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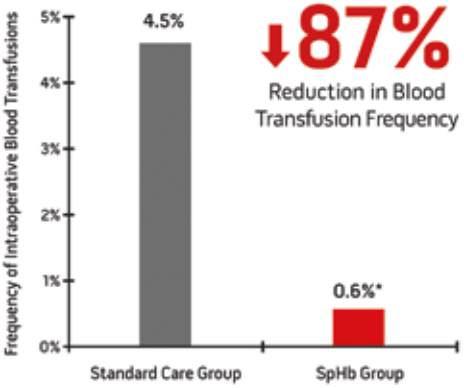

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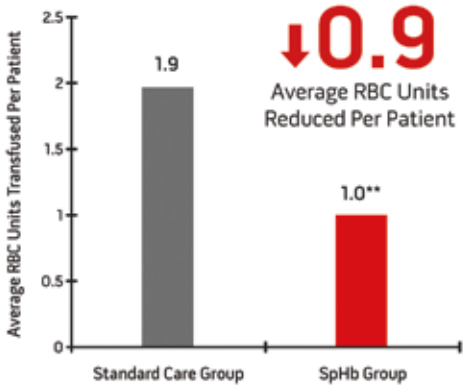

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[1]Ehrenfeld JM, et al. *American Society of Anesthesiologists.* 2010;LB05. [2]Awada WFN et al. Proceeding of the Society for Technology in Anesthesia Annual Meeting. 2013: p 51.

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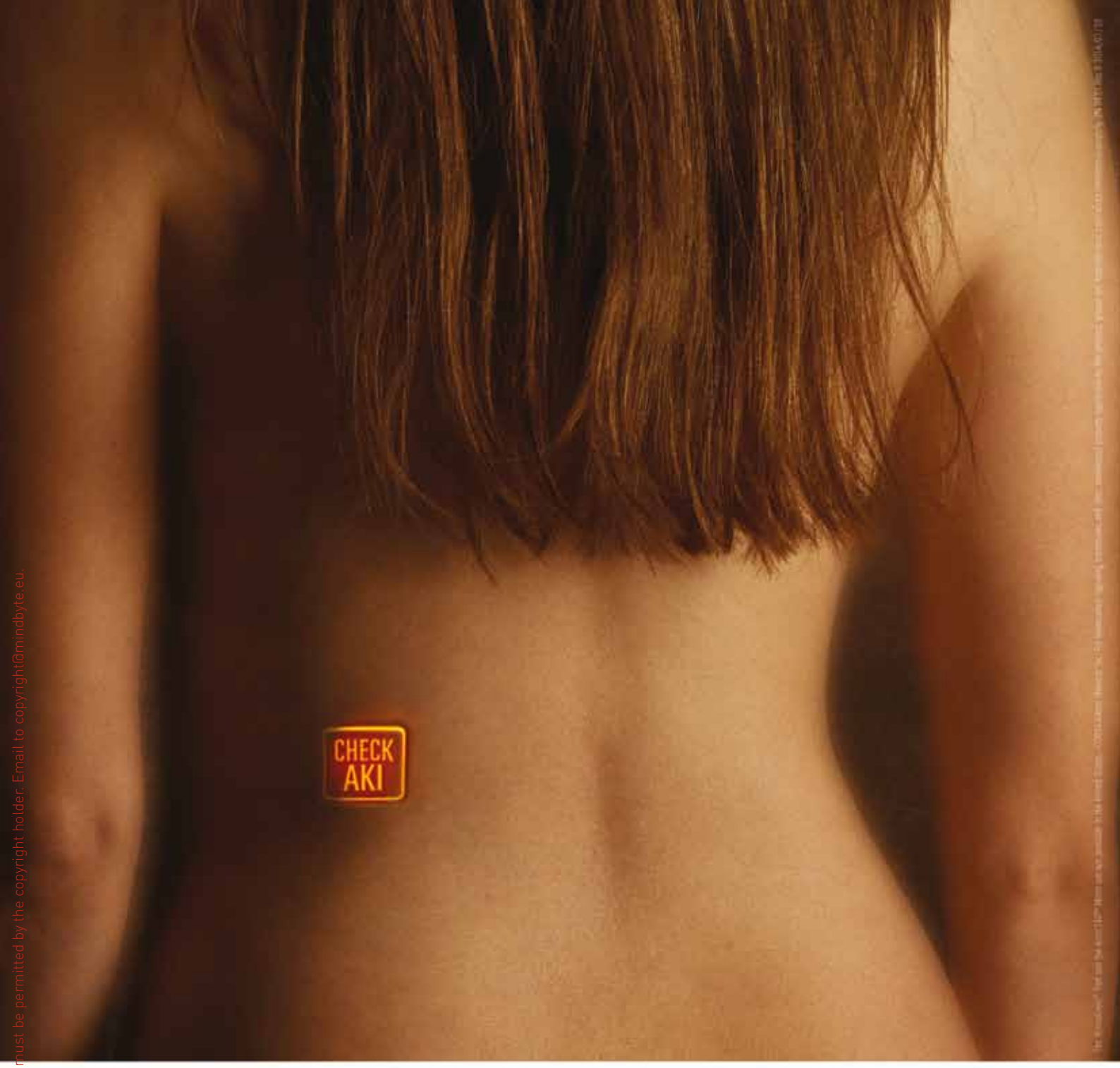

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GOAL-DIRECTED THERAPY

Goal-directed therapy (GDT) continues to be a subject of controversy in intensive care medicine, especially after the results of recent trials exploring its effectiveness. Our cover story this issue looks at two aspects of GDT. Azriel Perel addresses some of the remaining questions about the practice of perioperative goal-directed therapy. Despite evidence supporting its routine use, it has not been widely adopted. Perel examines some of the potential reasons for this gap between evidence and practice. Rebekah Thomson and colleagues explain the rationale for the use of GDT after cardiac surgery, and look at the outcomes, practicalities of implementation and cost-effectiveness.

Emanuel Rivers' contribution on sepsis will be published online shortly after this issue goes to print, to take account of the most recently published clinical trial results. Please visit the ICU Management website to make sure you are signed up for ICU Management Highlights, where this article will feature.

In the last in our Fluids series, David Gattas offers nine compelling reasons to investigate conservative fluid management in intensive care medicine more widely. Gattas asserts that the quality and quantity of clinical fluid science has markedly increased, particularly understanding which fluid to use.

Our Matrix section opens with a paper by Eleni Patrozou and Eirini Christaki on antibiotic management in the ICU. They focus on strategies aimed at optimising antimicrobial use within intensive care units, and explain general principles of antibiotic use in the ICU, including timing, antimicrobial selection, combination therapy, dosing, source control and duration. Next Djillali Annane considers what evidence-based care in the ICU is, and the potential role of big data, adaptive and other innovative designs for clinical trials. Annane concludes that intensivists need to improve the efficiency of methods to generate evidence-based care for the critically ill. Last, Kira Achaibar and Carl Waldmann write about prevention of venous thromboembolism (VTE) in critical care, which can include anti-coagulation therapy, mechanical prophylaxis and IVC filters, ventilator care bundles and critical care rehabilitation. They note that the number of patients receiving adequate thromboprophylaxis is poor currently.

In our Management section, firstly Richard Pugh and colleagues explain the use of frailty measurements in intensive care by summarising the current literature on frailty in the critically ill, and examine the feasibility of implementing a frailty score in clinical practice. They argue that using the Clinical Frailty Scale as a tool to assess patients referred to intensive care might facilitate discussions about treatment aims, and identify patients who are likely to need enhanced support following critical illness. Next, Leo and Simone Nefiodow discuss whether there is a correlation between health and economic growth. They explain that the development of leading industrialised nations is significantly determined by economic cycles: the Kondratieff waves. They argue that the new, sixth Kondratieff wave is the newly emerging second healthcare sector.

Bertrand Guidet, our Interviewee this issue, has a keen interest in elderly care, arguing that the issue of elderly patients is of paramount importance, because intensivists are at the centre of the process, needing to address ethical, financial and organisational issues. He answers questions about this and more areas of his expertise in this issue's Interview.

We visit Turkey for our Country Focus. M. Necmettin Ünal, President, Turkish Society of Intensive Care (TSIC) and Evren Ş̧entürk, Executive committee, TSIC, write about the activities of the Society and the development of intensive care medicine in Turkey since the first ICU was founded in Istanbul in 1959, They continue by writing about hot topics in Turkish intensive care medicine. Since intensive care medicine was recognised there as a supraspecialty in 2009, it has evoked several debates, including the role of directors of ICUs who do not have the Ministry of Health Diploma of Intensive Care. Several solutions have been proposed, however.

As always, if you would like to get in touch, please email **editorial@icu-management.org**

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Early Warning Response System: Sepsis Care Faster, Reduced Mortality Suggested

Harnessing vital signs information in the electronic health record (EHR) to develop an automated early warning and response system for sepsis led to a marked increase in sepsis identification and care, transfer to the ICU, and an indication of fewer deaths due to sepsis. A study assessing the tool, developed by Penn Medicine experts, is available online in the *Journal of Hospital Medicine*. It is believed to be the first published study implemented in a multi-hospital system.

The prediction tool uses laboratory and vital sign data in the EHR of hospital inpatients to identify patients at risk for sepsis. When certain data thresholds are detected, the system automatically sends an electronic communication to physicians, nurses and other members of a rapid response team (RRT), who perform a bedside evaluation and take further action if warranted.

The study developed the prediction tool using 4,575 patients admitted to the University of Pennsylvania Health System (UPHS) in October 2011. The tool was validated in a pre-implementation period from June to September 2012, when data on admitted patients was evaluated and alerts triggered in a database, but no notifications were sent to providers on the ground. Outcomes in that control period were then compared to a post-implementation period from June to September 2013. The total number of patients included in the pre- and post- periods was 31,093.

In both the pre- and post-implementation periods, four percent of patient visits triggered the alert. Analysis revealed 90 percent of those patients received bedside evaluations by the care team within 30 minutes of the alert being issued. In addition, the researchers found that the tool resulted in:

- A two to three-fold increase in orders for tests that could help identify the presence of sepsis;
- A 1.5 to two-fold increase in the administration of antibiotics and intravenous fluids;
- An increase of more than 50 percent in the proportion of patients quickly transferred to the ICU;
- A 50 percent increase in documentation of sepsis in the patients' electronic health record.

Craig A. Umscheid, MD, MSCE

The study found a lower death rate from sepsis and an increase in the number of patients successfully discharged home, although these findings did not reach statistical significance.

ICU Management spoke to lead author, Craig A. Umscheid, MD, MSCE, director of Penn's Center for Evidence-based Practice MD, to find out more.

You suggest that the EWRS could help triage patients for appropriateness of ICU transfer. Could you expand on that?

The mortality of those patients flagged and transferred to the ICU was much higher than those that were not. This suggests that this tool could have a purpose beyond what was originally planned. ICU beds are always at a premium, and as the literature demonstrates, the longer the delay in transfers to the ICU for patients who need it, the higher the risk of mortality. The potential purpose for this tool is there, but we haven't used it in that capacity yet.

Will EWRS improve detection of sepsis or are other tools/processes as important?

Our project was very much focused on detecting sepsis as early as possible. After the warning is triggered that a patient may have sepsis, there is a process in place that the "covering providers" (a nurse, an intern and the rapid response coordinator) go to the bedside and write a note after that encounter. It could be argued that an EWRS improves documentation and coding of sepsis, as well facilitating detection and care of patients with sepsis. In fact, the number of patients coded with sepsis increased during the intervention period.

Do most commercial EHR systems have this automated alert system available? How widely are they used?

Most large EHR systems have institutional users that have created these kinds of alert tools and shared them. There are a number of systems out there. However, most systems are only examining the test characteristics of the system and are not implementing them in practice.

Is the EWRS best used with a rapid response team or coordinator, or could it be used with existing staffing practices?

It can be used with existing staff, with an attending physician and a nurse. However, the benefit of a rapid response team (RRT) is the experience they build up. There are fewer than 200 triggers a month, so most attending physicians and nurses would not get more than 1-2 a year for each hospital. However, the RRT is present for each of these alerts, and therefore they build up experience and practice.

How can hospitals avoid alarm fatigue?

We need a balanced view. Having alerts is not positive if they become "guard rails". This is probably not so much of an issue when it comes to identifying sepsis early.

What further research is planned?

Now we are spending time on improving the prediction rules that drive this system. We are working on harnessing big data and using machine learning approaches to make predictions.

Reference

Umscheid CA, Betesh J, VanZandbergen C et al. (2014) Development, implementation, and impact of an automated early warning and response system for sepsis. J Hosp Med, 26 Sep. doi: 10.1002/jhm.2259. [Epub ahead of print]

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Highlights of the State of the Art Meeting 2014

Would you want to be admitted to hospital on a Sunday? As the NHS implements its drive to a full 7-day service, many in intensive care will say "we're there already!" On Day 1 of the conference, Professor Julian Bion will outline a project examining (in the light of the higher mortality rate associated with weekend admission) the cost-effectiveness of investing in consultant and specialist staffing at the weekend across the hospital sector.

80 speakers over the three days of the conference will set out expert views, insight, debate and progress on such areas as ebola, sepsis, fluids, feeding, novel therapies, latest research, disease management, patient safety, medical law, working conditions and future prospectives in intensive care.

Are you on the staff of one of the smaller ICUs? You may think it works well, but with the NHS driving towards greater efficiency, should ICM services be consolidated to be more cost-effective? Should your unit close? On Day 1 Professor Julian Bion, Dr Bob Winter and others will be talking about the centralisation of ICM services and the implications this will have for smaller units. Professor Julian Benger, the National Clinical Director for Urgent Care at NHS England, will brief delegates on the ongoing Review of Urgent and Emergency Care and how it will effect intensive care services.

How would the critical care sector deal with an influx of ebola cases? Dr. Tom Fletcher, a WHO infectious disease expert who saw the response to the outbreak in Guinea, will report first hand on his experience.

The widely adopted Liverpool Care Pathway was withdrawn last year following critical media coverage and an independent review of its effectiveness. Professor Paddy Stone will talk about its replacement, which has established five priorities for the care of people in their last hours and days, including the need for sensitive and effective communication with their relatives.

The conference includes a session focusing on patients: "The View From the Bed" on Day 2. Other highlights of SOA 2014 include the presentation of annual awards, when the Society and the Foundation recognise significant contributions to intensive care, and on Day 3, an audience with Prof Greet Van Den Berghe, who for many years has run the Clinical Department and the Laboratory of Intensive Care Medicine at KU Leuven in Belgium.

All presentations may diverge from the descriptions above, in response to circumstances.

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Critical Care In Resource-Poor Countries

The latest issue of *Global Heart* (www.globalheart-journal.com) focuses on the challenges of delivering critical care in resource-limited countries. Cardiovascular disease will soon surpass even human immunodeficiency virus (HIV) as the leading cause of mortality in Sub-Saharan Africa.

According to Guest Editors Vanessa Kerry, MD, MSc, and Sadath Sayeed, MD, JD, "Critical care as a clinical discipline in resource-rich settings is associated with high resource (financial, human, technological) intensity. For this reason, among others, critical care has received far less investment in resource-poor countries. Although numerous challenges to scaling up high quality intensive care services present themselves, even more opportunities to creatively innovate in this field exist that hold promise to move us closer to equity in global healthcare." They argue that investments in critical care need not be technology- or cost-intensive, but should be appropriate and effective.

"Critical care is an area of needed scale-up. Although the massive influx of effort and funding of HIV treatment has resulted in significant gains in life expectancy and health system strengthening, a lack of critical care resources in disadvantaged areas remains. Interventions in critical care in these settings are justified. In resource-limited settings, the majority of critically ill patients are children and young adults and avoiding preventable death would reduce mortality and disease burden as well as have socioeconomic impacts."

This issue of *Global Heart*, "Critical Care in Resource-Limited Settings," includes coverage by a group of experts on important topics pertaining to the delivery of healthcare to low-income countries. Key concerns explored include sepsis, ARDS, pulmonary vascular disease, cardiac care, influenza, providing ICU care in a challenging case, intensive care in low- and middle-income countries, HIV and critical care delivery, antimicrobial resistance, and the perspective of the American Thoracic Society.

PERIOPERATIVE GOAL-DIRECTED THERAPY
SOME REMAINING QUESTIONS

Azriel Perel, *MD*

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What is Perioperative Goal-Directed Therapy?

Perioperative mortality of patients undergoing high-risk surgery has been steadily declining over recent years. And yet this reduced mortality rate is still considered to be higher than anticipated (Pearse et al. 2012). Newer approaches aimed at improving perioperative outcome and reducing its associated costs have been recently proposed. These include fast-track surgery (Kehlet and Wilmore 2008), enhanced recovery after surgery (ERAS) (Knott et al. 2012) and the surgical home (Kain et al. 2014). However, the most significant and extensively studied strategy that has been suggested to decrease major perioperative complications and even death is that of goal-directed therapy (GDT). Perioperative GDT describes a variety of proactive therapeutic strategies that aim to achieve better patient outcome by improving the haemodynamic status in the perioperative period, especially in high-risk patients undergoing non-cardiac surgery (Boyd and Bennett 1999; Lees et al. 2009; Gurgel and do Nascimento 2011; Hamilton et al. 2011). Although the term 'GDT' has never been well defined, it is most often used to describe cardiac output (CO) maximisation by fluid loading ('flow-guided optimisation'), with or without additional therapies aimed at increasing global oxygen delivery (DO2) to pre-defined 'supra-normal' values. These and other physiological 'goals' have been used to guide GDT in a variety of clinical protocols and patient populations.

Although as early as 1999 the proponents of this approach claimed that "it may be considered unethical not to use perioperative GDT" (Boyd and Bennett 1999), and in spite of the large body of evidence that presumably supports its routine use, GDT has not been widely adopted (Cannesson et al. 2011; Miller et al. 2011; Cecconi and Rhodes 2014). This review attempts to examine some of the possible reasons for this considerable gap between 'evidence' and practice and to highlight some of the remaining questions surrounding the practice of perioperative GDT.

Questions Regarding the Pathophysiological Rationale of Perioperative GDT

The main physiological rationale for the claimed benefit of perioperative GDT is that major surgery generates a strong systemic inflammatory response and an overall substantial increase in oxygen demand. This response is normally met by increases in CO and in oxygen extraction. Patients that do not have the physiological reserve to increase CO to the required level that is necessary for adequate tissue perfusion may therefore be at higher risk of postoperative complications. Therapy aimed at increasing oxygen supply may therefore prevent or correct the oxygen deficit that may develop during an initial period of poor perfusion. GDT has been shown to improve sublingual and cutaneous microvascular flow, as well as blood flow to the gut mucosa, as evidenced by a higher gastric mucosal pH (pHi) and an increased oxygen tension in the perianastomotic colonic tissue. These mechanisms may well be responsible for the frequently reported decrease in postoperative complications in patients undergoing perioperative GDT, a decrease which has also been associated with their longer term survival (Rhodes et al. 2010).

However, the available pathophysiological data that may explain the benefits of GDT are still limited and incomplete (Kehlet and Bundgaard-Nielsen 2009), and the few studies that have shown improvement in microvascular blood flow due to GDT raise some further questions. For example, the finding that GDT is associated with increased gut mucosal pH could not be confirmed in a later study (Kehlet and Bundgaard-Nielsen 2009), and an observed GDT-induced increase in microvascular blood flow was not associated with differences in inflammatory markers or in overall complication rate (Jhanji et al. 2010).

