ICU MANAGEMENT

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Organ interaction

PLUS:

- Healthcare-Associated Bacterial Infections: Common Sources of Severe Sepsis Among People with HIV
- The Future of Glucose Control in the ICU
- Nutritional Failure: An Adaptive Response to Critical Illness?
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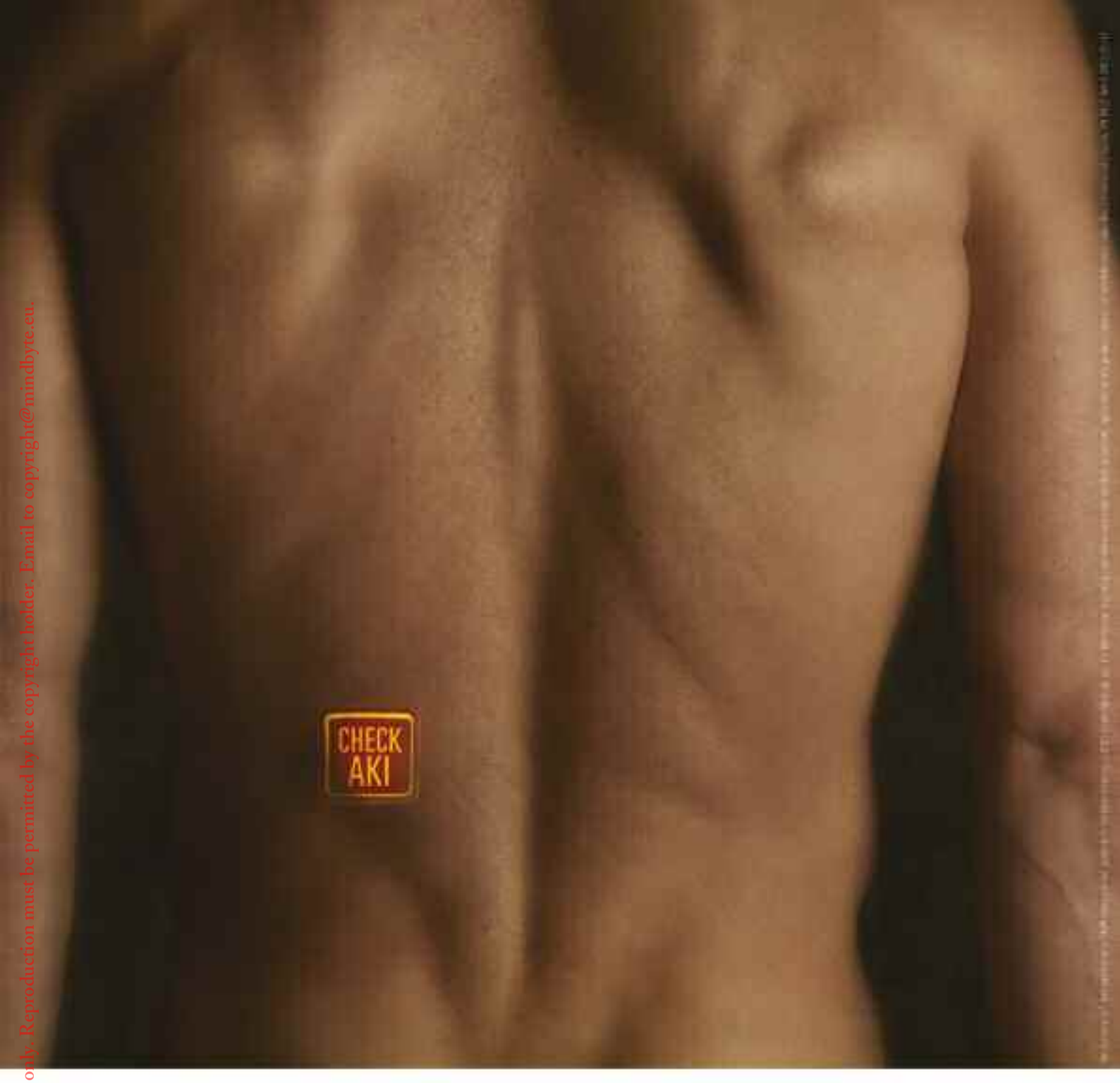

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ORGAN INTERACTION

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Organ interactions in critical illness may occur more often than we realise and physicians' failure to recognise and react to such scenarios is leading to a multitude of deaths worldwide. Management of bi-directional dysfunction and organ crosstalk has been evolving rapidly in recent years, however, meaning that increasingly complex illnesses are becoming treatable throughout geographically and economically disparate areas.

