that's how we came to where we are. I think that's the biggest challenge. And if you know logistics, then you know it's actually quite difficult to build, especially on the African continent. One of the challenges we have is to find enough capital—capital that will allow us to grow in a way that is sustainable.

What is your leadership style and what advice do you have for other leaders and managers? Any advice specifically targeted at female leaders?

I think women lead differently to men. I think my style is more collegial. Although I'm trying to make it a little bit less so, just to have a good balance between structure and getting along. I think my leadership style is more collegial and not autocratic in any way. The good thing about that is that it allows employees to take responsibility. I'm not giving anyone orders, I give them responsibilities, and I hold them accountable for the responsibilities I give them. I think that's absolutely important, and an interesting way to lead, in preference to shouting or telling people exactly what to do. I think it's important to allow people to rise to the occasion, to give them additional responsibility, and to allow them to grow into the jobs they have. So that's been my big leadership style.

> "I think you should own whatever leadership style you have"

I think, generally, women tend to be like that, and I don't think there's anything wrong with that. I don't think women should emulate other people's, or the other gender's leadership style. I think we should have our own way of leading, and I think we should understand that there are good parts about running a more collegial, more open and more diffused leadership system, instead of having it always top down where the CEO tells everybody what to do. I think sometimes we women feel like we have to learn and pretend to be men at work, but I don't think that's necessary. I think the world would be a better place and people would be treated very well and very kindly. I think the most important thing is that women should understand their own leadership style and make sure they are looking at their blind spots. If, let's say, you're very collegial, make sure that as you're being collegial, as you're allowing your staff to take responsibility for parts of the business, you also make sure you hold them responsible for those parts. And if you're more autocratic, then also ensure that you're creating a structure in which the people you're leading can also learn and grow in their jobs. I think you should own whatever leadership style you have.

What factors make LifeBank successful?

I think the biggest reason for that is that we had no money. When we launched, we launched literally with $35,000, and we made that last for two years. And because we had no money, everyone had to be super committed to the customers we had. We had to make sure that we were servicing them very well. We had to make sure we were focused on giving the best service we could to them. So that lack of money created a hyper focus on customer service, but also on excellence. We had to make sure that the little money we had went a long way. So that is what I think has made LifeBank so awesome—that hyper focus on our customers, and the fact that we are very excellent at discipline in terms of our operations.

How many people do you have working within LifeBank, and how many do you hope to expand this to?

We currently have about 22 staff, and in the next few years we're going to expand to about 50 people. ■

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Highlights from the I-I-I Blog (I expert, I question, I answer)

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Rana Awdish

Director of the Pulmonary Hypertension Program, Henry Ford Hospital; Medical Director of Care Experience, Henry Ford Health System; Faculty member, Wayne State University School of Medicine, Detroit, USA; Author of *In Shock*

Changing the culture of medicine - one conversation at a time

"As a physician in my own institution I was, at least in theory, an empowered minority. I had a voice, some measure of authority and personal agency. Yet, as a patient, I didn't feel at all empowered to be vocal about my needs or fears. I thought about how voiceless you become in many ways just through illness. And, perhaps more importantly, I realised that, if I felt that way, then the experience was far more common than I had understood it to be. Once I framed it that way for myself, I felt a responsibility to admit the ways in which my own system had in many ways failed me because, if it was failing me, then it was bound to be failing others." **See more at: https://iii.hm/k15**

Sarah Wickenden

CT3 Anaesthetics - Royal United Hospital, Bath, UK

Tea trolley teaching: the what, why and benefits

"'Bath tea trolley training' is a novel method of training that we have developed in Bath, UK over the past 3 years, and which we have used extremely successfully to provide multidisciplinary training in the workplace in our intensive care unit (ICU). It involves loading up a trolley with educational material on the top, and a pot of tea on the bottom: this trolley then travels around the ICU, with 1-2 trainers, providing 5-10 minute teaching sessions to ICU staff in their workplace during their usual working day (or even night shift!), followed by a cup of tea!" **See more at: https://iii.hm/k16**

Bruno Tomazini

Attending Physician, Intensive Care Unit - Sirio LibanÍs Hospital and Hospital das Clinicas da Universidade de S„o Paulo, Brazil

Time goes by and antibiotics linger on

"Antibiotics don't replace good doctors. Indiscriminate antibiotic use is a reckless attitude that not only dramatically increases healthcare costs, but also puts our patients' lives in danger. This is not an "I'll deal with it tomorrow" or "what difference one more day will do" type of thing. We already missed the bus.