The fact that the exact mechanisms by which GDT may provide benefit remain unclear may account for the existing confusion as to when exactly it should be instituted. Studies demonstrating the benefit of GDT were done in the pre-, intra-, and, very often, in the postoperative period. Since we have widely adopted the concept of early GDT in haemodynamically unstable critically ill patients, it may seem logical to apply the same approach to the perioperative period in order to prevent tissue hypoxia

as early as possible. It is therefore unclear why those who believe that GDT be practised only in the postoperative ICU, do so because of pathophysiological reasons or because of pragmatic ones.

More questions surround the pathophysiologic rationale of using GDT that is aimed at increasing cardiac index (CI) and oxygen delivery (DO2) to 'supra-normal' levels (> 4.5 L/min/m^2 and > 600 ml/min/m^2, respectively) (Lees et al. 2009). This approach has first gained popularity in the care of critically ill patients more than 20 years ago following Shoemaker et al.'s early studies (Shoemaker et al. 1988). However, it has since been abandoned in the critically ill as further studies failed to prove its effectiveness in this patient population. Its adoption as the recommended GDT approach stands in contradistinction to the main alternative strategy of GDT, which recommends that optimisation of flow-related parameters be done in an individualised manner and within the limit of the individual patient's cardiac capacity (Kehlet and Bundgaard-Nielsen 2009). From a purely clinical point of view, it seems also questionable that such 'supra-normal' values can be achieved in all patients undergoing high-risk surgery, including the old and frail. For example, in a small study where such a GDT approach was used in patients undergoing elective total hip arthroplasty under regional anaesthesia, only 65% of patients reached a DO2 > 600 mL/minute/m^2 in the GDT group (Cecconi et al. 2011). Even the proponents of this approach admit that the continued pursuit of haemodynamic goals in patients who do not respond, and especially those with significant heart disease, is harmful (MacDonald and Pearse 2011). Hence without a better pathophysiological reasoning it is hard to support this practice.

Questions Regarding the Evidence Supporting Perioperative GDT

Many studies have examined the potential benefit of a variety of perioperative GDT approaches. These studies have been included in a number of meta-analyses, which have concluded that perioperative goal-directed care reduces postoperative complications, days of hospital stay and subsequent mortality, especially in high-risk surgical patients (Boyd and Bennett 1999; Lees et al. 2009; Gurgel and do Nascimento 2011; Rhodes et al. 2010 Hamilton et al. 2011; Cecconi et al. 2013). The accumulating volume of evidence in favour of GDT has affected clinical practice in many places, the most prominent example being the endorsement of the use of oesophageal Doppler (ODM) for GDT in high-risk surgical patients by the United Kingdom National Institute of Health and Care Excellence (2011). This large body of evidence cannot be simply ignored, and therefore puts pressure on clinicians to either adopt GDT strategies or find a good explanation for why they do not. One such explanation may be the remaining doubt that many clinicians still have about the robustness of the GDT concept and the quality of the evidence supporting it.

> **"There is currently no evidence-based consensus on questions such as which goals should be targeted for various surgical procedures and which patient groups most benefit from a GDT strategy"**

It is well recognised that there are some distinct problems that are associated with the design and conduct of GDT trials (MacDonald and Pearse 2011; Cecconi and Rhodes 2014). These problems may have affected the results of many such trials, and may have contributed to the possibly erroneous conclusions of the many meta-analyses that GDT is indeed beneficial. Many of the GDT studies have included only a very small number of patients, and thus may have been affected by bias due to the lack of blinding. The treatment protocol of the control group may have also affected the results, as substandard care and learning contamination bias of this group may, respectively, either over- or under-estimate the true difference between the groups. Other factors that may have affected the quality of GDT 'evidence' are a possible publication bias, and the inclusion of early studies that showed a very significant GDT impact (that could not be repeated) in these meta-analyses. In addition, generalising the results of these 'positive' studies is not straightforward, as they have been done in very heterogeneous patient populations, undergoing different surgical procedures and carrying different levels of risk.

Evidence that Goal-Directed Therapy May Not Be Beneficial

There are a growing number of recent well-conducted randomised clinical trials, which have found that perioperative GDT does not provide clinical benefit. In patients undergoing laparoscopic segmental colectomy, GDT with a colloid/balanced salt solution was found to offer no advantage over standard therapy (Senagore et al. 2009). Another randomised study in major gynaecological surgery found no difference in the length of postoperative hospital stay and postoperative morbidity survey scores between the ODM-guided GDT and the control groups (McKenny et al. 2013). Another double-blinded controlled trial, including 179 patients undergoing major open or laparoscopic colorectal surgery, found that intraoperative stroke-volume (SV) optimisation conferred no additional benefit over standard fluid therapy. Moreover, in an aerobically fit subgroup of patients, intraoperative ODM-guided GDT was associated with delayed readiness for discharge and longer hospital stay (Challand et al. 2012). Another multi-centre trial found that GDT to near-maximal SV guided by ODM added no extra value to the fluid therapy using zero balance and normal body weight in patients undergoing elective colorectal surgery (Brandstrup et al. 2012). A randomised clinical trial of GDT within an enhanced recovery protocol (including fluid restriction) for elective colectomy did not reduce number of complications or hospital length of stay (Srinivasa et al. 2013b). A more recent randomised multi-centre trial in

142 patients scheduled for open major gastrointestinal surgery found that a perioperative haemodynamic protocol guided by a noninvasive CO monitor was not associated with a decrease in the incidence of overall complications or length of stay (Pestana et al. 2014). Last, but not least, the OPTIMISE multicentre trial of 734 high-risk patients undergoing major gastrointestinal surgery that used a CO–guided haemodynamic therapy algorithm, did not show any reduction in a composite outcome of complications and 30-day mortality compared with usual care (Pearse et al. 2014).

Although the OPTIMISE trial has failed to show the benefit of GDT, it also included an updated meta-analysis, indicating that GDT is associated with a reduction in complication rates. This meta-analysis, however, includes many studies done more than 10 years ago, and many in which a variety of GDT protocols and monitoring modalities have been used. As such, this meta-analysis cannot be used in support of the routine practice of straightforward CO maximisation. Furthermore, two other recent meta-analyses and systematic reviews have found no difference between GDT and control groups (Grocott et al. 2013; Srinivasa et al. 2013a). A third one concluded that GDT may lead to better outcome compared with liberal fluid therapy without haemodynamic goals; however, whether it is superior to a restrictive fluid strategy remains uncertain (Corcoran et al. 2012). In summary, there is currently no evidence-based consensus on questions such as which goals should be targeted for various surgical procedures and which patient groups most benefit from a GDT strategy. Moreover, the accumulating negative evidence regarding GDT has created new and significant criticism of this approach (Minto and Struthers 2012; Morris 2013; Wilson 2013).

Can GDT Increase the Risk of Fluid Overload?

The majority of studies describing perioperative flow-directed GDT, with or without the achievement of 'supra normal' CI and DO2, have been associated with the intervention group receiving significantly more fluids (Cecconi et al. 2011; Challand et al. 2012). This is easily understandable as the 'classic' GDT protocol starts with a "fluid challenge" (usually colloids), with the recommendation that it be repeated until the CO (or SV) does not increase by more than 10%. Another part of this protocol recommends that fluids be given also when the SV drops by more than 10%. The assumption behind this latter recommendation is that any decrease in SV is due to a reduction in cardiac preload. This is not necessarily true, as many other factors (e.g. surgical stress, contractility) may account for a decrease in SV. This has been nicely demonstrated by Hood and Wilson (2011), who found that reductions in SV of >10%, as measured by ODM, have a sensitivity of only 37% in identifying fluid responsiveness, and therefore may be related to other factors aside from preload. The proclaimed aim of continuously keeping the patients on the flat portion of the left-ventricular function curve by fluid administration, carries an obvious risk of iatrogenic fluid overload, since a considerable (and variable) part of the administered fluids does eventually leave the intravascular space (Jacob et al. 2007), necessitating repeated fluid loading. Such fluid overload may damage the endothelial glycocalyx and lead to the development of interstitial oedema in various organs and a considerable postoperative weight gain. Excessive fluid administration has also been shown to have deleterious effects on anastomotic healing and postoperative complications in digestive surgery, possibly because of a marked bowel wall oedema (Marjanovic et al. 2009).

> **"GDT is safe when practised correctly, but there are still significant impending questions regarding how to best do it"**

A 1999 *National Confidential Enquiry into Perioperative Death* in the UK highlighted over-hydration as a contributory cause in the genesis of postoperative problems leading to death (Callum et al. 1999), and recommended careful fluid management (the implication being restriction) in vulnerable patients and those most at risk, such as the elderly. The British consensus guidelines on intravenous fluid therapy for adult surgical patients (GIFTASUP) (Powell-Tuck et al. 2011) were also put together due to "concern that arose from a high incidence of postoperative sodium and water overload, and evidence to suggest that a more accurate fluid therapy would improve outcome". And yet the uncritical adoption of these guidelines may lead to fluid overload, as they recommend that GDT be applied in the pre-, intra- and postoperative periods. In order to prevent the possible complications of overzealous perioperative fluid administration, restrictive fluid management strategies have been explored. Such strategies have also been shown to reduce postoperative morbidity and to shorten hospital stay (Brandstrup et al. 2003; Nisanevich et al. 2005; Walsh et al. 2008). However, the concepts of 'liberal', 'standard' and 'restrictive' fluid management are not well-defined, and their lack of standardisation makes any pooling of data nearly impossible (Jacob et al. 2007). Nevertheless, the GDT approach should not be interpreted to recommend a forgiving attitude towards 'liberal' fluid administration without appropriate monitoring (Ghosh et al. 2011). Such an approach is demonstrated by the FOCCUS study, where fluid loading with 25 ml/kg of Ringer's solution was given in the 6 hours before major abdominal surgery (Cuthbertson et al. 2011).

Clinical Implications

The pathophysiological rationale and the evidence which support the adoption of GDT strategies in the care of patients undergoing major high-risk surgery cannot be disregarded. And yet, the emerging evidence that GDT may not be beneficial cannot be disregarded as well, leading some of the most enthusiastic proponents of this approach to ask whether it is "Time to move on?" (Cecconi and Rhodes 2014). GDT is safe when practised correctly, but there are still significant impending

BEYOND POINT-OF-CARE BLOOD GAS ANALYSIS

INNOVATIVE MINIATURE IN-LINE BLOOD GAS ANALYSER SUPPORTS RAPID AND FREQUENT BEDSIDE BLOOD GAS MEASUREMENTS AT CRITICAL TIMES

To address the challenges of maintaining control of patient physiology in the ICU and the associated need for fast response, proactive critical care, a revolutionary in-line patient dedicated arterial blood gas analyser has been newly introduced. Uniquely, the new Proxima miniaturised analyser, developed by Sphere Medical (Cambridge, UK), enables blood gas testing to deliver rapid and frequent results directly at a patient's bedside.

Current point-of-care testing (POCT) technologies have certainly significantly reduced turnaround times for critical tests. However, this has consequently increased the workload of front-line care staff, taking them away from the patient at key times to manipulate blood samples and cartridges for analysis. Furthermore, this still requires significant amounts of patient blood. The new Proxima represents the next step on in POCT as it is actually attached directly to the patient through their arterial line, meaning that for the first time blood gas results can be delivered, like blood pressure results, within the patient's bed space.

Unlimited blood gas sampling

The CE marked Proxima System incorporates a dedicated bedside monitor, as well as a miniature Proxima Sensor integrated into the patient's arterial line. This disposable transducer can be used for monitoring blood gases and electrolytes over a 72 hour period as many times as required without loss of patient blood. Proven to measure to laboratory analyser accuracy, results are rapidly displayed on the bedside monitor and can be electronically transferred for permanent record. The system also carries out all quality control checks that would be undertaken on a traditional blood gas analyser to ensure validity of test results.

Patient dedicated

Specifically designed for use in critical care environments, particularly for unstable patients, it enables frequent direct measurement of arterial blood samples to aid early decision-making and ensure closer control of therapy. Since the caregiver can stay right by the patient to take these important measurements, the system has the potential to decrease the nursing dependency of the patient. Each patient can now have their own dedicated blood gas analyser and any nurse time away from them is minimised.

Conserving blood

Due to the fact that it is in-line, the Proxima System enables closed blood sampling. When a blood gas analysis is required, blood is simply withdrawn from the patient directly into the Proxima Sensor without the usual need to open the line, take a sample and walk away for analysis. Once analysis is completed, all blood is returned to the patient, thereby ensuring blood conservation and reducing the possibility of hospital acquired anaemia and consequent transfusions.

Clinical validation

Proxima has been fully evaluated and validated in a clinical setting. A recent observational method comparison study at Queen Elizabeth Hospital, Birmingham, UK, confirmed excellent agreement between Proxima and standard blood gas analysis. The study results wholly met the primary end-point to demonstrate excellent agreement with the standard bench top blood gas analysers at the hospital; measuring various arterial blood parameters of intensive care unit patients with a range of clinical conditions, including trauma, head injury, post-surgical recovery and sepsis.

Dr Tom Clutton-Brock, Senior Lecturer Anaesthesia and Intensive Care Medicine, University Hospital Birmingham and Chief Investigator for the study, commented, *"The main aim of this study has been to determine whether Proxima gives the same clinical results as the reference bench top blood gas analyser when it is used on patients in a clinical environment. The answer is unequivocally yes. Just as importantly, the staff using the system really appreciated how simple it was to take a measurement with Proxima. We are really excited about the impact that this could have on management of sick and unstable patients."*

Proxima will be available to view on Stand 32 at the Intensive Care Society, State of the Art Meeting, London, 8-10th December 2014. Or, find out more at www.spheremedical.com and watch a seminar given by Dr. Tom Clutton-Brock discussing the challenges of maintaining control of patient physiology in the ITU.

SPHERE
RAISING THE STANDARD OF CRITICAL CARE

questions regarding how to best do it. Beyond the ones that have been raised in this review, these questions include the selection of the right patients, the right timing, the type of fluids that have to be used, the ability of new CO monitors to accurately track the response to fluid loading, the selection of specific protocol end-points, and more. When appropriate, the use of dynamic parameters, like the systolic (SPV) and pulse (PPV) pressure variations, stroke volume variation (SVV) and the plethysmographic variation index (PVI), may add important information regarding fluid responsiveness and prevent unnecessary fluid loading (Perel et al. 2013; Benes et al. 2014). The use of more advanced monitoring technologies may further improve perioperative haemodynamic management. Individual decisions about perioperative fluid management should be regarded as a 'therapeutic conflict', namely, recognising that each of the decisions (e.g., 'liberal', 'restrictive') may potentially cause harm, and taking into account the risk-benefit ratio of the individual patient. Last, but not least, the limitations of a single intervention (fluid management) to determine outcome have to be recognised, since many other factors, like type of anaesthesia, ICU availability, early mobilisation and adequate analgesia, may be of equal, and at times, greater importance. ■

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EARLY GOAL-DIRECTED THERAPY FOLLOWING CARDIAC SURGERY

FOCUS ON OUTCOMES AND PRACTICALITIES

Early goal-directed therapy (EGDT) is a therapeutic strategy based on haemodynamic monitoring and pre-defined goals. The roots of this approach come from observational studies in non-cardiac surgery that showed that poor post-operative outcomes and higher mortality were associated with decreased oxygen delivery in the perioperative period (Clowes et al. 1960; Shoemaker 1972).

Following those studies several strategies have been tested in clinical trials attempting to manipulate the cardiovascular performance in order to achieve haemodynamic goals associated with reduction of complications and survival outcome (Wilson et al. 1999; Shoemaker et al. 1988; Boyd et al. 1993; Lobo et al. 2000; Gan et al. 2002; Kern et al. 2002; Wakeling et al. 2005; Pearse et al. 2005; Noblett et al. 2006; Donati et al. 2007; Giglio et al. 2009; Mayer et al. 2010; Dalfino et al. 2011).

Rationale

The mechanism of this therapy is likely to be attributed to the improvement of oxygen delivery (Mythen et al. 1993; Mokart et al. 2002). A constant supply of oxygen is required for the mitrochondria to maintain aerobic metabolism. In health the cardiovascular system delivers the oxygen supply (DO2), and adapts to changes in metabolic demand to prevent cytopathic hypoxia (Navarrete et al. 2013). Once mitochondrial damage takes place, the insult becomes permanent (Hollenberg and Cunnion 1994), and correction of oxygen delivery is futile. The cellular oxygen demand following major surgery increases as a consequence of several factors, such as stress response to surgery, pain, shivering and anxiety among others (Routsi et al. 1993). Many cardiac surgical procedures involve cardiopulmonary bypass, which is associated with vasospasm, impaired platelet function and inflammatory response. This can result in impaired microcirculation and subsequent organ dysfunction (Silvestry 2012). The EGDT aims to prevent organ dysfunction by correcting the imbalance between oxygen consumption and oxygen delivery.

Evidence in Cardiac Surgery

Although postoperative mortality remains low following cardiac surgery (about 1-5%, dependent on surgical procedure and preoperative comorbidities), complications remain moderately high, and are associated with prolonged postoperative care (Ghotkar et al. 2006), longer intensive care unit (ICU) stays and worse long-term survival (Pivatto et al. 2010; Gaudino et al. 2007). Patients with complications use a greater amount of resources (Scott et al. 2005), and therefore these patients are associated with higher healthcare costs.

Few studies have investigated the role of GDT in cardiac surgery (Polonen et al. 2000; Mythen and Webb 1995; McKendry et al. 2004; Kapoor et al. 2008; Smetkin et al. 2009). Unfortunately, the evidence is limited by the fact that these studies are on small sample sizes from single centres, and with single blinding.

In a recent meta-analysis of EGDT in cardiac surgery (Aya et al. 2013), no improvement in mortality with GDT was found. However, EGDT can reduce the risk of postoperative complications and length of stay. The mortality in the control group was already low in these studies; in fact there were two studies with zero mortality, so that in order to observe a real difference in mortality larger studies with sufficient statistical power are required.

Outcomes Measures in EGDT

Choosing outcome measures for studies in a population with low mortality rates can be problematic. Complications associated with cardiac surgery remain an important issue, which is widely reported within the literature. Combining complications for outcome measures and designing a study based on composite end points will have multiple confounding factors, and may dilute the impact of the intervention, but selecting an appropriate primary outcome is challenging.

Postoperative complications go together with an increased length of stay and more costly care (Speir et al. 2009). It is not therefore a surprise that a lower incidence of postoperative morbidity is often accompanied by shorter length of hospital stay. However, length of stay is heavily influenced by clinical decisions on discharge readiness, social factors and patients' perception of relative independence. These outcome measures may remain too crude, and more objective measurements should be adopted.

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A study investigating the effects of EGDT on gut perfusion was conducted, which was shown to be of benefit and was associated with improved outcome (Mythen and Webb 1995). Gastric tonometry has been described as the haemodynamic monitor of choice, as the gut is particularly sensitive to episodes of ischaemia (Heard 2003). However, it is not widely used within the ICU, and its effectiveness at assessing blood flow by translation of pH has been criticised (Uusaro et al. 1995). Other markers of end organ perfusion may be considered when choosing an appropriate outcome measure.