The severely injured, polytraumatised patient has taken centre-stage of late, both driving and benefiting from recent advances in trauma care. The first article in this issue of ICU Management, by Dr. Dieter Weber and Prof. Zsolt Balogh, discusses the importance of understanding organ crosstalk and polytrama to assist clinical prediction of illness severity and diagnosis. The authors provide a definition for polytrauma and highlight the complex pathophysiology of inflammation, providing a specific focus on crosstalk between the kidney and other organs. Our second article, "How to Understand Organ-Organ Interactions" focuses on polycompartment syndrome (PCS) and offers a review of the different aspects of PCS and the interactions between individual compartments. In this in-depth article, Dr. Manu Malbrain describes the key role that the abdomen plays in PCS and the effect that intra-abdominal hypertension (IAH) has on different organ systems, along with recommendations to compensate for these effects. The final article in our Cover Story, from Drs. Samir Shah and Daniel Clair, discusses critical limb ischaemia (CLI), with an emphasis on revascularisation, undertaken via open surgery or endovascular intervention as the foundation of therapy.

Our series topic this year will be Sepsis Management, and in this issue Drs. Jared Greenberg and John Kress discuss an area that is insufficiently recognised by clinicians and healthcare practitioners: healthcare-associated bacterial infections as common sources of severe sepsis among people with HIV. The authors call to mind that patients are now presenting to ICUs with greater amounts of prior healthcare exposure and thus may be more likely to develop severe sepsis from antibiotic-resistant bacterial organisms than from opportunistic infections. They suggest that current recommendations for the prevention and management of healthcare-associated infections do not account for a patient's HIV status; thus, this is an area that requires further study.

In the first Matrix Feature of the year, Prof. Jean-Charles Preiser provides an analysis of the future of glucose control in the ICU. He puts forth that the question of whether outcome will be improved by maintaining BG within a narrow range can only be answered when rapid, accurate, interference-free, inert, and cost-effective continuous glucose monitoring (CGM) systems are validated for clinical use. He concludes that CGM systems and individualised insulin algorithms are promising tools that will enable us to avoid the three domains of dysglycaemia associated with increased mortality. The second of our Matrix Features is by Drs. Michael Casaer and Dieter Mesotten. The authors recognise that there is an important discrepancy between the amount of EN we think we are giving and what is really taken up by the patient. As such, in their article, "Nutritional Failure: An Adaptive Response to Critical Illness? "they discuss the importance of nutritional intake in critical illness as well as the incidence of nutritional interruption and nutritional loss.

In this issue, the area of focus for our Management section is early warning. Dr. Heather Duncan and Peter van Manen, Managing Director of McLaren Electronics, describe a software platform that is used for Formula One telemetry, which has been adapted for use in critically ill patients. This enables real-time principal component analysis and predictive modelling, which are promising solutions for developmental physiological changes and patient specific variations.

Our interview for this issue is with Dr. Sean Bagshaw, Clinician Scientist and Associate Professor in the Division of Critical Care Medicine at the University of Alberta, Canada. Dr. Bagshaw offers an overview into the most up-to-date research in the field of acute kidney injury and also continues on the topic of organ crosstalk by telling us which organ interactions he thinks are posing the greatest challenge to physicians.

Italy is the country of focus with Drs. Lorenzo Ball and Maria Vargas along with Prof. Paolo Pelosi discussing an area of intensive care in which Italy holds antique tradition: the tracheostomy. Optimisation of percutaneous and surgical tracheostomy techniques is one of the challenges of modern ICU management and different approaches have been developed throughout Europe. In this article, authors analyse the results of the Italian experience in tracheostomy practice, matching them with the European context.