"We can rely on evidence-based knowledge and self-discipline all doctors have, and with a pinch of goodwill and time, things will settle. Of course, this is a lie. Changes like this only come from the top down. But there is a light at the end of a vancomycin bottle. Antibiotic Stewardship Programmes might be the answer we were looking for." **See more at: https://iii.hm/k17**

Christine Schulman

Critical Care Clinical Nurse Specialist - Legacy Health, Portland, Oregon, USA; President, American Association of Critical-Care Nurses Board of Directors (2017-2018)

If you had a magic wand, what is one thing you would change about healthcare and why?

"The one thing I would change to improve our healthcare system won't take magic —it's achievable today. I would empower all direct care nurses as bedside leaders, innovators and catalysts for change. Why? Because empowering our clinicians at the front line of care results in better patient outcomes, satisfaction and cost containment—all key ingredients to thriving in these uncertain times for healthcare."

"Imagine decreasing infections, delirium and other adverse events, and shortening patient lengths of stay and ventilator days, just by having the care providers closest to the patient devise solutions. I don't have to imagine it—I've seen it and know it works." **See more at: https://iii.hm/k18**

Jan Bakker

Professor, Columbia University; New York University, USA; Erasmus MC, Erasmus University, Rotterdam, The Netherlands

Burn till you're out

"In a point prevalence survey study in 2013 (46% response rate), we found a very low rate of burnout (4.4%) in Dutch intensivists, where their medical directors reported an incidence of 7.4% in that year. These numbers are strikingly different from any other study in critical care, even when corrected for differences in scoring methods. What could be the key differences between the ICU care in the Netherlands and the U.S. that make up for this difference? In my perception, the significant organisational differences in the critical care systems, the differences in the judicial systems and the culture of claims between the U.S. and the Netherlands make up, for a large part, for the major difference in burnout between the systems. Current organisation of critical care in the U.S. drains the fuel of nurses, doctors, residents and fellows. Changing the organisation of care and improving the integration of hospital management in the process of care are key to solving a problem that endangers patients, doctors, nurses, residents and fellows alike."

See more at: https://iii.hm/k1a

Arun Radhakrishnan

Latrobe Regional Hospital, Traralgon, Australia

What does it mean to be an intensivist? A philosophical view of intensive care

"Intensive care is about saving lives and should also be about saving quality of life—they must necessarily be mentioned in the same breath. What we do must be beneficial to the patient—in other words, it is wise to question interventions that are offered or performed in the absence of a clear benefit to the patient, and also to society.

"It is, most importantly, making the patients feel they are being treated as human beings at all stages of their illness, including during the dying process. "

See more at: https://iii.hm/k19

Eoin Kelleher

Specialist Anaesthesia Trainee 2, Connolly Hospital, Dublin, Ireland

See more at: https://iii.hm/k1b

AGENDA

For a full listing of events visit https://iii.hm/aly

JUNE

4-8 NeuroIntensive Care: Update 2018 Como, Italy **https://iii.hm/jxj**

8-11 41st Annual Conference on Shock Coronado, USA **https://iii.hm/jxk**

9-13 9th World Congress of the World Federation of Pediatric Intensive and Critical Care Societies Singapore **https://iii.hm/jxl**

10-12 The Future of Critical Care - Brainstorming Meeting Edinburgh, UK **https://iii.hm/jxm**

12-15 36th Vicenza Course on AKI & CRRT Vicenza, Italy **https://iii.hm/jxn**

14-15 4th World Congress and Exhibition on Antibiotics and Antibiotic Resistance Barcelona, Spain **https://iii.hm/jxo**

28-29 Neurosciences in Intensive Care International Symposium 2018 Paris, France **https://iii.hm/jxp**

JULY

9-10 Rapid Response System 2018 Manchester, UK **https://iii.hm/jxq**

AUGUST

28-30 International Hypothermia and Temperature Management Symposium Sydney, Australia **https://iii.hm/jxs**

SEPTEMBER

1-4 40th ESPEN Congress on Clinical Nutrition & Metabolism Madrid, Spain **https://iii.hm/jxt**

8-12 European Emergency Medicine Congress (EUSEM) 2018 Glasgow, UK **https://iii.hm/jxu**

12-15 European Society of Regional Anaesthesia & Pain Therapy Congress Dublin, Ireland **https://iii.hm/jxv**

15-19 European Respiratory Society International Congress Paris, France **https://iii.hm/jxw**

20-22 European Resuscitation Council Congress 2018 Bologna, Italy **https://iii.hm/jxx**

OCTOBER

20-24 ESICM LIVES Paris, France **https://iii.hm/jxy**

25-27 9th International Baltic Congress of Anaesthesiology, Intensive Care and Pain Management Vilnius, Lithuania **https://iii.hm/jxz**