The most commonly reported and investigated complication following cardiac surgery is acute kidney injury (AKI). AKI occurs in around 30% (Rosner and Okusa 2006) of the cardiac surgery population, and is associated with increased short-term and long-term mortality.

Though AKI has many confounding factors in cardiac surgery, the pathogenesis of postoperative renal dysfunction includes hypoperfusion that remains undetected when relying on basic haemodynamic monitoring such as heart rate, blood pressure and central venous pressure.

Goals

The use of cardiac output monitoring and flow-related goals is the basis of EGDT strategy. In a subgroup analysis, Hamilton et al. (2011) demonstrated that those studies that used flow-related goals were able to reduce mortality after non-cardiac surgery. This approach could help in preventing organ hypoperfusion (Pearse et al. 2005) and particularly acute kidney injury (2014). A meta-analysis by Brienza et al. (2009) confirmed this notion in the non-cardiac surgical population.

Practicalities of Implementation

Implementing EGDT in the cardiac surgery population is simple, as therapy should start on arrival in the intensive care unit. Intraoperative use of EGDT is complex, as the use of cardiopulmonary bypass makes the fluid status of the patient difficult to assess.

Intensive care units provide the ideal setting for patients recovering from cardiac surgery for several reasons:

1. Each patient has additional nursing staff;
2. ICUs are familiar with the use of minimally invasive cardiac output devices;
3. Continuous monitoring allows the implementation of an EGDT protocol and adaptation to the patient's needs.

Intensive care nurses are familiar with such equipment, and most cardiac output monitoring technologies are able to assess stroke volume changes, and provide the ability to implement the simplest component of EGDT (Thomson et al. 2014).

> **"EGDT following cardiac surgery can be achieved using a stratified approach to fluid administration"**

The ease in application of an EGDT protocol was demonstrated in several studies in both non-cardiac and cardiac surgery populations (Pearse et al. 2005; McKendry et al. 2004; Thomson et al. 2014), which were all implemented by nursing staff.

A safe and effective protocol should include safety triggers for nursing colleagues to escalate potential harm to the medical staff. In the cardiac surgery population this might include central venous pressure (CVP) monitoring to be used as a safety mechanism. A sharp rise of 5mmHg in CVP or more during a fluid challenge should prompt the nursing staff to cease fluid administration (Cecconi et al. 2011; Cecconi et al. 2013). This allows medical staff to exclude right ventricular dysfunction and/or cardiac tamponade, which are common concerns applicable to cardiac surgery patients in the immediate postoperative period.

Cost-Effectiveness

Despite extensive evidence that supports the effectiveness of EGDT in improving outcomes, its implementation is still not clearly accepted. The main concern comes from the additional costs that a routine protocol of EGDT may imply for the health system. A recent cost-effectiveness study (Ebm et al. 2014) enlightens this reasonable concern: goal-directed therapy decreased costs by £2,631.77 per patient and by £2,134.86 per hospital survivor. The authors conclude that the additional costs can be offset by savings due to reduced costs resulting from a reduction in complication rates and hospital length of stay.

Cardiac surgery is associated with complications, such as infection, respiratory failure and acute kidney injury (AKI). AKI requiring renal replacement therapy (RRT) occurs in 1% of patients (Rosner and Okusa 2006), which increases mortality and postoperative complications such as infection, is associated with an increased duration of stay, and may go on to require further long-term RRT. Renal replacement therapy and prolonged ventilation are both available only within the ICU. Not only are there associated costs, but there is an impact on bed availability, and this can lead to cancellations of elective surgery. EGDT has demonstrated reductions in ICU stay, as optimising haemodynamics ensures patients' readiness for discharge is achieved on average four hours earlier (Thomson et al. 2014).

Conclusion

Early goal-directed therapy following cardiac surgery can be achieved using a stratified approach to fluid administration. Preventing hypervolaemia, maintaining flow and sustaining organ perfusion can improve patients' outcome, reduce cost and length of stay. ■

For full references, please email **editorial@icu-management.org**, visit **www.icu-management.org** or use the **article QR code**.

Antibiotic Therapy in the ICU

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CONSERVATIVE FLUID MANAGEMENT IN INTENSIVE CARE MEDICINE

NINE REASONS TO INVESTIGATE MORE WIDELY

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Asserting the existence of a state of permanent controversy is a staple during presentations on the topic of resuscitation fluids. Clinical audiences recognise a cliché when they hear it, and may disengage. This is unfortunate, since there has been a steady crescendo in the quality and quantity of clinical fluid science in the last two decades. In particular, our understanding of *which* fluid to use has been greatly improved. Large-scale clinical trials are now providing high quality answers to questions of *how much* fluid we should use and *when* we should use it. There are at least nine reasons to believe that a programme of clinical research investigating conservative or restrictive fluid strategies may yield benefits for critically ill patients.

1. Traditional Paradigms Influencing Clinical Fluid Practices Are Broken

Small, underpowered studies are incapable of revealing what benefits and harms are really being experienced by patients who receive intravenous fluid. This is especially true where intervention effect sizes are small, and the use of surrogate physiological outcomes is widespread (Yudkin et al. 2011; Ioannidis 2005). Colloids, for example, do not deserve to be entrenched in widespread ICU practice, are not associated with improved survival, are expensive, and may be harmful in some cases (Perel et al. 2013). Almost every patient in hospital is exposed to intravenous fluid, and they are entitled to expect that the science guiding their use is constantly improving.

2. Bolus Fluid Administration is Guided by Weak Evidence

Clinical practice guidelines recommend a bolus fluid challenge of at least 2 litres in a 70kg patient with sepsis and hypoperfusion (Dellinger et al. 2013); smaller boluses of fluid are among the most common interventions in the ICU. There were no randomised controlled trials of fluid resuscitation in sepsis patients, which reported mortality, until 2008 (Hilton and Bellomo, 2012). Arguably, recent trials are undermining the usual practice of bolus fluid resuscitation, and constructive criticism of liberal fluid boluses should not be dismissed (Marik 2014).

3. We Need to Explain Unexpected Results Arising from Recent Large Clinical Trials

Bolus fluid was associated with increased mortality in the FEAST study (Maitland et al. 2011), a landmark trial of 3600 children with severe infection in resource-limited settings in Africa. It isn't clear if or how these results should be applied to our own practice, but the size and quality of this study demands that we should find out. The ProCESS (ProCESS Investigators et al. 2014) and ARISE (The ARISE Investigators and the ANZICS Clinical Trials Group 2014) trials have provided no additional support for current goal-directed fluid resuscitation, and are prompting reflection (Surviving Sepsis Campaign 2014).

4. Positive Fluid Balance is Associated with Increased Mortality in the ICU

Post-hoc analyses of large ICU trials have examined positive fluid balance as a risk factor for mortality. This association has been observed in patients with sepsis (Boyd et al. 2011) and renal failure (Payen et al. 2008), and raises unanswered questions about causality. It is unknown if fluid intake and/or fluid balance are valid therapeutic targets in most critically ill patients.

5. Conservative Fluid Strategies are Relevant in ICU Patients with Lung Injury

The FACTT study (National Heart Lung Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network et al. 2006) randomised 1000 patients with acute lung injury to a conservative or liberal fluid strategy. It is one of the highest quality studies of this intervention in critical illness. Conservative fluid management improved lung function, and shortened the duration of mechanical ventilation. In a different ARDSnet study (ARMA lower tidal volume), investigators followed up with a later report of an independent association between negative cumulative fluid balance and lower mortality (Rosenberg et al. 2009).

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6. Conservative Fluid Strategies are Important in Surgical Patients

Fluid restriction is a common component of Early Recovery After Surgery (ERAS) and fast-track programmes (ERAS Society 2014), particularly in colonic surgery (Brandstrup et al. 2003). It is possible that trauma patients may also benefit from conservative fluid administration (Wang et al. 2014). These surgical patient groups are frequently managed in critical care areas, and there is no reason to think that the surgical benefits of fluid restriction would disappear when illness acuity is higher and ICU length of stay becomes longer.

7. Fluid Conservation may be Beneficial via Minimisation of Sodium and/or Chloride Exposure

If fluid conservation is demonstrated to be beneficial in more ICU patients, understanding the mechanism(s) of action will be required to maximise its efficacy and safety. It may be the dose of water that is most important, or the electrolyte composition of the fluid, or both. Unbuffered crystalloids that are relatively high in sodium and chloride cause more acid-base and metabolic derangement (Burdett et al. 2012), but we would be repeating mistakes of the past if we use this circumstantial evidence to make strong recommendations to change practice. Larger-scale, high quality clinical research can solve this puzzle too (Young et al. 2013).

8. There May Be Harms Associated with Conservative Fluid Strategies

Fluid restriction has been investigated most thoroughly in major abdominal surgical patients; intensive care medicine can learn from this. It is important to note, for example, that harm has been associated with fluid restriction in some surgical trials (Vermeulen et al. 2009). It is possible that harm may be avoided by tailoring fluid conservation to individual patients, an approach that is especially feasible during general anaesthesia (Pearse et al. 2014). In ICU patients, we must continue to insist that longer-term, patient-centred outcomes are included in trial design. In the FACTT study, an inconclusive but concerning association was observed between fluid conservation and decreased long-term neuropsychological function (Mikkelsen et al. 2012).

9. There is Probably a Secular Trend Toward Fluid Conservation Happening Already

In the study of early goal-directed therapy by Dr Rivers and coworkers (Rivers et al. 2001) the intervention group received around 5 litres of fluid in the first 6 hours of resuscitation (44.3% mortality at day 60). Around ten years later, the intervention group in the ProCESS study (ProCESS Investigators et al. 2014) received almost half this amount (21% mortality at day 60). This is only an association, but in the ARISE study (The ARISE Investigators and the ANZICS Clinical Trials Group 2014) even less fluid was administered in the first 6 hours (18.6% mortality at day 90). Anecdotal reports of international variation in fluid volume practice, as well as a trend to give less fluid to patients may soon be able to be confirmed (The George Institute for Global Health 2014).

ICU outcome does vary internationally, and may be improving over time for a variety of reasons (Bellomo et al. 2007; Prin and Wunsch 2012; Kaukonen et al. 2014). The hypothesis that fluid exposure may be responsible for a small part of this is an exciting and worthwhile area for intensive care medicine to investigate.

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ANTIBIOTIC MANAGEMENT IN THE ICU

Antimicrobial management in the intensive care unit (ICU) represents an ongoing challenge for critical care clinicians. The goal of this review is to focus on strategies aimed at optimising antimicrobial use within intensive care units.

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Antimicrobial management in the intensive care unit (ICU) represents an ongoing challenge for critical care clinicians. In the ICU setting broad-spectrum antibiotic consumption is often unavoidably high, and antimicrobial resistance rates are increasing in many parts of the world (Brusselaers et al. 2011). Early and appropriate antimicrobial administration is paramount in critically ill patients with suspected or confirmed infection and sepsis (Kumar et al. 2006). However, in hospitals with high rates of multi-drug-resistant pathogens, appropriate antimicrobial choices are limited to few options like carbapenems, colistin and tigecycline. Moreover, critically ill patients present profound pathophysiological changes, altering the pharmacokinetics of the administered antimicrobials, and failure to achieve target serum concentrations is not uncommon (Lipman and Boots 2009; Roberts and Lipman 2009). Lastly, apart from procalcitonin-based algorithms, other validated diagnostic and prognostic biomarkers that could assist in determining antimicrobial treatment duration and guide de-escalation strategies are lacking. The problem of reduced antibiotic development in combination with growing antimicrobial resistance calls for better use of currently available antibiotics. The goal of this review is to focus on strategies aimed at optimising antimicrobial use within intensive care units.

General Principles of Antibiotic Use in the ICU

1. Timing

When clinically indicated, antibiotics should be administered as soon as possible. A retrospective analysis of the Surviving Sepsis Campaign database, which included 17,990 patients with sepsis and septic shock from 160 ICUs in Europe, South America and the United States, confirmed the association between mortality and timing of antibiotic administration. The study results showed that in-hospital mortality risk increased linearly for each hour delay before the administration of the first antimicrobial dose (Ferrer et al. 2014). Guidelines recommend that the first antimicrobial dose is administered within 1 hour after the onset of hypotension in sepsis (Kumar et al. 2006; Dellinger et al. 2013), and within 4 hours of arrival to the hospital in community-acquired pneumonia (Blot et al. 2007).

2. Appropriate Antimicrobial Selection

For serious infections it is appropriate to start with **broad spectrum antibiotics** in order to ensure adequate coverage for possible resistant pathogens, with de-escalation of antimicrobials targeted to the causative agents once cultures and susceptibility data are available (Leone et al. 2014). The choice of antibiotics used should account for the identity and susceptibility pattern of the bacteria commonly isolated in that unit, as there is considerable variability in the spectrum of potential pathogens and the susceptibility patterns between different ICUs, even within the same institution. Inadequate initial antibiotic therapy is associated with elevated mortality, which in the case of sepsis has been shown to be 8 times higher than the risk in those who receive adequate coverage (Garnacho-Montero et al. 2003).

3. Combination Therapy

The use of **combination therapy**, including two antimicrobial agents from different classes, in order to achieve synergistic or additive effects has been a controversial topic for years. Most studies evaluating the benefit of combination therapy have not shown a mortality benefit, with the only exception being *Pseudomonas* bacteremia and carbapenemase-producing *Klebsiella pneumonia* bacteremia (Hilf et al. 1989; Paul et al. 2004; Leibovici et al. 1997; Safdar et al. 2004; Daikos et al. 2014). However, in critically ill patients combination therapy may be appropriate for empiric treatment, especially in cases where infections due to resistant organisms are suspected. In such cases, combination therapy increases the chance that the empiric antimicrobial coverage is adequate. Patient **risk factors** for colonisation or infection with multi-drug resistant pathogens should be taken into account, including recent antibiotic use and hospitalisation, prolonged hospital stay, dialysis and the presence of invasive devices (Kollef 2001).

4. Dosing

a. Loading Dose

Deciding on the **first dose of antibiotic** in a septic patient is probably equally important as timing. Loading doses are frequently needed in order to ensure therapeutic concentrations, as in the setting of increased volume of distribution (Vd) standard doses may result in suboptimal drug exposure. Higher initial doses should therefore be considered, particularly in the case of hydrophilic antimicrobials such as aminoglycosides, vancomycin, colistin, glycopeptides and add hyphen between beta-lactams (Udy et al. 2013).

b. Individualised Approach

The **dosing strategy** for antibiotics should take into account the mode of action of the drug and individual patient characteristics that influence pharmacodynamics and pharmacokinetic factors, in order to maximise bacterial killing, prevent the development of antimicrobial resistance, and avoid concentration-related adverse drug reactions.

i. Dosing Intervals

Evaluation of the antibiotic kill characteristics in experimental models suggests different **dosing intervals** for different classes of antibiotics.

1. For concentration-dependent agents (such as aminoglycosides, colistin, quinolones, vancomycin) the antimicrobial effect is maximal when the free drug peak concentration in a dosing interval exceeds the minimum inhibitory concentration (MIC) by 8-10 times (Cmax/MIC>8-10). This has been translated into single daily (or extended interval) dosing for aminoglycosides (Buijk et al. 2002; Hatala et al. 1996; Mavros et al. 2011; Barza et al. 1996).
2. For time-dependent agents (such as beta-lactams) the killing effect is almost entirely related to the time for which levels in tissue and plasma exceed the MIC of the offending pathogen (fT>MIC). Penicillin and monobactams are reported to require at least 50-60% fT>MIC, cephalosporins need a 60-70% fT>MIC, whereas carbapenems require a 40% fT>MIC (Craig 1998). These antibiotics lack a post-antibiotic effect, and, once the levels fall below the MIC, bacterial growth immediately resumes, leading to treatment failure and promotion of bacterial resistance. Modifying antibiotic delivery in order to improve the probability of obtaining fT>MIC targets has been shown to decrease mortality. Hence, dosing regimens for beta-lactams are being re-evaluated, and, at least for critically ill patients with resistant pathogens, extended or continuous dosing is recommended (Dulhunty et al. 2013; Falagas et al. 2013; Roberts et al. 2014b; Goncalves-Pereira and Povoa 2011; Seyler et al. 2011).

For concentration-dependent with time dependence agents (such as quinolones, daptomycin, glycopeptides, tigecycline, linezolid), the antimicrobial effect is defined by the area under the curve (AUC) of free drug over a 24 hour period over the MIC. For example, contemporary vancomycin dosing regimens target an AUC/MIC≥ 400 for serious methicillin resistant Staphylococcus infections (Liu et al. 2011).

ii. Pharmacokinetic Profile

Current antibiotic dosing recommendations are based on patient populations that were not critically ill. However, critical illness is characterised by multiple organ dysfunctions, inciting pathophysiological changes that may alter significantly the antibiotic pharmacokinetic profile (Blot et al. 2014). Without dose adjustments, suboptimal dosing may lead to therapeutic failure and increased mortality. Therefore, in the context of guidelines, individual patient characteristics should be considered:

1. Increased Volume of Distribution (Vd)

The Vd is a proportionality constant that relates the amount of drug in the body to the observed concentration in the plasma. The Vd in critically ill patients is commonly altered as a result of the pathophysiology of sepsis and severe illness, hypoalbuminaemia and reduced protein binding, frequently performed interventions such as cardiopulmonary bypass and mechanical ventilation and specific pathologies such as pancreatitis (Felton et al. 2014).

As an example, sepsis and septic shock are characterised by increased volume of distribution due to vasodilation, increased capillary permeability leading to capillary leak and fluid shifts to the interstitium. Aggressive intravenous fluid resuscitation leads to further increase in the volume of total body water and Vd (Hosein et al. 2011).

The clinical importance of increased Vd is particularly important for hydrophilic antimicrobials, such as beta-lactams, aminoglycosides, vancomycin and colistin that have a low Vd. If loading doses are not increased, sub-therapeutic antimicrobial levels will lead to therapeutic failure. On the other hand, no major influence is expected for lipophilic antimicrobials such as quinolones as their Vd is high (Roberts and Lipman 2009).

> **"…reduced antibiotic development in combination with growing antimicrobial resistance calls for better use of currently available antibiotics"**

2. Hypoalbuminaemia

Hypoalbuminaemia, defined as albumin < 2.5 mg/dl, results in increased levels of unbound drug. The unbound drug, which is the pharmacodynamically active form, is available for distribution and elimination resulting in increased Vd and augmented clearance respectively, leading to failure to maintain high plasma concentrations (Ulldemolins et al. 2011). The effect of hypoalbuminaemia in the PK/PD is important for drugs with increased protein binding such as daptomycin, ceftriaxone and ertapenem, as their volume of distribution in the view of hypoalbuminaemia may increase up to 100% (Roberts et al. 2014a).

3. Clearance

The clearance of a drug is defined as the volume of plasma cleared by the drug per unit time. Critical illness and sepsis frequently involve multiple organ dysfunction, including acute kidney injury leading to decreased clearance of antimicrobials, accumulation and toxicity. The impact of acute kidney injury (AKI) on the antimicrobial concentrations depends on the extent of renal function compromise. Dose reductions for renally cleared antimicrobials are recommended; however, underdosing may be a significant risk as other pathophysiologic parameters, such as the increased Vd that frequently is combined with AKI in cases of sepsis, major surgery and extensive burns often compen-

sate for the reduced clearance, particularly in the first 48 hours of treatment. Furthermore, alternative elimination pathways may compensate for the decreased renal clearance (Blot et al. 2014).