Please send your responses to me at **editorial@icu-management.org.**

Jean-Louis Vincent

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RESEARCH NEWS

New Drug Reduces Heart Damage, Study Suggests

A single dose of an investigational anti-inflammatory drug called inclacumab significantly reduces damage to heart muscle during angioplasty, a recent international clinical trial has found.

The study, which was led by Dr. Jean-Claude Tardif, Director of the Research Centre at the Montreal Heart Institute, affiliated with the University of Montreal, was presented at the American College of Cardiology conference, San Francisco, on 10 March.

To study the effects of the drug, Dr. Tardif and his team administered a single dose of inclacumab to patients and then measured their levels of troponin 1, which is a marker used clinically to diagnose heart attack. They found that inclacumab reduced troponin l levels by 24%.

The trial involved 530 patients with myocardial infarction whose median age was 61, and 78.9% of whom were men. Patients were randomised to receive an infusion of inclacumab at 20 mg/kg, inclacumab at 5 mg/kg, or placebo one to 24 hours before angioplasty. Markers for heart damage were then measured at eight, 16 and 24 hours after angioplasty.

"Inclacumab could indeed become an integral part of the therapeutic arsenal of modern cardiology if we can reproduce these results in subsequent studies. We could use the drug for a broader patient population, or for all patients who present with a heart attack, but this will require further study," explained Dr. Tardif.

Each year, approximately 35,000 coronary artery angioplasty procedures are conducted in Canada to treat atherosclerosis, while more than one million are conducted in the US. Atherosclerosis occurs when the arteries are obstructed with deposits of fat (cholesterol), calcium and cellular waste, and over time lose their elasticity and narrow, thus slowing down or blocking blood flow. Resulting complications, such as angina, heart attack and stroke, ultimately call the need of an angioplasty, which is a percutaneous intervention that dilates the narrowed artery to re-establish blood flow. However, heart tissue can become damaged during an angioplasty, and an inflammatory cascade can lead to other complications.

Inclacumab is an antibody that blocks P-selectin, a molecule that drives inflammation and plays an important role in vascular disease. A single dose of inclacumab may provide benefits, stressed Dr. Tardif.

Source:University of Montreal via ScienceDaily

Diabetes Medication May Prevent Patients from Developing Heart Failure

Commonly prescribed to lower blood sugar in diabetic patients, GLP-1 medications appears to also protect these patients from developing heart failure, according to a study at Henry Ford Hospital in Detroit.

The retrospective study looked at 4,427 diabetic patients who were taking blood-sugar-lowering medications at Henry Ford Hospital between January 1, 2000 and July 1, 2012. Of these patients, 1,488 were taking GLP-1 medications (glucagon-like peptide-1 analogs and dipeptidyl peptidase-4 inhibitors) and 2,939 were not.

Over an observation time of 663 days, there were 281 hospitalisations, of which 184 were due to heart failure, and 158 deaths. The researchers also looked into hospitalisations and deaths from other causes.

Results were adjusted for factors such as gender, age, race, coronary disease, heart failure, duration of diabetes, and the number of anti-diabetic medications taken, in order to identify the effect specifically attributable to taking GLP-1 medications.

Use of GLP1 medications was associated with a reduced risk of hospitalisation for heart failure or any other reason, as well as fewer deaths.

"Diabetic adults die of heart disease two to four times more than those without diabetes," said lead investigator of the study Dr. David Lanfear. "These preliminary results look very promising," he said, adding: "However, this was a retrospective study and this subject needs further investigation."

There are more than 25 million adults and children in the US with diabetes, according to the American Diabetes Association. The ADA estimates that nearly 80 million people may be pre-diabetic, with nearly two million new cases diagnosed in adults in 2010.

Source:Henry Ford Health System via ScienceDaily

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DISCUSSION & QUESTIONS

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POLYTRAUMA AND ORGAN CROSSTALK

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Trauma is a leading cause of death and disability around the globe (World Health Organization, 2008). Its management is evolving rapidly and today offers previously unseen levels of care. Increasingly complex injuries are becoming salvageable, both in civilian and military settings, and throughout geographically and economically disparate areas. The severely injured, polytraumatised patient is centre-stage, both driving and benefiting from recent advances in trauma care. This article focuses on the polytraumatised patient, and the pathophysiology of the systemic implications and sequelae from these injuries.