30 Oct - 3 Nov 7th Congress of the European Academy of Paediatric Societies (EAPS 2018) Paris, France **https://iii.hm/jy0**

NOVEMBER

1-3 7th Annual Johns Hopkins Critical Care Rehabilitation Conference Baltimore, USA **https://iii.hm/jy1**

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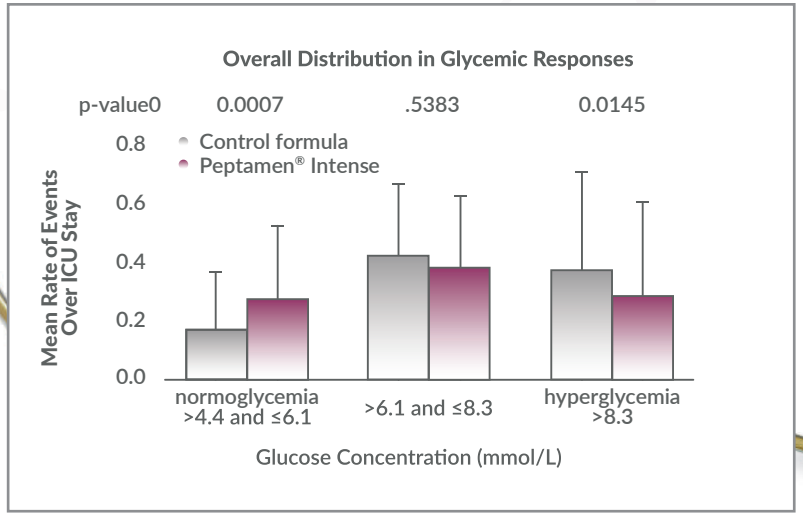

- 11% reduction in glycemic excursions (p = 0.01)
- 11% reduction in the frequency of insulin administrati on (p = 0.048)

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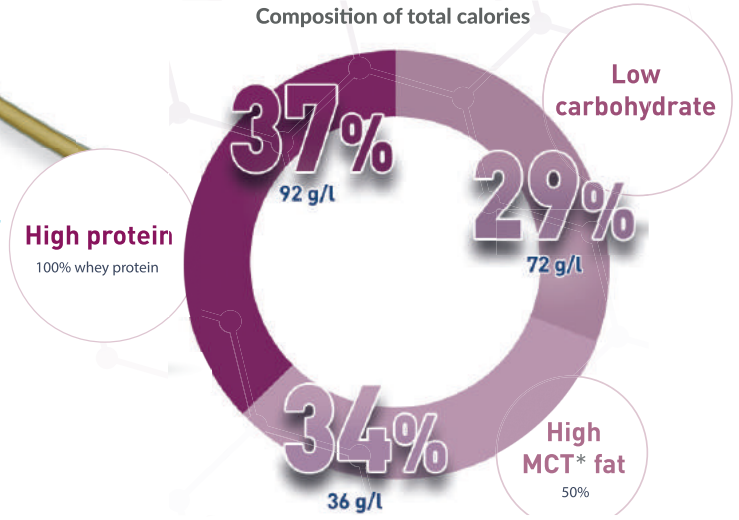

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2. Ochoa, et al. JPEN 2017;41(2):289
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4. Wieser, Cohen, Ochoa J, Huhmann M. JPEN, 2017. ASPEN CNW Abstract
5. Alberda C et al. Intensive Care Med 2009; 35: 1728 – 1737

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Luciano Gattinoni, MD

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Thomas W.L. Scheeren, MD, PhD

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Professor of Anesthesiology and Intensive care Department of Anesthesiology, Critical Care Program Montreal Heart Institute, and Centre Hospitalier de l'Université de Montréal, Université de Montréal Université de Montréal Montreal, Quebec, Canada

Post-Operative Cognitive Dysfunction (POCD) & Delirium: Preventing Damage and Improving Outcome – Clinical Advances in Brain Monitoring and Cerebral Oxygenation

Basil Matta, BA, BAO, BCh, MB, FRCA, FFICM

Divisional Director, MSK. Digestive Diseases, Major Trauma and Perioperative Care Medicine Clinical Lead – Cambridge University Hospitals Trust Consultant, Anaesthesia and Critical Care Associate Lecturer, University of Cambridge Cambridge, UK

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Azriel Perel, MD

Professor of Anesthesiology and Intensive Care Department of Anesthesiology and Intensive Care Sheba Medical Center, Tel Aviv University Tel Aviv, Israel

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