On the other hand, renal clearance of antimicrobials, may be augmented by hyperdynamic conditions including sepsis, volume overload, high cardiac output and use of positive inotropes leading to suboptimal antimicrobial concentrations. In such cases clearance of antimicrobials may increase up to three-fold (Udy et al. 2011). Additional pathophysiologic parameters such as hypoalbuminaemia may further increase clearance, as stated before.

Renal replacement therapy (RRT) is commonly applied in patients with AKI, but marked unpredictability in antimicrobial clearance has been described. In general hydrophilic antimicrobials, with low protein binding and increased renal clearance, are more efficiently removed. High interpatient variability limits the applicability of general guidelines, and calls for locally established dosing regimens during RRT, based on the type of RRT performed (Blot et al. 2014).

Hepatic dysfunction can affect the elimination of antimicrobials, which are metabolised by the liver or undergo transintestinal clearance. In general livers' metabolic capacity have to be reduced by >90% before drug metabolism is significantly affected (Park 1996).

iii. Therapeutic Drug Monitoring

It is evident that predicting antimicrobial concentrations in the critically ill patient is nearly impossible, which calls for the application of therapeutic drug monitoring (TDM) in daily practice in order to optimise dosing. TDM relies on direct measurement of serum antibiotic concentrations, which are then interpreted in the context of therapeutic ranges. TDM is routinely used in the administration of antimicrobials, characterised by a narrow therapeutic window and substantial risk of toxicity, such as aminoglycosides and glycopeptides. However, it has been supported that TDM is likely to be beneficial for other agents such as beta-lactams, quinolones and linezolid (Roberts et al. 2010; Scaglione et al. 2009).

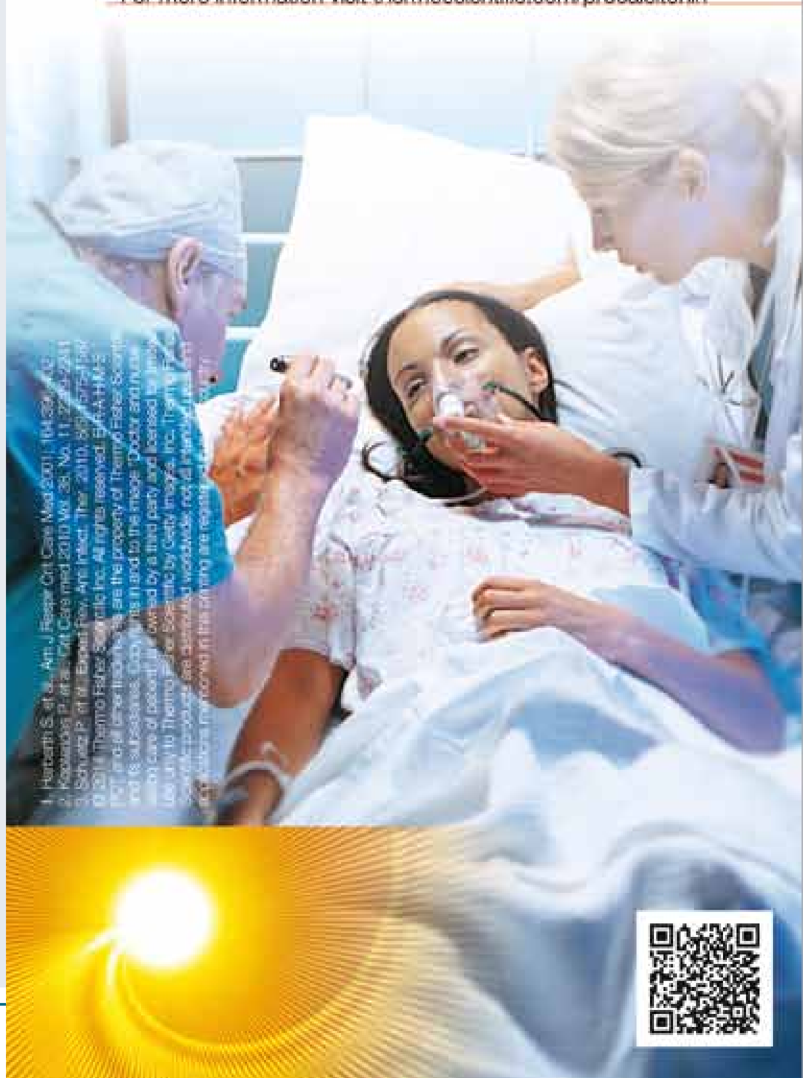
5. Source Control

Importantly, together with antimicrobials adequate source control encompassing abscess drainage, wound debridement, surgical excision of necrotic tissue and device removal is paramount for the successful control of an infection (Marshall and al Naqbi 2009).

6. Duration

Administration of early empiric broad-spectrum antimicrobial coverage for all epidemiologically relevant and possibly resistant pathogens implies daily reassessment of treatment, and transition to a narrower-spectrum regimen once culture results and susceptibilities are available. Provided that the infection source is controlled, short antibiotic courses (< 7 days) are sufficient for most infections in the critically ill patient, with a few exceptions (Lipman and Boots 2009). More specifically, shorter (3-8 days) rather than longer (10-21 days) antimicrobial courses have been shown to be equally efficacious in the treatment of ventilator-associated pneumonia (Singh et al. 2000; Ibrahim et al. 2001).

Biomarker-based algorithms are often used to guide antibiotic de-escalation strategies (Pierrakos and Vincent 2010). Procalcitonin (PCT) is the most widely studied biomarker in antibiotic initiation and de-escalation algorithms in the critical care setting. PCT has some diagnostic and prognostic utility in the management of



critically ill patients, since it is elevated in patients with severe sepsis, septic shock and bacteraemia, and its decline is associated with better prognosis (Reinhart and Meisner 2011). PCT-based algorithms are associated with shorter duration of antibiotic treatment without compromising ICU outcomes (Bouadma et al. 2010; Schuetz et al. 2012; Povoa and Salluh 2012).

Surveillance and Stewardship

Surveillance of nosocomial infections, antibiotic use and antimicrobial resistance rates in the ICU is an essential tool for infection control measures and antimicrobial stewardship strategies (Bergmans et al. 1997; De Bus et al. 2014). Knowledge of the prevalence of infections and the indication-based antibiotic prescribing rates in a certain unit can help guide preventive interventions that aim to reduce both antimicrobial use and resistance. Researchers from Belgium compared two antibiotic treatment algorithms with the actual empiric therapy for hospital-acquired pneumonia regarding the proposed regimens' spectrum of activity and appropriateness of treatment. The study, which was performed in a 36-bed tertiary centre ICU with a moderate prevalence of MDR pathogens, involved one strategy based on overall bacterial resistance rates (local ecology-based algorithm [LEBA]) and another based on individual patient respiratory surveillance cultures (surveillance culture-based algorithms [SCBA]). While both strategies conferred similar rates of appropriate antimicrobial coverage, SCBA was associated with the use of less overall and broad-spectrum antibiotic prescribing (De Bus et al. 2014).

Conclusion

Prompt and appropriate management of infections in critically ill patients is vital in order to limit mortality and morbidity. Antibiotic dosing requires special considerations because of altered drug pharmacokinetics in these patients, and therapeutic monitoring is often needed in order to achieve maximal efficacy, decrease the risk of antimicrobial resistance and minimise toxicity. ■

For full references, please email **editorial@icu-management.org**, visit **www.icu-management.org** or use the **article QR code**.

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EVIDENCE-BASED CARE IN THE INTENSIVE CARE UNIT

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By taking the Hippocratic Oath, physicians commit to practising their art according to the current best scientific knowledge. For that purpose, all physicians need full access to the best knowledge (see Figure 1). The necessary steps include continuous innovation in healthcare, followed by appropriate translation of innovative care into routine practice and eventually reassessment of remaining gaps in knowledge to foster new innovations. Ideally this chain makes the wheel of progress by which people live longer in good health. In practice, a substantial number of routinely used health interventions have never been tested in a rigorous scientific manner. Moreover, interventions used routinely for decades eventually demonstrated harm to people.

It is a complex task to define what the current best scientific knowledge is. First, a clear-cut and relevant clinical question needs to be formulated. The most common clinical scenarios are how best to diagnose a specific disease or condition, and how to treat the patient. Then, these clinical scenarios should be translated into a research question that should be meaningful for both physicians and researchers. Typically, in the diagnostic domain, questions are formulated as: "In patients with disease or condition X, is diagnostic test A better than diagnostic test B? For therapeutic interventions, research questions are usually formulated as: "In patients with disease or condition X, is intervention A superior to intervention B? The systematic approach to formulate research questions is usually referred to as the PICOM approach. Briefly, this approach requires defining a precise population (P), explicit experimental intervention (I) and comparator (C), patient-centered outcomes (O) and study designs that are relevant to address the question (M).

Generating evidence in medicine, and more specifically in the intensive care unit, always started with clinical observations. Obviously, research questions arise mainly from clinical observations. In addition, observational studies are part of the process of addressing relevant research questions not only in the diagnostic domain, but also for therapeutic interventions. For example, at the time of the polio pandemics, observations of patients dying from respiratory paralysis raised the issue of compensating lung function. The introduction of artificial ventilation, mainly by iron lungs, prevented death in almost all patients. In this case, clinical observations allowed the generation of evidence-based care for these patients without the need for more convincing data. Owing to an international effort - STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) – www.strobe-statement.org – the conduct of cohort, case-control and cross-sectional studies may now follow high quality standards minimising biases. More interestingly, recent years have been characterised by the emergence of 'Big Data' in the field of critical care medicine. The concept of big data followed the rapid development of health electronic records with automatic and systematic storage of almost all data for all patients. Thus, the way to perform observational studies may be revolutionised. Indeed, there are no longer concerns about sampling, sample size, selection bias and generalisability, as all data from all patients are used. However, there are still several issues that need to be addressed before evidence generated via big data can be translated into routine practice. First, tools to standardise collection of data and in particular qualitative information are still lacking. Second, traditional statistics in medicine are based on the concept of sampling a population according to the probability of rejecting or not the null hypothesis. In the big data era, data from the whole population are used. Subsequently, sample size and power are no longer relevant issues. Obviously, the use of massive data also likely decreases the clinical relevance of type I errors. Finally, defining a null hypothesis might be also meaningless. Even more, it might be a limiting factor to innovation. Indeed, getting access to all information from all patients may disclose characteristics of a disease or a condition, or of an intervention, that would never be seen in selected samples of a population. Thus, the use of big data may result in new concepts and new ideas beyond traditional views in the field of critical care medicine.

Information from observational studies and information derived from big data may still not be sufficient to generate firm evidence that an intervention should be used in routine practice. While they play a major role in correctly defining the population of interest, the experimental intervention and best comparator, and outcomes, randomised controlled trials remain so far the gold standard for establishing evidence-based treatments. Unsurprisingly, thousands of randomised trials have been conducted in the field of critical care medicine, and their number is continuously growing as well as the number of related systematic reviews. Yet the proportion of evidence-based interventions in the intensive care unit remains worryingly low. Moreover, the way experimental interventions are tested through randomised controlled trials is far from being efficient. Indeed, for each specific research question, almost everything has to be restarted from zero, i.e. building a new group of investigators and methodologists, finding new funding, designing new case report forms and new data management processes, recruiting new centres, new patient populations, contracting new insurance, and so on. Then, usually it may take from 5 to 10 years to get a research question answered. Of note, if the trial appeared to be positive a confirmatory trial would likely be requested

Hydration in Enterally Fed Patients

Combined results of surveys of practice and knowledge across Western European countries

Cooper SC[1], Holdoway A[2], Lecko C[3], Benati G[4], Plantefeve G[5], Preiser J-C[6], Serlie MJ[7], Schneider S[8]. A European expert working group. Dudley Group NHS Foundation Trust, UK[1]; Independent dietitian, UK[2]; NHS England, UK[3]; Ospedale Morgagni Peirantoni, Italy[4]; Victor Dupouy Hospital, Argenteuil, France[5]; Erasme University Hospital, Belgium[6]; Academic Medical Centre Amsterdam, Netherlands[7]; Nice University Hospital, France[8].

Rationale

- Enteral tube feeding (ETF) is not uncommon among acute and community patients. (2.6 million NG placed across Europe, 2010)[1]
- Patho-physiological states may vary considerably among in-patients, altering water homeostasis.
- Water content of commercially available feeds varies between 76-92%.
- To understand:
  - how the delivery of feed and water via an enteral tube may vary (e.g. continuous *vs.* bolus; with or without pump)
  - what if any European guidelines are available for hydration in the enterally fed patient
  - about the variations in practice and any guidelines across Western Europe with respect to hydration in enterally fed patients.
- Both over and under-hydration may lead to deleterious outcomes, increasing morbidity and mortality.

Methods

- On-line national surveys were carried out in the United Kingdom, Belgium, The Netherlands and a further survey in French speaking Belgium, Switzerland and France.

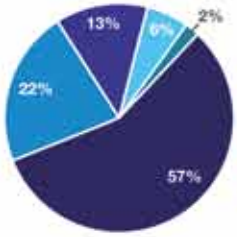
  The surveys were conducted through the following professional associations during 2012/2013 in order to gather the opinions of health professionals involved in clinical nutrition:
  - BAPEN (British Association for Parenteral & Enteral Nutrition), PENG (Parenteral & Enteral Nutrition Group of the British Dietetic Association), SFNEP (French Society for Clinical Nutrition & Metabolism), SBNC (Belgian Society of Clinical Nutrition), VVKVM (Flemish Society of Clinical Nutrition), SIZ Nursing (French Association of IC Nurses), NVO (Dutch Association of Nutrition), V & VN (Dutch Nurses Association) sub-department.
- The survey was designed to find out about their knowledge; of guidelines, methods for evaluating hydration status, perceived barriers to hydration, consequences of dehydration and identification of at risk patients.
- The results from the four surveys over the five Western European countries were then combined.

Results

- 835 respondents were included in the survey from the four surveys covering the five countries.
- The response rate was approximately one-third.
- 62% of respondents had greater than 10 years experience in the field of nutrition.
- 36% of respondents were active members of a nutrition team (11% skipped the question).

Hydration Guidelines:

- 32% of respondents were aware of specific hydration guidelines for enterally tube fed patients, 5% were developing guidelines, 59% reported to have no such guidelines and 10% said they 'don't know'.
- When asked about what type of guidelines they used, 72% failed to answer the question. Of the 28% who did answer this question (235/835):
  - the majority (57%) stated that they used local hydration guidelines
  - 23% reported to use patient specific guidelines
  - 14% reported to use national guidelines
  - 7% said they used other enterally fed patient guidelines.



Profession of respondents
- Dietitians
- Nurses
- Doctors
- Pharmacists
- Other

Years of nutrition experience of respondents
- 0-2 years
- 3-5 years
- 5-10 years
- >10 years

Responsible group for implementing hydration guidelines in ETF
- Nutrition team
- Dietitian
- Nurses
- Audit dept
- Don't know
- Other

Method used to administer hydration
- Bolus with pump
- Bolus without pump
- Continuous without pump
- Continuous with pump
- As flushes before/ after meds
- Other

Barriers to providing hydration:

1st Available nursing time
2nd Equipment availability
3rd Knowledge
4th Equipment difficult to use
5th Timing around feed/ medication

Preferred hydration assessment method:

1st Biochemical markers (24%)
2nd Clinical examination (21%)
3rd Fluid balance chart (20%)
4th Urine output/colour (20%)
5th Food chart (14%)

Concerning dehydration side-effect:

1st Cardiovascular issues
2nd Confusion
3rd Poor wound healing
4th Urinary tract infections
5th Constipation

Most at risk patient group:

1st Elderly
2nd Stroke
3rd Dysphagic
4th Cancer
5th Neurological conditions (non-stroke)

Summary

- An experienced cohort of respondents across Western Europe revealed a lack of national guidelines regarding hydration in the enterally tube fed patient, a diverse group with differing requirements.
- There was wide variation in the implementation of hydration guidelines, assessment of hydration status and the identification of who was responsible for providing the hydration prescription.
- Nutrition professionals prioritised their concerns regarding the consequences of dehydration and the patient groups at most risk.
- Further evaluation of the scale of the issue of hydration amongst enterally tube fed patients and formation of European guidance will be looked by the working group.

References: 1. Millennium report 2010.

Disclosure of interest: *This work has been committed to the working group and to all co-authors by Covidien.*

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before adopting the evidence. Running a second trial will add more years before people may consider that the research question has been fully addressed. Therefore, a growing number of trialists are considering moving away from this conventional view of conducting randomised studies. Some of them are suggesting, whenever relevant, doing adaptive clinical trials that may allow saving time and money. For example, in a single adaptive trial, several interventions or several doses of an intervention may be tested simultaneously for the same disease or condition. In such trial design, it is the accumulation of information during the conduct of the trial that may be used to adapt tested interventions or, sometimes, the targeted population. Others are considering building large population-based cohorts to be followed up for decades within a prospectively designed framework. Then, within these cohorts, interventions may be easily tested in random samples along the way of the cohort follow-up. This concept may also be of interest in the critical care field. For example, it may have the advantage of getting the full trajectory of the critically ill including pre-illness and long term post-illness follow-up. Such 'within population-based cohort' randomised trials use the cohort infrastructure, and allow investigation of different interventions in parallel, thus saving time and money. Finally, within the population-based cohort, patients may be always benefiting from best evidence-based care.