Traditionally, multiple anatomical injuries were thought and considered as independent events and concepts. However, recent research points towards far more complicated and interacting systems, such that individual injuries can no longer be regarded in isolation (Gruen et al. 2012). Rather, the trauma stimulus manifests individual anatomical injuries, but triggers a whole body, inflammatory phenomenon, which may herald morbidity and mortality well beyond what simple summation of the individual injuries would suggest. Organ crosstalk is central in these events. Improved understanding of these events may assist clinical prediction of their severity and their diagnoses, as well as guide appropriate timing of intervention.

Definition of Polytrauma

The term polytrauma is used liberally among clinicians, and is also common in trauma literature. However, there remains little consensus on its precise definition (Butcher et al. 2009). Usually, the term is used to convey a degree of seriousness, and it is used where there are injuries affecting multiple anatomical regions, in combination with a physiological compromise. There are necessarily both anatomical and physiological aspects in the definition of polytrauma. While a loose definition is not a major issue among casual communication among clinicians, a more strict definition is essential for research, education, clinical resource allocation and the planning of trauma care (Butcher et al. 2009).

A practical and useful definition of polytrauma needs to be easy to apply, reproducible, and accurate. Furthermore, it needs to be measurable early in clinical care to be clinically relevant. In a recent review, our centre proposed a definition for polytrauma as two body regions with an anatomical injury score ≥3 in addition to a measurable systemic inflammatory response syndrome (SIRS) on at least one day during the first three days of admission (Butcher et al. 2009).

The systemic inflammatory syndrome is proposed as a surrogate marker of such physiological derangements, and characterises the polytrauma patient (Butcher et al. 2013). However, as severe anatomical injury in two body regions is almost uniformly associated with SIRS, this anatomical injury pattern alone could be sufficient in defining polytrauma, and alleviate the need to calculate daily SIRS scores.

> *"These three pillars—severe injury, physiological compromise, and remote or uninjured organ dysfunction—in the definition of polytrauma highlight the importance of organ crosstalk in the mechanism of post-injury organ failure"*

The physiological derangements encountered in polytrauma patients distinguish these patients beyond their anatomical injuries. Above certain anatomical injury thresholds, independent physiological derangement becomes evident (Butcher et al. 2013). The severity of the inflammatory syndrome that drives this pathophysiology varies, but all the patients experience inflammatory reactions and their consequences, beyond those that are attributable to the anatomical injury alone.

In summary, polytrauma is best described by severe, multiple region anatomical injury with associated physiological derangement. The anatomical injury to certain organs and the associated physiological compromise put uninjured

organs at risk of organ dysfunction or failure. These three pillars—severe injury, physiological compromise, and remote or uninjured organ dysfunction—in the definition of polytrauma highlight the importance of organ crosstalk in the mechanism of post-injury organ failure.

The Inflammation of Trauma

Trauma stimulates an inflammatory response (Gruen et al. 2012). The precise triggers and methods of its activation, its subsequent pathological behaviour, and its complete clinical manifestations are complex and remain incompletely understood; these areas continue to be the subject of intense research. Improved pathophysiological understanding will hopefully translate into novel treatment strategies aimed at modulating these responses for the benefit of the patient (Namas et al. 2009).

It is clear that the initial trigger for inflammation arises due to the mechanical forces exerted on the body during the trauma event. Through tissue injury, and perhaps exacerbated by associated shock, cellular mechanisms trigger the release of a large number of inflammatory mediators to act on the immune system through both the innate and adaptive pathways (Gruen et al. 2012). These pathways and their associated systems normally exist for the purposes of tissue healing and restoration of physiological homeostasis after injury. However, in polytrauma patients, these systems may become overwhelmed and descend into a vicious cycle, leading to dysfunctional and maladaptive consequences. Positive feedback loops resulting in runaway reactions are seen in multiple pathways, such as with the alarmins released by the initial tissue injury, and also by the immune response activation (Namas et al. 2009).