> **"The proportion of evidence-based interventions in the intensive care unit remains worryingly low"**

Undoubtedly, we need to improve the efficiency of methods to generate evidence-based care for the critically ill. Big data and innovative designs for clinical trials are likely to become more and more diffused among critical care researchers, and ICU physicians are likely to be adopting more and more the conclusions generated from these new tools. In recent years, it has become obvious that medical education still poorly prepares physicians for evidence-based practice. There is a need to teach medical students early how to accurately formulate clinical and research questions, how to accurately search and summarise the available literature, and how to generate evidence-based practice. ■

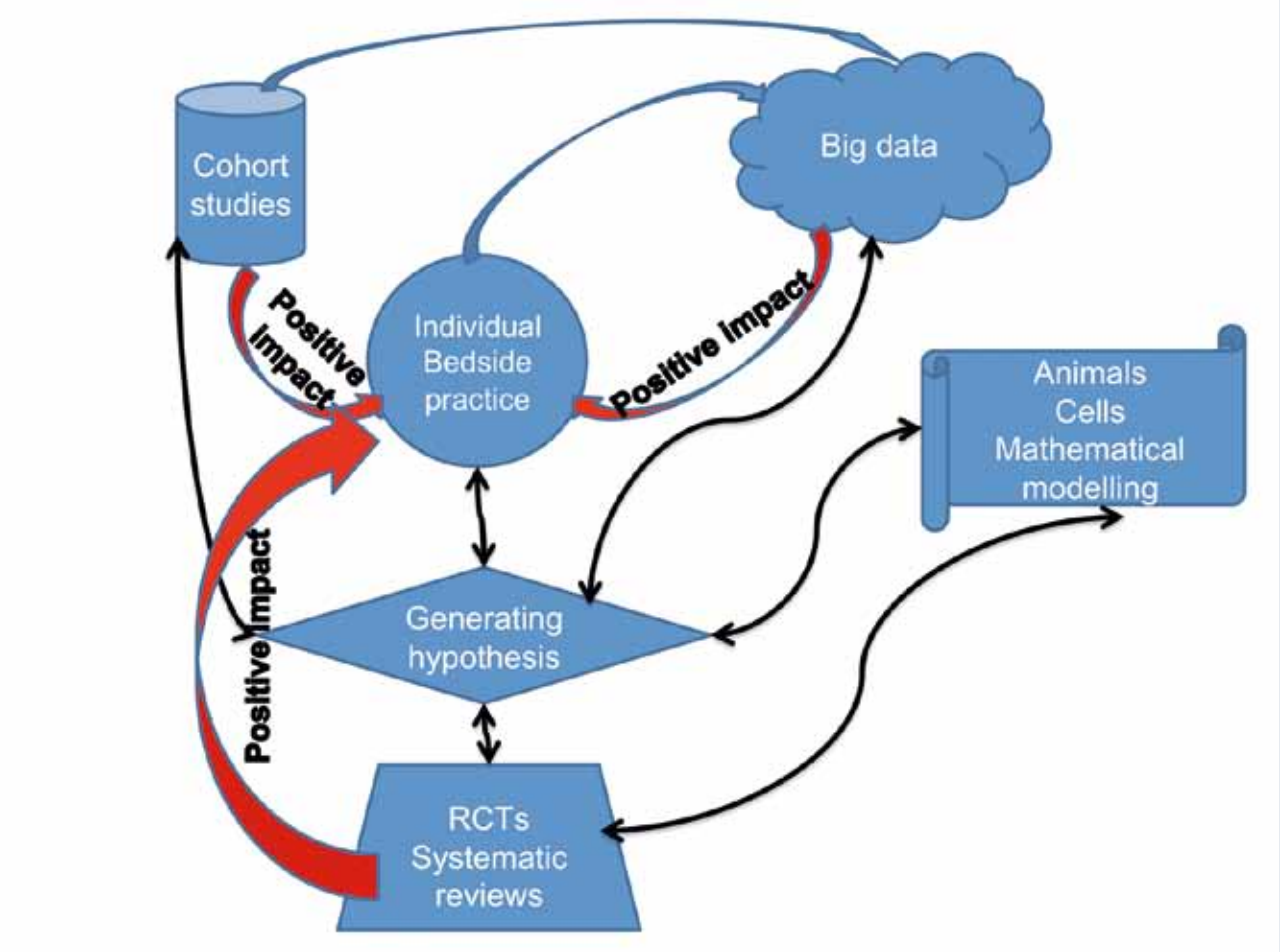

Figure 1

PREVENTION OF VENOUS THROMBOEMBOLISM IN CRITICAL CARE

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Venous thromboembolism (VTE) is commonly encountered and difficult to manage in critical care. Furthermore, pulmonary embolism (PE) is seen as a preventable cause of death in the hospital population. It is beholden to us to ensure that all steps are taken to assess the risk to patients, and once identified, ensure appropriate prophylaxis is put in place.

Why is it Important to Prevent VTE in Critical Care?

Venous thromboembolism (VTE) carries significant mortality in the critical care population, and therefore needs to be addressed both at a local hospital and at national level. The All-Party Parliamentary Thrombosis Group at the House of Commons in the UK stated: "In general, people are well aware of the risk of a form of VTE called deep vein thrombosis (DVT) which is regularly associated with air travel, however, the risk of contracting VTE during or following a hospital stay is far greater" (Morrison, 2013).

VTE is common in the ICU and potentially life threatening

Intensive care unit (ICU) patients are at an even higher risk for both deep vein thrombosis (DVT) and pulmonary embolism (PE), often due to their clinical presentation and factors associated with an ICU admission e.g. prolonged immobility, sedation and neuromuscular blockade to facilitate ventilation (Hunt 2014). For a critical care patient, developing a large pulmonary embolus occluding the pulmonary arterial bed may cause potentially irreversible right ventricular failure, an acute life-threatening condition. In a large USA study the mortality from pulmonary emboli in acute hospitalised patients was estimated to be 8.2% in 2005 (Park et al. 2009).

VTE is challenging to recognise and manage in the critical care population

Pulmonary emboli are more difficult to diagnose in this patient population, and require complex treatment. A high index of suspicion is required for early detection. Clinical and autopsy series show over 50% of cases are not clinically suspected, and hence not managed (Tapson 2008). Furthermore, patients with known DVT and no symptoms of PE have been diagnosed with PE on ventilation-perfusion scans (Berlot et al. 2011).

Management of critical care patients with large pulmonary emboli causing circulatory collapse requires thrombolysis; however, this may be contra-indicated. A multi-discipline approach, exemplified by the Swedish model, is needed to determine the optimal management for a given critical care patient and address challenges of transfer to a tertiary centre with appropriate cardiothoracic services and ECMO (extracorporeal membrane oxygenation) facilities if required (Svennerholm 2014).

What are the Current VTE Prevention Guidelines?

The American College of Chest Physicians (ACCP) has outlined the standard in the 9th Edition of antithrombotic guidelines published in Chest 2012 (Guyatt et al. 2012). They strongly recommend (Grade 1a evidence) anticoagulant thromboprophylaxis with unfractionated or low molecular weight heparin in high thrombosis risk patients. For high bleeding risk patients the ACCP has recommended against the use of anticoagulant drugs (Grade 1b) and optimal use of mechanical thromboprophylaxis. Despite the lack of strong clinical data in critically ill patients, graduated compression stockings (GCS) or intermittent pneumatic compression (IPCs) may be preferable to *no prophylaxis* in patients at appreciable risk for VTE who are also at high risk for bleeding (Grade 2c).

What is the incidence of VTE?

VTE is the most common preventable cause of death in hospitals. The overall incidence of VTE is 1 in 1000 cases causing significant morbidity and mortality (Park et al. 2009). The VITAE study estimated that each year in Europe almost 300,000 cases of pulmonary embolism occur (Cohen et al. 2007). However, it is widely recognised that we underestimate the burden of VTE, and for every case where PE is documented as cause of death there may well be several cases that remain undiagnosed (Berlot et al. 2011).

How Can we Prevent VTE?

National Health Initiatives

Venous Thromboembolism (VTE) Risk Assessment in England, produced by NHS England, is a new programme designed to increase hospital admission screening of patients to identity VTE risk. Questions are targeted around mobility, thrombosis and bleeding risk. Of the 3.5 million adult patients admitted to NHS-funded acute care between January and March 2014, 96% of these received a VTE risk assessment on admission (VTE Prevention England 2014)

National standards and guidelines for practice in the UK have been outlined by the NHS Modernisation Agency in the *10 High Impact Changes for Service Improvement and Delivery* (2004) and the National Institute for Health and Care Excellence (NICE) in *Venous thromboembolism* (2010). The NHS Modernisation Agency suggest that adopting VTE prophylaxis as part of ventilator care bundles in critical care could not only lower VTE incidence, but potentially reduce ICU length of stay and increase hospital bed capacity (NHS Modernisation Agency 2004)

A prospective quality improvement study at Kings College Hospital, London examined the impact of mandatory documented VTE risk assessment on hospital-acquired thrombosis (HAT) events (Roberts et al. 2012). The authors found a significant reduction in hospital-acquired thrombosis events after implementation.

However, even with greater focus on risk assessment the proportion of HAT attributable to inadequate thromboprophylaxis remained at 22.4%. This conclusion was also supported by the ENDORSE study (Kakkar et al. 2010), a multinational cross-sectional survey designed to assess the prevalence of VTE risk in the acute hospital care setting, and to determine the proportion of at-risk patients who receive effective prophylaxis. In the UK, of the patients assessed as being at risk of VTE, only approximately 60% are receiving recommended levels of prophylaxis. Germany was the only country to exceed 80% of patients receiving recommended levels of prophylaxis. Poor compliance with the ACCP guidelines is likely due to lack of education surrounding the issue, but also for many critically ill patients anticoagulation is contraindicated, and therefore alternative thromboprophylaxis measures need to be considered.

Anti-Coagulation Therapy

Numerous factors surrounding anticoagulation in critical care patients are debated including type, duration and dose of drug. The current evidence suggests low molecular weight heparin (LMWH) is the most cost-effective thromboprophylaxis in the acutely ill patient based on 30 day DVT, PE and mortality rates in a population of over 10,000 patients (McGarry et al. 2004; Cook et al. 2011) However, it is well understood that the bioavailability of LMWH is difficult to predict in critically unwell patients, and therefore unfractionated heparin with regular monitoring may allow greater control over the patient's coagulation. Duration of anticoagulation should be planned as part of the ongoing VTE risk assessment. It should be noted VTE up to 90 days post hospital discharge is termed as a hospital-acquired thrombosis; therefore a VTE plan on discharge should be clearly documented (National Institute for Health and Care Excellence 2010). The dosing of anticoagulation is challenging in this population, and should be ideal body weight based for LMWH and monitored carefully with regular activated partial thromboplastin time (APTT) testing for unfractionated heparin.

However, anticoagulation is not always appropriate in the critical care population; approximately 10% of the ENDORSE trial patients were contraindicated to anticoagulation (Kakkar et al. 2010). Absolute contraindications include: active haemorrhage, acquired bleeding disorders, concurrent use of anticoagulants e.g. warfarin, lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours or within previous 4 hours, acute cerebrovascular accident, thrombocytopenia (platelets < 75 x 109/l), uncontrolled systolic hypertension (230/120 mmHg or higher) and untreated inherited bleeding disorders (National Institute for Health and Care Excellence 2010). Furthermore, some critical care patients who are anti-coagulated appropriately still develop VTE (Berlot et al. 2011), perhaps due to a hyper-coagulant state or because they are refractory to anticoagulant therapy. Hence, we should aim to modify our VTE prevention and not only rely upon pharmacological prophlyaxis.

Mechanical Prophylaxis and IVC Filters

What are the options for high- risk patients with an absolute contraindication to anticoagulation or who are awaiting surgical procedures for which we have temporarily stopped anticoagulation? The ACCP suggests a role for mechanical prophylaxis, graduated compression stockings (GCS) and intermittent pneumatic compression (IPC) devices in this instance. Whilst there is only Grade 2C evidence, a non-harmful intervention that may prevent VTE in a high risk population is recommended by the the ACCP and National Institute for Health and Care Excellence (NICE) (Guyatt et al. 2012; National Institute for Health and Care Excellence 2010).).

Alternatives to pharmacological prophylaxis include traditional inferior vena cava (IVC) filters. However, difficulty inserting the filter in high-risk patients, safe retrieval of the device and short- or long-term traceability have limited their use. MHRA Regulating Medicines and Medical Devices issued an alert in 2012 concerning serious complications related to IVC filter retrieval, and strongly recommend planned retrieval of the device as soon as possible once clinically not required (MHRA Regulating Medicines and Medical Devices 2013).

More recently a triple lumen CVC catheter with an added IVC filter attached has been developed for the same cohort of patients. The catheter can be inserted through femoral access at the bedside. and placement confirmed on x-ray imaging with an uncomplicated retrieval (Angel 2014). However, as this is a novel device there is limited data on long term outcomes. Both IVC filters and Angel® catheters are only temporising measures until a more permanent method of thromboprophylaxis can be implemented.

Ventilator Care Bundles and Critical Care Rehabilitation

Ventilator care bundles, including graduated compression stockings or intermittent pneumatic compression devices, anticoagulant therapy, elevation of the head of the bed to reduce aspiration risk and effective sedation management all lead to enhanced patient safety, reduced hospital standardised mortality ratios and lowering the risk of VTE (NHS Modernisation Agency 2004).

When considering VTE prevention we need to look closely at whole body rehabilitation, including optimal and appropriate use of sedation, physical and occupational therapy in the earliest days of critical illness to aid better functional outcomes at hospital discharge and increased ventilator-free days (National Institute for Health and Care Excellence 2009; Schweickert et al. 2009).

The PROTECT study (PROTECT Investigators et al. 2011) highlighted that over one-third of PEs diagnosed in clinical practice occur in patients admitted to the ICU without PE or DVT, and that most pulmonary emboli happen during the initial days of hospitalisation, with peak incidence at day 6. Therefore we need to protect patients as early as possible to avoid the implications of VTE in the critical care population.

Conclusion

The impact of venous thromboembolism in the critically ill patient is a significant problem. Whilst there are several national health initiatives and standards outlined for the prevention and management of VTE the number of patients receiving adequate thromboprophylaxis is poor. Furthermore, the critical care population poses a difficult challenge to balance the risk of bleeding against thrombosis. New options are needed to decrease the risk of VTE when anticoagulation is contraindicated. Pulmonary embolism is more common than clinically recognized, and it happens early in the course of the hospitalisation. Incorporating VTE prophylaxis into ventilator care bundles, improving healthcare professional awareness of the issue and optimising critical care rehabilitation are all measures that will improve adequate thromboprophylaxis provision on an individual patient basis.

For full references, please email **editorial@icu-management.org**, visit **www.icu-management.org** or use the **article QR code**.

Key Messages

1. We need to *Identify* high risk patients early on during their hospital admission.
2. *Recognise* anticoagulant prophylaxis may not be suitable for all patients therefore consider other interventions to protect against VTE.
3. *Focus* on sustained education of healthcare professionals to increase adequate prophylaxis delivery.

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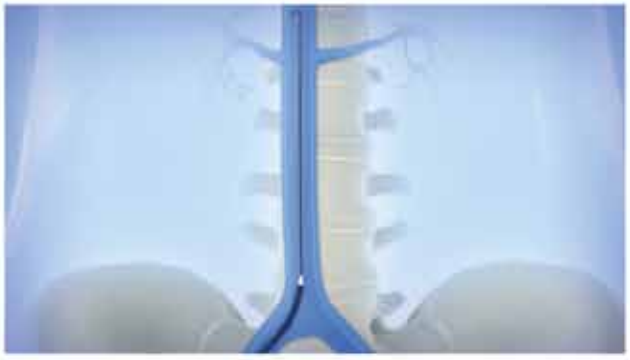

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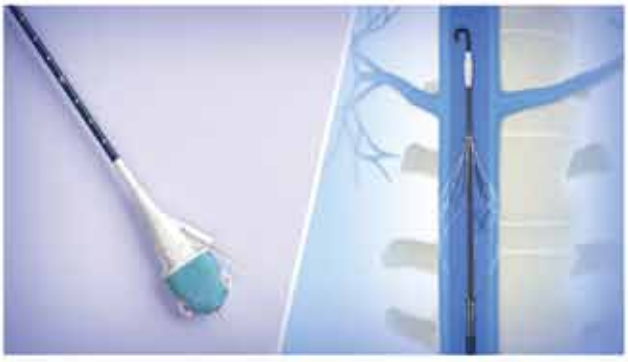

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A CRITICAL AGE

THE INFLUENCE OF FRAILTY MEASUREMENTS ON PROGNOSIS AND MANAGEMENT IN INTENSIVE CARE

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While prognosis of elderly patients in intensive care is often seen as poor, this is largely due to deficits that can be described with the vocabulary of frailty and its measures. Using the Clinical Frailty Scale as a tool to assess patients referred to intensive care might facilitate discussions about treatment aims, and identify patients who are likely to require enhanced support for re-enablement after critical illness.

The increase in the proportion of patients over the age of 65 by 50% in the coming decades has been dubbed the "silver tsunami". It poses an unprecedented challenge to critical care to deliver equitable care to appropriate patients. The decision on which patients are suitable for intensive care treatment is a continuing debate, and age in itself is not a reliable predictor for outcome in an individual. Frailty is a measure of a patient's physiological rather than chronological age, and is based on a detailed social and functional history. Assessments in ICU patients may improve prognostication, but feasibility of assessments is not known.

In this article we will summarise the current literature on frailty in the critically ill, and examine the feasibility of implementing a frailty score in the clinical practice of intensive care medicine.

Introducing a Frailty Score for the Critically Ill – Which One?

Frailty can be described as an accumulation of deficits, 'the frailty phenotype', characterised by decreased strength, low energy, weight loss, slowed movement and reduced physical activity (Fried et al. 2001). There is a range of assessment tools for frailty (de Vries et al. 2011), and this is illustrated in studies assessing the link between preoperative frailty and outcome from surgery (see Table 1). Some of these assessments are not possible in patients with critical illness, as they depend on assessment of a non-stressed patient, providing opportunity for demonstration of fitness (e.g. gait speed), physiological measurement (e.g. spirometry) and cognitive ability. Studies assessing frailty in the critically ill will therefore use frailty assessments that are by necessity based on an accurate history of the patient's premorbid state.

Study	Population	Methodology	Outcomes
Pol 2011	All patients Vascular	Prospective cohort; n=142 (ICU admissions, n=23)	GFI (15-item questionnaire) predicts post-op delirium
Sundermann 2011	Age ≥74 Cardiac surgery	Prospective; cohort; n=400	CAF (FP criteria, ADLs, body control, serum albumin, creatinine and BNP, spirometry) predicts 30-day mortality
Afilalo 2012	Age ≥70 Cardiac surgery	Prospective cohort; n=152	Gait speed superior to FP and MSSA in predicting in-hospital mortality or major morbidity
Green 2012	Age ≥60 Cardiac (TAVI)	Prospective cohort; n=159	Novel composite frailty score (grip strength, gait speed, ADLs, serum albumin) predicts 12-month mortality
Stotecky 2012	Age ≥70 Cardiac (TAVI)	Prospective cohort; n=100	MGA score (MMSE, MNA, ADLs) predicts 30-d and 12-month mortality
Robinson 2013	Age ≥65 Colo-rectal/ cardiac	Prospective cohort; n=201	Number of "frailty traits" (including "Up and go" time, ADLs, Charlson score, serum albumin, anaemia) predicts LOS, complications and readmissions

Table 1. Studies Evaluating Frailty Measures in Patients Undergoing Elective Surgery Prior to ICU Admission

The use of frailty to help predict outcome in the critically ill is still in its infancy, and it is not certain which frailty measurements are best suited to be used in the critically ill population. Over the last four years we have started to explore how descriptions of frailty could be used by clinicians at the bedside in the ICUs of two District General Hospitals in North Wales. Both units admit between 650 and 750 patients per year.

Firstly we explored the feasibility of using different frailty assessments. We reviewed 56 sets of notes from patients admitted to the ICU aged 70 and above, and assessed their frailty with six tools selected from the critical care and wider literature. These were the Clinical Frailty Scale (CFS) (Rockwood et al. 2005); Identification of Seniors at Risk tool (ISAR, McCusker et al. 1999); Barthel index (Wade and Collin 1988); Katz Index (Katz et al. 1970); the DUKE activity status index (Hltaky et al. 1989) and the Survey of Health, Ageing and Retirement in Europe (SHARE, Romero-Ortuno et al. 2010).

The mean age of patients was 80 (SD 4), and 33 of the patients were male. Four patients came from care homes, and 22 lived on their own. Evidence for functional or social history in medical records was scanty. The median CFS was 6 (=moderately frail, IQR 4-6), ISAR 3 (IQR 2-4), Barthel Index 75 (IQR 60-100) and Katz 6 (IQR 4-6). Based on note review only we were unable to complete DUKE index and SHARE for the majority of patients.

"Our preliminary work would suggest that age doesn't matter in critical illness, once frailty is assessed. So why should it not be routinely measured?"

Of the frailty scores tested, the CFS showed the most promise. A higher CFS, but not age over 80, was associated with higher mortality ($p<0.045$). A CFS of 6 or more was also associated with a hospital length of stay of 15 days or more ($p<0.02$), but not with longer ICU length of stay. Similar associations could not be established for any of the other tested measures.

We then assessed the reproducibility of CFS frailty assessment between observers. We introduced the CFS into routine clinical practice for a 2 month trial by adding assessment documentation to admission documentation, and admitting staff were asked to assess patients' frailty at a point two weeks prior to admission. Two medical students were blinded to results of initial assessments, and independently interviewed 30 patients and/or relatives in order to obtain CFS values for two weeks and one year prior to admission. Twenty (66.7%) patients had identical CFS scores, 6 patients (20%) had a difference of 1 and 4 (13.3%) had a difference in score >1. There was strong correlation between CFS taken by clinical staff and those taken by the investigators (Spearman's rho 0.64, $p<0.0001$) and between CFS two weeks prior and one year prior to admission (Spearman's rho 0.79, $p<0.0001$).

Studies to date assessing frailty in patients following ICU admission have used a variety of measures based on the frailty Phenotype (FP), and/or the Clinical Frailty Scale (see Table 1). The study by Le Maguet and colleagues is of particular interest as the FP and CFS appear to perform differently in predicting outcomes: prevalence of pre-critical illness frailty ranged from 23% (CFS) to 41% (modified FP), depending on which frailty measure had been utilised (Le Maguet et al. 2014). Patients identified as frail according to CFS were significantly more likely to be discharged to a location other than home, and to have increased ICU, hospital and 6-month mortality. With the exception of ICU mortality, patients identified as frail according to FP did not experience worse outcomes of statistical significance (Le Maguet et al. 2014).

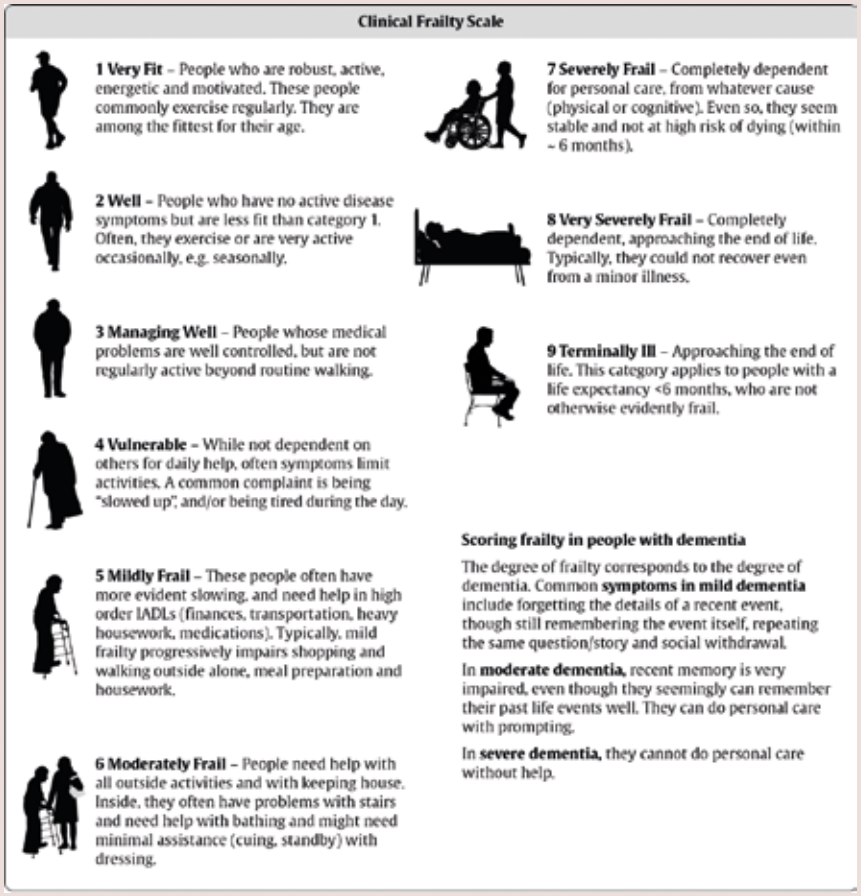

Figure 1. Clinical Frailty Scale
Source: Rockwood et al. (2005) Reproduced by kind permission.

Frailty as a Predictor of Outcome in the Critically Ill

Although the relationships between co-morbidity, functional limitation and outcome from critical illness have been explored over a number of years, the concept of frailty as applied to an ageing critically ill population is a relatively new one. Studies to date assessing frailty in patients following ICU admission have used a frailty score based on the frailty Phenotype (FP) and/or the Clinical Frailty Scale and are summarised in Table 2. These studies report outcomes from a population more generally representative of critically ill elderly patients than preoperative assessment studies summarised in Table 1, and increased frailty was associated with worse outcomes in all studies.

In the largest study of frailty and critical illness to date, Bagshaw used the CFS to assess 421 patients over the age of 50, and found the prevalence of frailty, as defined by a CFS > 4, to be 32.8%. Frail patients were older, were more likely to be female, and had more comorbidities and greater functional dependence than those who were not frail. In-hospital mortality was higher (32% v 16%) and remained higher at 1 year (48% v. 25%); major adverse events were more common (39% v 29%). Frail survivors were more likely to become functionally dependent (71% v 52%), have significantly lower quality of life and were more often readmitted to hospital (56% v 39%) (Bagshaw et al. 2014).

In a separate small study, insight into the dynamic nature of frailty in patients with critical illness is provided by Baldwin and colleagues (2014), who assessed recovering patients approaching hospital discharge and considered over 80% to be frail according to Frailty Phenotype.

Conclusion

Our preliminary work would suggest that age doesn't matter in critical illness, once frailty is assessed. So why should it not be routinely measured? Frailty is common in critically ill patients and is associated with poorer outcomes (in terms of ICU and hospital mortality), may require greater hospital resource utilisation (in terms of hospital length of stay), and following hospital discharge is associated with greater degree of disability, dependence and intermediate-term mortality. Of the number of frailty assessment tools that have been applied to the critically ill, the Clinical Frailty Scale (CFS) currently has merit as a predictor of short-term and intermediate-term outcomes, and a simplicity that could facilitate application by non-geriatrician specialists. Simplicity and reproducibility are likely to make the CFS a tool that is suitable for clinical practice and research. Potential applications could be the impact of frailty on outcomes in critical care and on rehabilitation needs post critical illness.

Acknowledgements

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Study	Population	Methodology	Outcomes
Bagshaw 2014	Age ≥50 ICU admission	Prospective cohort; n= 421	CFS predicts hospital and 12-month mortality, ICU and hospital lengths of stay, adverse events, and post-discharge dependence
Masud 2013	Age ≥65 Burns ICU	Retrospective cohort; n=42	CFS predicts ICU mortality
Baldwin 2014	Age ≥65 ICU admission	Prospective cohort; n=22	FP criteria (measured prior to hospital discharge) predicts 1-month disability and 6-month mortality
Le Maguet 2014	Age ≥65 ICU admission	Prospective cohort; n=196	Modified FP criteria and CFS predict ICU mortality; CFS predicts hospital and 6-month mortality

Table 2. Studies Evaluating Frailty Measures after ICU Admission

Abbreviations used in Tables
ADL = Activities of Daily Living, **BNP =** Brain Natriuretic Peptide, **CAF =** Comprehensive Assessment of Frailty, **CFS =** Clinical Frailty Scale, **FP =** Frailty Phenotype, **GFI =** Groningen Frailty Indicator, **MGA =** Multidimensional Geriatric Assessment, **MMSE =** Mini-Mental State Examination, **MNA =** Mini-Nutritional Assessment, **MSSA =** MacArthur Study of Successful Aging, **TAVI =** Trans-catheter Aortic Valve Implantation

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HEALTH – THE ECONOMIC GROWTH ENGINE OF THE 21ST CENTURY

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Is there a correlation between health and economic growth? Can the healthcare sector be an answer to the current weak economic growth in the leading industrial nations?

So far, the economic development of the industrialised nations has been disappointing during the 21st century. And the situation would be even worse, had the administrations not helped the economy by taking on enormous debt and had central banks not flooded the financial markets with practically interest-free money. The industrial nations are obviously not able to leverage their economies with the existing concepts.

The biggest barrier to economic growth is low productivity at the level of society as a whole. Too many resources are being lost on the societal level due to disorder, destructiveness and crime – due to the so-called entropic sector. Entropy is a term taken from physics that describes the disorder of a physical system. Here the term is used to demonstrate the global social disorder.

Disorder has become a worldwide mega problem for the global economy and a mega destructive market. Worldwide money laundering has increased twentyfold from 1990 until 2009 and had almost reached 2,000 billion US dollars (1,568 billion Euros). Corruption and bribery are at a record high all over the world and in 2013 caused at least five percent of all economic costs (4,000 billion US dollars / 3,137 billion Euros). Patent protection and copyrights are systematically being ignored or evaded. Piracy on the world's oceans is increasing, making global commerce more difficult and more expensive. Annual losses from environmental damage make up about 10 percent of the world´s gross national product. Cyber crime is growing by double-digits, computer virus attacks and counterattacks are increasing and have led to a new type of warfare, so-called cyber warfare between companies, institutions and countries. Millions of people all over the world work for illegal organisations (the number of Russians, who are active in criminal organisations is estimated at 300,000). During their lifetime, up to 70 percent of women all over the world become victims of physical, psychological or sexual violence with partially permanent damage to their health. This list could go on and on.

If we add up the damages, losses and costs that accumulate every year in this sector, we get an amount of at least 14,000 billion US dollars (10,979 billion Euros) for the year 2006 (Nefiodow 2014). That was more than the United States gross national product. Based on our own calculations, global entropy has increased to 18,000 billion US dollars (14,116 billion Euros) in 2013.

The entropic sector plays a key role in the global economy, because the enormous losses, damages and costs that incur year after year in this instance have turned this into the most significant barrier for the economic and social development. After all, the free market economy cannot function efficiently without a sufficient number of honest businessmen, public officials and politicians.

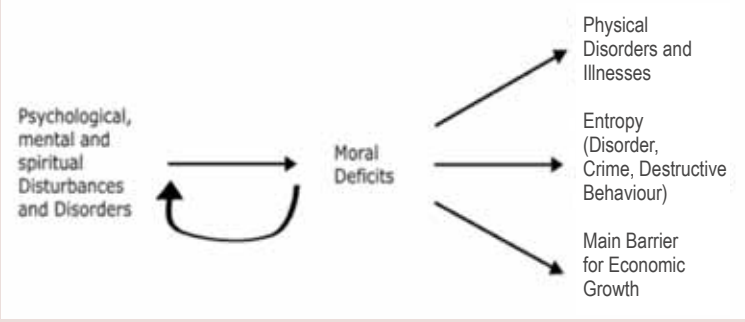

Figure 1: The Relationship between Moral Deficits – Entropy – Inner Health

Entropy and Health

What are the causes for the entropic sector? They are moral deficits. But these deficits can also be viewed from a different perspective; they can be seen as health deficits (see Figure 1).

This becomes apparent if you draw a comparison with the behaviour of healthy people. A psychologically healthy person does not cheat. A mentally healthy person does not use drugs. A socially healthy person has a sense of community, advocates wellbeing of all people and does not harass others. A spiritually healthy person has a trusting relationship with God, strives for reconciliation, truth and peace and does not spread hatred and violence. Inner disturbances and diseases and the social misconduct caused by them are the deeper reasons for global entropy (see Figure 1).

At this point, I would like to elaborate on the term health. The World Health Organization (WHO) definition of health is a state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity. In 1997 the Executive Board of the WHO provided some food for thought with a broader definition of health: "Health is a dynamic state of complete physical, mental, social and spiritual wellbeing and not merely the absence of disease or infirmity." This was once again highlighted in the 2005 Bangkok Charter for Health Promotion in a Globalised World: "Health is one of the fundamental rights of every human being and encompasses mental and spiritual wellbeing."

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THE TRADITIONAL HEALTHCARE SYSTEM

- Medical technology
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- Health spas/sanatoriums
- Company health services
- Health as a competitive factor, training and continuing education (e.g., in people skills), human resource development, health management
- Other (health-related)
- Skilled trades (e.g., for orthopaedic products), sporting goods and sports facilities, health publications, medical EDP etc.

THE NEWLY EMERGING HEALTHCARE SECTOR

- Biotechnology
- Naturopathic treatments, natural products, all natural foods
- Complementary/alternative medicine
- Homeopathy, classic acupuncture, electroacupuncture according to Dr. Voll, kinaesiology, bioresonance therapy, anthroposophic medicine, magnetotherapy, Dr. Rath's cellular medicine, biofeedback, quantum healing, traditional Chinese medicine, ayurvedic medicine, Reiki etc.
- Environmental protection (predominantly)
- Agriculture, diet, food
- Wellness/fitness, tourism (health tourism)
- Architecture (healthy living), building and construction industry (healthy building materials), textile industry (allergy-free and breathable textiles and clothing), the senses (colour therapies, aromatherapies, music therapies),
- Self-medication and self-care
- Participation of illness costs, rising self-care
- Workplace health management
- Company health insurance funds, company sponsored fitness programmes, cafeterias, welfare centres, health seminars, preventive medical checkups, good health bonus
- Psychology, psychiatry, psychotherapy, psychosomatic medicine
- Religion/spirituality

Figure 2: The Health Value Chain of the Sixth Kondratieff
Source: Nefiodow 2014

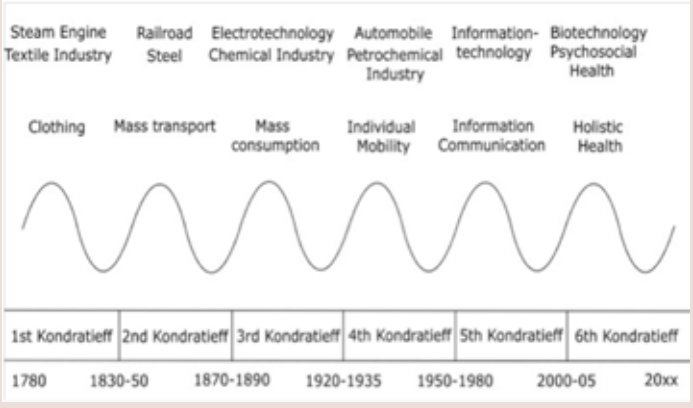

Figure 3: The Six Long Waves of Economic Development
Source: Nefiodow 2014

According to the WHO, terms like disease and health are no longer limited to the body. They are systems concepts. There are also sick souls; there are social diseases; there are sick families, companies and societies.

If you apply the WHO definition to the marketplace, we can distinguish between two sectors of the healthcare system (see Figure 2):

The Traditional Healthcare

Over the past two centuries, the traditional healthcare sector made tremendous progress. The history of medicine over the past two centuries was a real success story.

But this success story is about to end. Since the late 20th century, the new medical advances are no longer sufficient to adequately deal with the dynamics and complexities of modern life and its high demands on the physical, emotional and mental strength of human beings. As a result of these and other trends (e.g. longer life expectancy of people and the increasing social disarray), the number of diseases and costs in the healthcare sector continuously increase in all countries.

The traditional healthcare system does not provide health based on the definition by the WHO. It is not geared towards holistic healing, but mainly towards the treatment of physical diseases. It is not well prepared for the demands of the 21st century. What we call the traditional healthcare system today is in fact not a healthcare system at all. The correct label would be disease care system, since more than 95 percent of expenditures go towards the research, diagnosis, treatment, administration and management of diseases. In contrast, only limited means are available for prevention, preventive medical checkups and healing.

Dementia is one example. In 2010, the US federal health insurance programmes Medicare and Medicaid spent approximately 140 billion US dollars (109,8 billion Euros) to treat dementia, but only 0,5 billion (0,39 billion Euros) to research its causes (Coy 2012): a ratio of 280:1.

The most important source of economic growth in the industrialised nations is productivity. The low productivity level of the traditional healthcare sector is its biggest problem. The productivity is too low, because the costs caused by medical technology advances are not counterbalanced by the cost savings they produce (Schneider, Markus et al.); and because they – as mentioned before – are not geared towards healing, but rather the treatment of disease symptoms. As a result, costs keep increasing. In the meantime, global health expenditures are now 12,000 billion US dollars (9,466 billion Euros) and there are more and more sick people, more and more diseases despite high spending, despite more research, more pharmaceuticals and medical technology, an increasing number of doctors and other healthcare professions and ever more remedies and healthcare products.

How can those two barriers – big losses, expenses and damages of the entropic sector and the high costs and low productivity of the traditional healthcare system – be overcome? In the past, growth barriers were overcome by developing the new Kondratieff cycle.

What is a Kondratieff Cycle?

Kondratieff cycles are economic fluctuations averaging about forty to sixty years. They are triggered by groundbreaking innovations, which are called basic innovations to distinguish them from other innovations. When we summarise the existing studies, so far, six Kondratieff cycles were empirically determined from an economist's point of view (see Figure 3):

The 1st Kondratieff cycle begins towards the end of the 18th century. The trigger is the steam engine. The most important application takes place in the textile industry.

The 2nd Kondratieff is the era of big steel and the railroad. Two major new industries develop during the 3rd Kondratieff: the electrotechnical and the chemical industry. The 3rd Kondratieff ends with the world economic crisis of the late 1920s and early 1930s.

"We leave the growth patterns of previous Kondratieff cycles behind. Now the human being takes centre stage"

The 4th Kondratieff was supported by the automobile and the petrochemical industry. This long cycle drew to an early close due to the massive crude oil price increases of the 1970s.

The 5th Kondratieff is carried by modern information technology. No other technology was able to even remotely exhibit comparable economic dynamics and widespread effect during the second half of the 20th century. This cycle ended with the global recession of 2002-2004. Simultaneously, the sixth Kondratieff began. This long cycle is in its early stages, but is not able to fully develop primarily because of the two mentioned barriers.

The healthcare economy is the carrier of the new, sixth Kondratieff. The weak economic growth in the industrial nations can be overcome by its promotion and extension.

The Newly Emerging Second Healthcare Sector

The main carrier of the sixth Kondratieff will be the new emerging healthcare sector (see Figure 2). Biotechnology holds a special position (see Figure 4). It is not just a brand-new technology, it is one of the two basic innovations of the sixth Kondratieff, because it will improve productivity in handling physical diseases, it will reduce costs significantly, it will improve our competence in avoiding diseases and our competence in healing.

Naturopathic treatments, complementary and alternative medicine belong to the new value chain (see Figure 2). They have expanded for many years and now play an important role. There is still immense healing potential hidden in this area and a large market for all players in the healthcare system.

Big portions of environmental protection are also a part of this new value chain. When you take a closer look, most environmental protection measures only serve the environment at first glance; protecting the health of human beings is the stronger motive.

The wellness industry, fitness studios and health tourism have expanded strongly. Companies increasingly have come to realise that employee health has become a strategic weapon.

Two additional protagonists in the new emerging healthcare sector are psychotherapies and spirituality/religion, which can help in reducing entropy. Psychotherapies could effectively contribute to entropy reduction, if – as established in our book – they could reduce the theoretical deficits (Nefiodow 2014). Unlike the situation in spirituality where its effectiveness has been scientifically proven. Many studies prove that religious beliefs have a healing effect on the body, soul and spirit. Raphael Bonelli of the University of Vienna and Harold Koenig of Duke University in the US have analysed all studies that were published between 1990 and 2010 on the relationship between health and religion, and concluded that there is a positive correlation between Christian faith and health in 74 percent of these studies (Bonelli and Koenig 2013).

The Kondratieff Cycle as an Economic Engine

To understand why the sixth Kondratieff is going to take on the role of economic growth engine, the example of the fourth Kondratieff is meant to demonstrate how this type of growth engine is built and how it works (see Figure 5).

The basic innovation that triggered the fourth Kondratieff was the automobile. Two large new

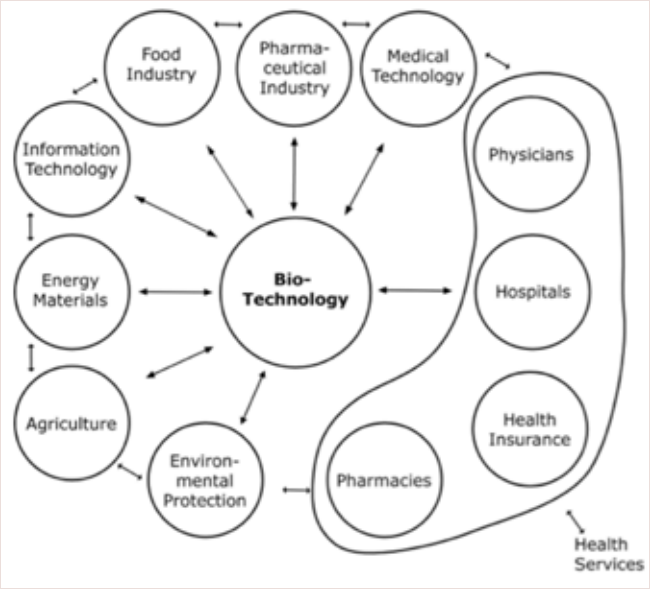

Figure 4:
The Biotechnology Value Chain
Source: Nefiodow 2014

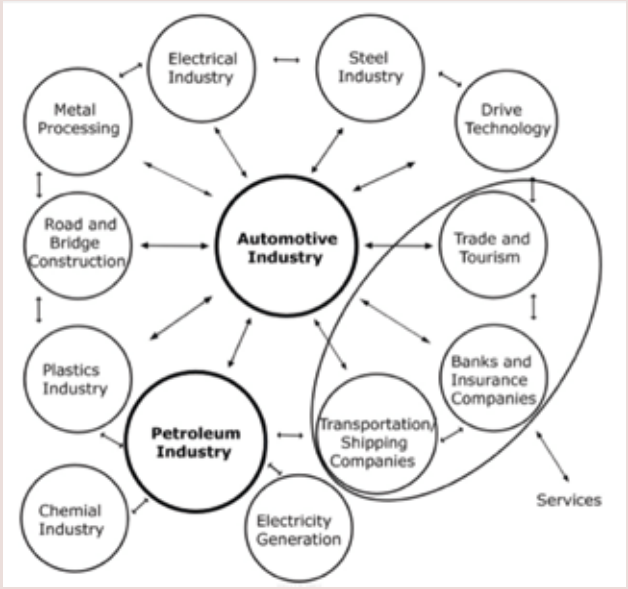

Figure 5:
Value Chain of the Fourth Kondratieff
Source: Nefiodow 2014

industry sectors developed from its commercialisation: the automotive industry and the petrochemical industry (see Figure 5). During the fourth Kondratieff, they were the most important private employers and the largest investors in research, development and production. For more than half of a century they significantly defined economic growth, and as leading industries, they affected the economic system like a locomotive affects a train: they put all wagons of the train in motion.

If we stay with the image of a train, the individual wagons represent the sectors of the economy, which benefited from the automobile. This included highway, bridge and road construction companies, steel and tyre manufacturers, manufacturers of fuel power stations and gas-fired power plants as well as countless suppliers of metal, electric, electronic and plastic parts. Numerous service providers were also a part of the "wagons" of the train: gas stations, car dealers, repair shops, transport companies, banks, insurance companies, tourism and the leisure industry. All of these "wagons" built a global network of suppliers, customers, retailers and users, which created millions of new jobs. And the entire train in motion illustrated– metaphorically speaking – the fourth Kondratieff. In those countries where the automobile and petrochemical industry boomed, full employment was the result. Every fifth job in the U.S.A. and every seventh job in Germany became dependent on the car during the fourth Kondratieff. The healthcare sector will take on a similar role as a growth engine during the sixth Kondratieff.

Conclusion

We explained that the sixth Kondratieff is a health-related cycle. A detailed analysis of the current growth barriers and growth potential in fact shows that the healthcare system, when it is geared toward the needs of the 21st century and extended to the human being as a whole, can lead to a strong and sustainable upswing (Nefiodow 2014). Outside of the healthcare system there is presently no other candidate through which industrialised nations can achieve full employment. This means that for the first time in history, the focus of economic and social development is not on a machine, a chemical process or hardware technology, but rather the human being with his physical, mental, psychological, social, ecological and spiritual needs, problems and potential. We leave the growth patterns of previous Kondratieff cycles behind. Now the human being takes centre stage. This is the message of the 6th Kondratieff: the healing of man is the best programme for the future. ■

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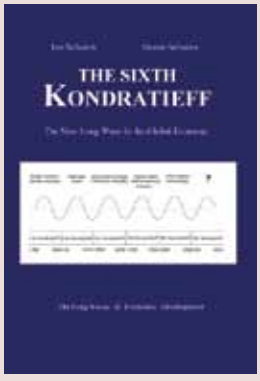

Editor's note:
Leo Nefiodow has been awarded the Bronze N. D. Kondratieff Medal 2014 by the International Kondratieff Foundation and the Institute of Economics Russian Academy of Sciences. The ceremony was held in Moscow on 12 November 2014.

Further reading:
Leo Nefiodow and Simone Nefiodow 'The Sixth Kondratieff. The New Long Wave in the Global Economy'. Available from Amazon.

ELDERLY CARE IN THE ICU

INTERVIEW WITH PROFESSOR BERTRAND GUIDET

Professor Bertrand Guidet is Director, Medical Intensive Care, St. Antoine Hospital, Paris, France and Medical Director, APHP Hospitals, East Paris.

You have a long-standing interest in ICU care and elderly patients. What prompted your interest?

We should not consider the ICU as a unique unit. It is part of the hospital and there is treatment before and after ICU. This is true for all ICU patients, but particularly for elderly patients. If you deny ICU admission for an elderly patient, what will happen to them? Maybe they will be admitted to an intermediate care unit, to a geriatric care unit or to internal medicine. If you admit a patient to the ICU what will the level of care be, what about: the ethical issues if the treatment is not successful, the discharge criteria, the relationship with the family and the relatives? This is a paradigm for the whole process and also deals with distributive justice. If you have constraints, because you do not have enough ICU beds, how do you cope? You have to make a choice. You will try to choose the patient that will benefit the most from ICU treatment. You might be wrong in both ways. You might admit a patient that should not be admitted, or refuse admission to a patient who could have benefited from ICU care. The issue of elderly patients is of paramount importance because of the elderly population, and because we are at the centre of the process in the ICU – with ethical and financial considerations and organisational issues.

When we talk about the 'elderly' patient with specialists the threshold is usually 80 years of age. The threshold should be at least 75, certainly not 65 (in some studies they talk about 65-75 years as 'young old'). Age by itself does not say anything. The concept of frailty is more important than age, and you should probably collect information that describes precisely the patient you are talking about, including nutritional and functional status, quality of life, family and so on. This is very important information that we are not collecting on a daily basis. We use severity scores such as SAPS II, APACHE, but these do not cover any of the conditions specific to the elderly, such as cognitive impairments, cachexia or depression etc. This information is key for predicting mid- and long-term outcomes. If we want to assess whether an elderly patient should be admitted, we should not only consider immediate severity such as organ dysfunction, but also the underlying disease, functional status and quality of life. In our ICE-CUBI study (Boumendil et al. 2012) we found that if you ask for the information (e.g. "How many drugs do you take, did you fall in the last three months, have you been admitted to the hospital, what is your functional status according to the activities of daily living (ADL) score?") you are able to collect it, even in an emergency situation. I convinced my colleagues that we need to collect this information for the decision-making process, whether via the patient, the family or the general practitioner. This is key for decision-making.

At the Durban World Congress Ethics Round Table most participants agreed that age cannot be the sole criterion on which healthcare decisions be made (Guidet 2014). They also agreed that it is important to provide data showing that outcome differences between elderly and nonelderly patients are partly related to decisions to forgo life-sustaining treatment. Do sufficient clinical trials include this data currently?

A big issue is related to the admission of elderly patients. Firstly, all the papers on triage are biased, because they only

consider the patients that were proposed for ICU admission. They do not consider pre-selection by the patient him/herself, the family, general practitioner or emergency physician and so on. So when you say, "I refuse 30% of the patients", what is the prioritisation process? Secondly, you will have two different policies: an open policy or a strict admission policy. If you have a liberal admission policy, so that you admit the elderly patient when there is a possibility of improvement, you will have to decide during the ICU stay whether you continue treatment without any limitation or if you introduce some sort of limitations. For example, I favour a liberal admission policy, but after 3-4 days we need to sit around the table with the team, the nurses, physicians and afterwards with the family and ask what we do from here. The opposite, if you have a very strict admission policy, e.g. admit only good candidates with no co-morbidities, single organ failure, who are easy to diagnose and treat, is that you will very rarely have to discuss end-of-life decisions during the ICU stay, but at the same time you will deny ICU admission to some patients that could in fact have benefited. My point is that there is a relationship between the admission policy and end-of-life decision policy while in the ICU.

"If you deny ICU admission for an elderly patient, what will happen to them?"

You are leading the current clinical trial on Impact on Mid-term Mortality of Guidelines for ICU Admission of Elderly Patients Arriving in Emergency Departments (ICECUBII) (Assistance Publique-Hôpitaux de Paris) Please explain how you arrived at your hypothesis, and comment on any early findings and progress of the trial.

The ICECUBII study is funded by the French Ministry of Health. It is a randomised crossover study: half the hospitals will provide their usual standard care and half of the hospitals will admit all elderly patients from the emergency department, given that they have no active cancer, no cachexia and have preserved functional status, as defined by an Activities of Daily Living (ADL) score above 4. The primary endpoint is mortality at 6 months.

According to our previous ICECUBI study (Boumendil et al. 2012; 2011), we did not find any benefits of ICU admission for elderly patients, so there is no ethical problem with the study. We plan to include 3000 patients. We have around 500 left to include, so hopefully the last inclusion will be at the end of the winter in around March 2015. Then we have 6 months follow-up, and we need to clean the database, which will hopefully be at the end of 2015. I don't have any data related to mortality in both arms. I have some data relating to the percentages of patients admitted to the ICU in both arms, and it's higher in the intervention arm, i.e. the patients who had to be admitted to the ICU.

In the preceding study (ICECUBI), only around a quarter of eligible patients were admitted to intensive care. Did this finding surprise you?

In fact it's higher than this. Our starting point was the emergency department. We showed that emergency physicians proposed only one out of four patients for admission. Among the proposed patients one of two was finally admitted, so the total selected is one out of eight, which is a huge triage. None of the papers about triage assess this pre-triage process. I was not expecting such a selection. I expected perhaps one out of four, but not one out of eight.

You have observed that Advance Care Directives, when communicated, are of great assistance to the treating doctor. Should these be more widely used?

Firstly, Advance Care Directives are rare. Secondly, even if they exist they are not very often used, and if they are used we do not really know the impact in terms of outcome. But I think this is a nice piece of information to have. We should not use it as a law, but if it is clear and updated it certainly can contribute to the decision-making process. It's a piece of paper, and it should not substitute for direct conversation and interaction that you need to have with the patient and the family. It's just one piece of information you need to consider and which may change according to the patient's condition.

In a recent editorial (Rusinova and Guidet 2014) you say that the awareness of risks/ rewards of treatment and a genuine dialogue between physicians and patients and families are becoming a priority and outweigh the impact of age in clinical decision-making. How can ICU services facilitate this kind of dialogue?

We miss a lot of opportunities for interaction with the patient and their families. We overlook opportunities to get information from the nurses, who have a lot of information through discussion with the patient and the family. It depends on the countries and the situation. Some physicians are very reluctant to talk directly to the patient and the family in order to get information about the willingness to receive intensive treatment. In the ICECUBI study ((Boumendil et al. 2012; 2011), in more than half of the cases the family of the patient was able to answer. Yet they were asked only in 10% of cases. When you consider their willingness to be admitted or not, it has a profound impact on the decision. If the patient says, "No, I don't want to be admitted to the ICU", he is not admitted. If a patient or the family says, "I want to be admitted, I need intensive care treatment", then they are admitted. So we generally do not ask the patient or the family. However, if we do ask them, it has an impact on the decision, so we need to do it. We have a manuscript in preparation about this huge issue.

I would like to emphasise that ICU is a team. If you want to improve the outcome, I don't feel that it will be a fancy new ventilator or a new drug that will do the job, but the key elements of culture and climate in the ICU, that is if the people working in the ICU have good communication, respect, ability to change and training. If staff are struggling, if they don't communicate well, if there are, for example, problems with the head nurse, problems with the nurses and physicians, at the end of the process the patient will get suboptimal care. My point about looking at organisation is that it includes how the manager or leader should work in order to engage the whole team, including the cleaners. An

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ICU has to be clean and well organised, especially because we have to work sometimes in an urgent situation, e.g. cardiac arrest, three patients admitted at the same time. We need solidarity amongst the team and to share the same goals.

It means you need to share the decision-making process. Sometimes you need to sit down and talk about wrong decisions together, maybe in a debriefing session or with the help of a psychologist. For example, we do a common morbidity and mortality review across the hospital.

You organised a European Society of Intensive Care Medicine survey, which looked at the organisation and management of critical care globally. Can you tell us more?

Dr. Yên-Lan Nguyen and I did a survey about different ICU networks across the world, looking at the type of participating ICUs. We have shown that when you have bigger hospitals and bigger ICUs you have better organisation and maybe better outcomes. We have submitted a paper looking at the volume/ outcome relationship, and found that in most cases there was a relationship.

You commented in an editorial on research into night-time discharge (Guidet and Bion 2014), "If we had at our disposal a drug which could reduce mortality by 20-50%, we would all be using it. Avoiding night-time discharge is that drug." How can ICUs achieve this?

We wrote an editorial accompanying a paper from the ANZIC group (Gantner et al. 2014) and considering from the literature that roughly 15% of patients are discharged out of hours. This group was more often readmitted and had higher mortality. We need to reduce this percentage that did not decline over time, at least in Australia and New Zealand. In our editorial, we proposed some recommendations to reduce off-hours discharge or to improve the selection process for patients that should be discharged. In most cases, if you discharge the patient during the night, it's to cope with the pressure, and you need to admit another patient. The response has to be a short-term response. Maybe during the morning rounds we need to select the patient that could have been discharged in the afternoon, or in the long term have more ICU beds, or intermediate care beds. In most cases when you say discharge, it's discharge mostly from the ICU to the ward.

This interview will appear in ICU Management's Winter issue, which has a cover story on early goal-directed therapy. What do you see as the main challenges in early goal-directed therapy?

There are two terms – early and goal-directed. Early, I fully agree, the sooner the better. Again it goes with the relationship of the ICU with the other parts of the hospital – the emergency department, the wards, the operating theatre. You need good communication, you need to reduce the delay, particularly for septic shock and anaphylaxis. Goal-directed is much more difficult e.g. for shock. What are the goals, what are the right algorithms? Several papers this year are raising concern about usefulness of the goals. What is optimum cardiac outputs, mean arterial pressure, for example – we don't know. We need a kind of integrative approach towards the patients. We need first to look at tissue perfusion (mottled skin, cutaneous refilling time, lactate, urine output). Those are simple tools, simple clinical science that you can collect at the bedside. My approach would be much more patient-oriented instead of figures-oriented e.g. mean arterial pressure, it's nonsense! If there are no signs of tissue hypoperfusion and MAP is 62 mmHg, do we really need to increase blood pressure? And when you talk about an elderly patient with stiff arteries or a patient with previous renal failure maybe they will need more. ■

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STATE OF INTENSIVE CARE IN TURKEY

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The history of intensive care (IC) in Turkey has followed a somewhat similar pattern to other European countries (see Figure 1). The first intensive care unit (ICU) was founded in a state hospital in Istanbul in 1959. The first attempts to institute intensive care in several cities were performed almost exclusively by anaesthesiologists. In 1977 those pioneer anaesthesiologists attended their first international meeting of Intensive Care Medicine (ICM) in Paris. With the influence of this meeting, the Turkish Society of Intensive Care (TSIC) was founded in 1978.

Although the pioneers of ICM were anaesthesiologists, the founding committee members of the society were all from different specialties (surgeons, internists, pulmonologists, neurosurgeons and cardiac surgeons). Yet the interest of other disciplines was minimal until recent years. As a consequence, ICM remained almost as a "subspecialty" of anaesthesiology. As a result, TSIC and the Turkish Society of Anesthesiology and Reanimation (TSAR) played a crucial role in the clinical and administrative development and the scientific progress in representing ICM. Today the majority of intensivists are anaesthesiologists. The changes in administrative structure and the renewal of the requirements for the intensive care supraspecialty have caused big discussions among primary specialties (see Hot Topics in Intensive Care in Turkey, page 46).

Healthcare System in Turkey

The Ministry of Health (MoH) is the main health service provider in Turkey; universities and private sectors have a complex connection with the MoH on which they are financially dependent. In recent years, there has been a radical change in the Turkish healthcare system, the so-called "Health Transformation Programme" (HTP). One of the first steps of HTP was the unification of several former "state insurance programmes" under a single umbrella, named "General Health Insurance" (GHI). Family medicine was supported, popularised, and organised with a computerised system. A stepwise system from primary to tertiary levels of health care centres and hospitals was introduced. However, this did not prevent over admission to the university hospitals.

The reimbursement of health services is organised generally around several "packages", with only a few exceptions. A performance-based supplementary payment system was also initiated for physicians. This system has advantages

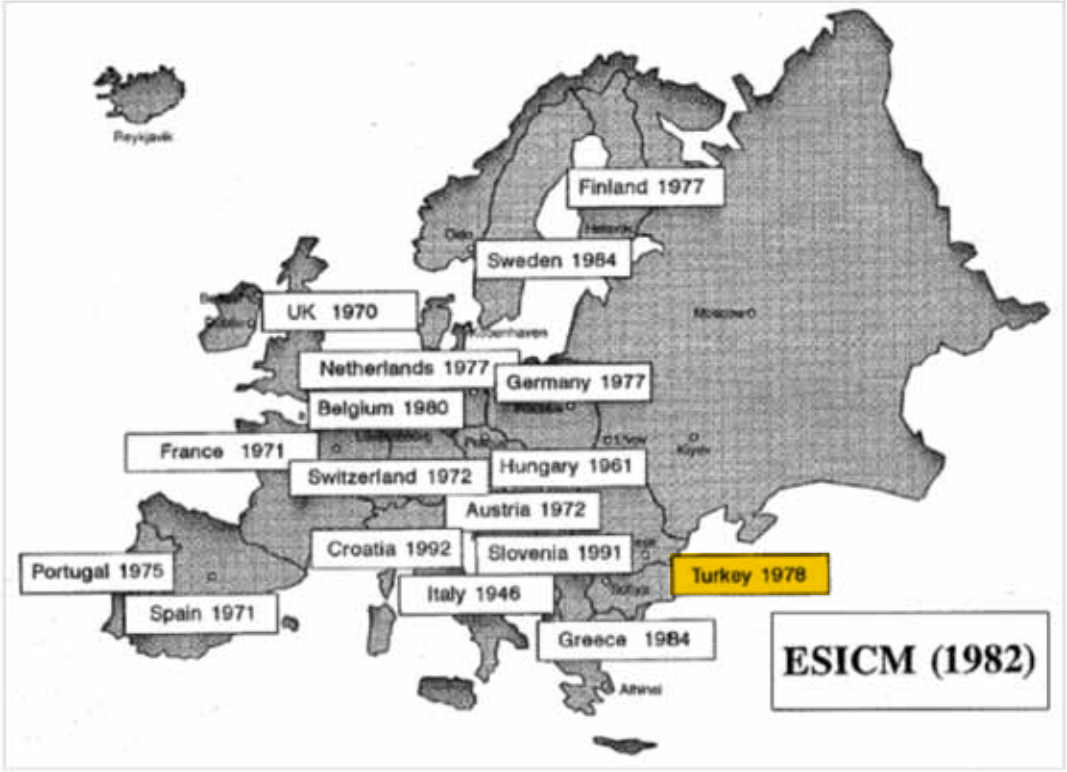

Figure 1. The History of Intensive Care

and disadvantages, and has been discussed and criticised in equal measures since its introduction. The most important drawback of this system concerning the ICU is that the reimbursements of ICUs are performed almost exclusively in "package programmes"; as a result, hospital managements rearrange their ICU policies according to these programmes (which are not necessarily parallel with medical obligations). The majority of private hospitals are also connected to GHI and therefore to the MoH.

ICUs in Turkey

In Turkey there are approximately 27,000 intensive care beds (adult, paediatric and newborn), of which 12,661 are in tertiary level ICUs, meaning that they are capable of treating severe critical illness with multiple organ dysfunctions (see Table 1, and Figure 2). The intensity of ICU in Turkey is shown in Figure 3. In Table 1, the numbers of beds are listed. Most of the ICUs are working in a closed system with a director.

> "We think that the Turkish Society of Intensive Care will represent intensive care to a better place in the national and international arena"

Intensive Care Medicine Education

Graduates of medical faculties have to pass a central examination to become a specialist. Residency training lasts for five years; during training in anaesthesia, one year of rotation is obligatory in the ICU according to recent regulations. Obligatory rotation periods in other main specialties were not strictly specified. According to the new constitution of the specialisation programme in medicine, intensive care becomes a supraspecialty for anaesthesiology, pulmonology, general surgery, internal medicine, neurology and infectious diseases where training lasts three years. Anaesthesia has been recognised as the main discipline for the supraspecialty training. The base programme of the training is defined by the MoH and the Scientific Committee as consistent with the Competency Based Training programme in Intensive Care Medicine for Europe (CoBaTrIce). The details of the programme are determined by the protocols of the different disciplines within each centre.

Since 2012 specialists need to have a good mark on a central examination to start the supraspecialty in intensive care medicine (ICM). There are 27 University Hospitals and 4 MoH Research Hospitals that have education programmes for the ICM supraspecialty. After acceptance of the new regulation, several

	Total Number ICU beds	Adult ICU beds 1st, 2nd and 3rd degree	Adult 3rd degree ICU beds
Private Hosp.	10 460	6102	3081
MoH Hosp.	11 523	7652	2457
University Hosp.	5063	3473	2082
Total	27 046	17227	7620

Table 1. Number of Beds

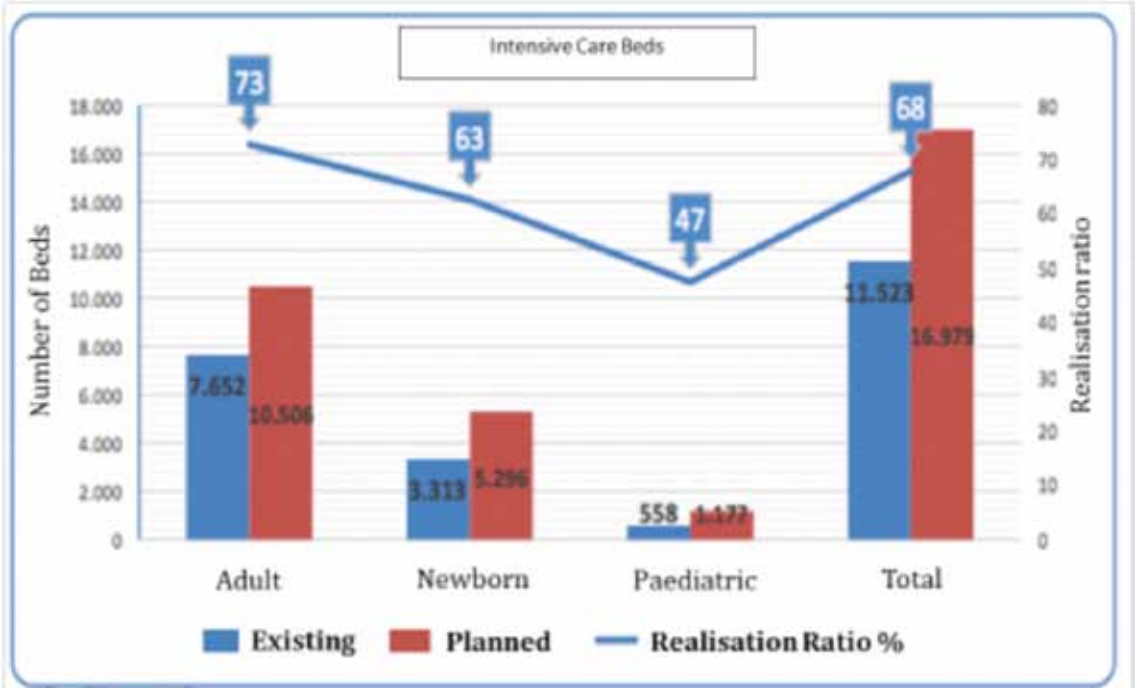

Figure 2

doctors from six base specialities, who have been working at intensive care units for at least five years applied to the MoH to get the intensivist certificate. Only 208 intensivists, 166 of whom are anaesthesiologists, received this certificate. After objections and court decisions, approximately 225 certificated intensivists exist in Turkey, and the main specialty of 180 certificated intensivist is anaesthesiology.

Scientific Activities

Since its foundation, TSIC has organised several scientific activities:

1. Congress: From the beginning the Society co-organised its congress within the Turkish Anesthesia and Reanimation Congresses; in 1997 it was held as a separate National Intensive Care Congress. Since then, the 17th congress has been organised for 2014 with more than 650 attendees. The congress is a biennial event of 3-4 days duration.
2. International Intensive Care Symposium: this is also a biennial event (alternating with the national congress), and the 19th was organised in 2013. For the global masters of ICM, the meeting in Istanbul has become a tradition.
3. Courses in different topics of ICM, such as Mechanical Ventilation, Sedation-Analgesia in ICU, Renal Replacement etc. (Each topic is organised 3-4 times a year in different cities of the country as weekend courses). To date, 16 courses on mechanical ventilation have been given.
4. Co-organisations with "sister" societies: Panels in congresses of TSAR, the Society of Cardiovascular and Thoracic Anesthesia and Intensive Care, Society of Nutrition, Society of Resuscitation, etc.

Statistics (2012)	
Total Population	73,997,000
Gross national income per capita (PPP international $)	18,190
Life expectancy at birth m/f (years)	72/78
Probability of dying between 15 and 60 years m/f (per 1,000 population)	150/75
Note: DATA FOR UNDER FIVE NOT AVAILABLE	
Total expenditure on health per capita (Intl $)	1,144
Total expenditure on health as % of GDP	6.3

Source: World Health Organization Global Health Observatory http://www.who.int/countries/tur/en/

International Position

Turkish delegates to the national council of the European Society of Intensive Care Medicine (ESICM) have been elected from the TSIC members since the institution of this council.

Turkish intensivists are invited to give lectures in international meetings such as ESICM, ISICEM, in several countries, intensive care societies, and meetings, etc.

Since 2005 Turkey has also been a centre for the second phase of the EDIC examination, a popular choice for candidates, especially from Asian countries. The first EDIC diploma awarded to a Turkish intensivist was in 2003; since then, further intensivists (all from anaesthetic origin) have passed the EDIC-examination. TSIC publishes its official journal (Journal of the Turkish Society of Intensive Care) every three months. This journal is principally dedicated to reviews and educational aspects; however, studies have also recently been published in this journal; attempts to join the international indexes continue.

In conclusion, TSIC has represented and will represent the intensive care community in Turkey. There are many problems to be solved, such as shortage of nurses, reimbursements of ICUs, educational issues, etc. We think that the Turkish Society of Intensive Care will represent intensive care to a better place in the national and international arena. ■

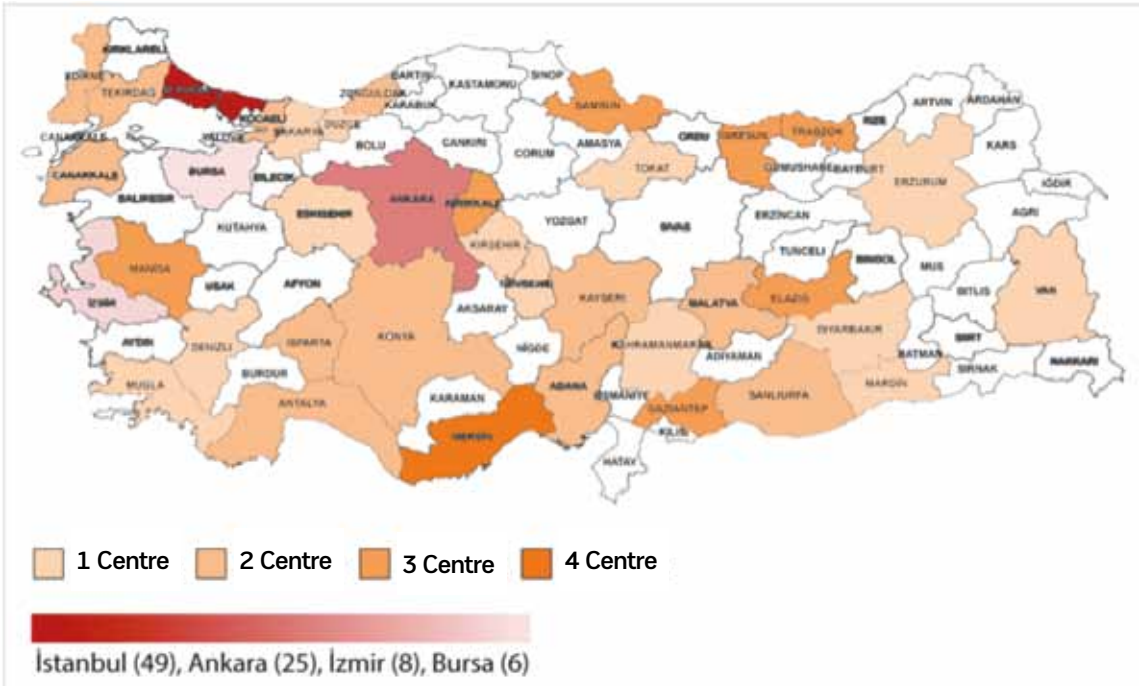

Figure 3. ICU Distribution in Turkey

HOT TOPICS IN INTENSIVE CARE IN TURKEY

PROBLEMS, WEAKNESSES AND THREATS

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In Turkey intensive care was not a separate specialty for years, and was managed mainly as a subspecialty of anaesthesiology. In 2009 a new regulation was announced by the Ministry of Health (MoH) in which intensive care medicine (ICM) was recognised as a supraspecialty. Regarding this regulation, ICM education has a duration of three years after primary specialty training in anaesthesiology, pulmonology, internal medicine, general surgery, neurology and infectious diseases. The MoH also founded a "Scientific Committee of ICM" to establish the intensive care training curriculum that is consistent with the Competency Based Training programme in Intensive Care Medicine for Europe (CoBaTrice). This regulation has evoked several debates.

"Uncertified" Intensivists

There are more than 1000 anaesthesiologists and other specialists such as pulmonologists, general surgeons, neurologists, chest surgeons and cardiovascular surgeons working in and directing ICUs in Turkey, who do not have the MoH Diploma of Intensive Care. The Diploma of Intensive Care has been given to only 208 physicians after initial assessment. A number of scientific activities, including papers published in international publications covered by the Science Citation Index in addition to some educational activities (e.g. editorship or associate editorship for books or journals, authorship for book chapters, editorship for book translation, at least five activities in a congress, adviser for thesis etc.) are required for the diploma, which is not the case for the majority of these people, who are only clinicians, and not scientists or educators. Thus there are still more than 800 experienced doctors, mainly anaesthesiologists and also some other main specialties, who do not have the diploma and work on ICUs. What will happen to them? Do they have enough enthusiasm to carry on their functions in ICU? Who will be responsible in case of legal problems? How can we employ these un-certified intensivists in intensive care, and how can we employ them as trainers for intensive care residents in teaching hospitals? And so on. There are several unanswered questions and as a result several statements of claim at courts.

Because of these problems, the MoH has proposed a draft act to parliament. According to this, a documentation of clinical performance in an ICU of at least 3-5 years plus an examination appears to be a good solution, in order to give the MoH intensive care diploma to these applicants, but it is still a subject that needs to be debated in parliament and, more importantly, between intensivists.

Intensive Care Education

The duration of education for the supraspecialty in intensive care has been decided as three years. However, one year of the anaesthesiology residency period is still dedicated to ICM. Residents in anaesthesiology argue that this is unfair for two reasons: first, if they are not intending to make a supraspecialty education, this year would make no sense; and second, if they intend to make this supraspecialty fellowship, their education should be 2 years.

On the other hand, colleagues who have started the supraspecialty education ask whether they will have a "difference" compared to older colleagues who do not "officially" have the ICM diploma, but have directed an ICU for years.

Determining the curriculum, organising the "board", and similar questions remain also as issues of discussion between the Turkish Society of Intensive Care (TSIC) and other societies. Around eighty-five percent of intensivists who have the diploma are members of TSIC and anaesthesiologists. A "scientific board" has to be founded with a fair and rational distribution among the different disciplines, taking into consideration the distribution of the intensivists in the country.

Shortages

Currently, the most important problems appear to be the "official" ones, but there are also other problems like the shortage of nurses and other personnel such as physiotherapists and clinical pharmacists. This shortage leads usually to non-optimal management; causing a further financial problem. On the other hand there is no formal education for intensive care nurses.

Previously, dealing with ICM was a "prestige" among the physicians. Today, increased workload leads often to burnout: the combination of relatively low income and longer working hours has made the supraspecialty unattractive.

There is a shortage of level 3 ICU beds in Turkey. The ratio of ICU beds/ hospital beds has to be increased, which is also planned by the MoH. The lack of "post-ICU care" (e.g. home care, nursing homes) is an issue, leading to an unnecessary increase in ICU stay, the need for further ICU beds and personnel and increased cost.

Reimbursement

Last, but not least, the insufficient and irrational payment of General Health Insurance to ICM has led to

the fact that the hospital management does not want to invest in ICUs. Reimbursements are not case-sensitive and are standardised according to the patient's care requirement level graded by the insurance system according to the level of ICU. Therefore, more serious patients with increased expenses result in pecuniary loss for intensive care units and hospitals.

According to the general health insurance system in Turkey reimbursement mainly depends on days of stay in the ICU. Therefore, additional therapeutic approaches, advanced therapies, increased use of antibiotics all increase the expenses but not the income of ICUs.

Proposed Solutions

The TSIC and MoH are planning new strategies for some of these problems.

MoH's act proposing re-certification of intensivists will be put on the agenda of the Turkish Parliament within a few months.

MoH is targeting the number of ICU beds to be ten percent of hospital bed capacity, and plans to regenerate palliative care units. With the new system ICU beds will be used more efficiently.

TSIC is changing its structural organisation. Several new working groups and a dynamic feedback system interacting with intensivists and intensive care units of the country will be the principal source for determination of future policies. In addition to national activities, international relations will be improved to restate the active role of the society. The diversity, frequency, contents, and organisational structure of scientific and educational activities will be re-evaluated and re-organised according to reports from relevant working groups in addition to extended advisory boards.

> "The combination of relatively low income and longer working hours has made the supraspecialty unattractive"

TSIC has organised a new activity together with the Global Sepsis Alliance and MoH to increase sepsis awareness, increase education of healthcare staff, and decrease prevalence and mortality of sepsis in Turkey. On 12 September 2014 the first stage of the programme started with the simultaneous appearance of Dr. Mehmet Müezzinoğlu, Minister of Health, in the 14 biggest hospitals in 13 cities of Turkey. A TSIM working group and very powerful trainer team, including approximately 215 intensivists mainly from teaching hospitals and university hospitals, will continue planned educational activities in every city of Turkey for years to come under the organisation of the Ministry of Health. ■

AGENDA

DECEMBER	
3-5	International Sepsis Forum, New Challenges Paris, France www.internationalsepsisforum.com
4-5	Airway for Anaesthesiologists 2014 Copenhagen, Denmark www.airwaymanagement.dk
7-10	Update on Antibiotic Therapy in the ICU Rome, Italy www.intensive.org
8-10	Intensive Care Society State of the Art Meeting 2014 London, UK www.ics.ac.uk
JANUARY 2015	
11-16	5th Annual Winter Symposium in Intensive Care Anaesthesia and Emergency Medicine 2015 Vail, USA www.colloquium.com.au
17-21	Society of Critical Care Medicine 44th Critical Care Congress Phoenix, USA www.sccm.org
FEBRUARY	
1-6	5th International Winter Symposium of Intensive Care Medicine 2015 Zermatt, Switzerland kongress2.imk.ch/wintersymposium2015/Home
6-7	20th International Symposium on Infections in the Critically Ill Patient 2015 Barcelona, Spain www.infections-online.es
9-11	Japanese Society of Intensive Care Medicine 42nd Annual Meeting 2015 Tokyo, Japan www2.convention.co.jp/42icm/index.html
17-20	Acute Kidney Injury: Controversies, Challenges and Solutions, Advances in Critical Care - Continuous Renal Replacement Therapies 20th International Conference 2015 San Diego, USA www.crrtonline.com
24-27	Canadian Critical Care Conference 2015 Whistler, Canada www.canadiancriticalcare.ca
MARCH	
17-20	35th International Symposium on Intensive Care and Emergency Medicine (ISICEM) Brussels, Belgium www.intensive.org

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