Clinically, the inflammatory response may be first detected by observation of the four clinical parameters that define the SIRS (Butcher et al. 2013). If the inflammation is more severe, physiological measures of organ failure will manifest. Thus, there is a progression from SIRS to severe SIRS (defined as the presence of organ dysfunction), then to multiple organ dysfunction syndrome, and ultimately to multiple organ failure syndrome, and death. In this progression there is a gradual and accumulating loss of organ function. The inflammatory processes affect all the organs of the body, and are physically remote to the local inflammatory reactions in the organs exposed to the mechanical injury of the initial stimulus (White et al. 2011).

The magnitude of the inflammatory response to trauma is influenced by multiple factors, which are summarised in Table 1. These include the demographic and genetic background of the patient, the severity of the shock associated with the trau-

Table 1. Variables Affecting the Magnitude of Inflammation

1. The Magnitude of Tissue Injury:	Injury severity Injury pattern
2. Patient Factors:	Genetic predisposition Age Gender Co-morbidities/medication
3. Shock Factors:	Severity of shock Length of hypoperfusion
4. Treatment Factors:	Magnitude of resuscitation Quality/type of resuscitation Second hits/interventions

ma presentation, the extent of tissue injury, and the treatments received. Data are available to demonstrate different inflammatory responses according to patient age (Panda et al. 2009) and gender (Angele et al. 2000). The response may also be influenced by individual genetic variations. Similarly, the patient's pre-existing medical conditions and associated treatments will affect the situation. In terms of the treatments, these may be divided into those targeting the resuscitation in general, and those being trialled to modify the inflammatory response in the hope of improved outcome. In the former case, an excellent example where recently improved understanding has changed practice is the former use of large volumes of crystalloid during initial resuscitation. The adverse impact that these infusions have on inflammation is now well observed, and as a result, large volume crystalloid infusions are no longer routine (Gruen et al. 2012). In the case of treatment for targeting inflammatory pathways, the differential effect of tranexamic acid, depending on the time of administration (CRASH-2 Collaborators, 2011), may potentially be the result of differences in the inflammatory processes in patients before and after three hours.

Crosstalk Between the Kidney and Other Organs

Acute kidney injury (AKI) in shocked patients was historically thought to be the result of reduced renal perfusion. However, in the hyperdynamic circulation associated with a SIRS, an increased total renal perfusion is actually observed (White et al. 2011). Instead of being a total organ perfusion issue, the AKI is manifested by local alterations in the renal microcirculation, and activation of renal cell apoptosis. This appears to be the result of signals originating from soluble and cellular inflammatory mediators from both local and distant sources (White et al. 2012).

The diagnosis of AKI in a septic patient is associated with an increase in morbidity and mortality beyond that predicted purely by the renal dysfunction (White et al. 2011). Indeed, renal replacement therapy would otherwise be able to ameliorate this problem. The worsened clinical outcome arises because AKI usually occurs hand in hand with other organ dysfunction (presumably the result of similar inflammatory processes in other organs), and because the AKI affects other organs. There is crosstalk between the kidney and these other target organs in both directions. The heart, lung, brain, liver and intestines have all been demonstrated to be intimately involved in these crosstalk signals (White et al. 2012).

> *"Integral to this inflammatory response is a well-coordinated system of communication, by neural and endocrine means, involving tissues of all sizes, from individual cells to entire organs"*

To provide an example, the effect of AKI on the lung has been the focus of research for some time; it is well observed that patients with AKI often develop an acute lung injury (ALI) (White et al. 2012). The excess mortality associated with this, as well as the pathophysiology of the ALI, cannot be accounted for merely by the volume overload associated with the AKI. Changes in pulmonary vascular permeability as well as alterations in salt and water transportation through the air-pneumatocyte interface have been demonstrated secondary to AKI. Because of these alterations, there is decreased clearance of alveolar fluid and the lung becomes oedematous. Furthermore, pneumatocyte apoptosis is increased in ALI, and there is an organ-wide increase in local cytokine concentration. Then, in turn, the ALI releases further signals, and it is suggested that the acute kidney and lung injuries may form a self-propagating, vicious cycle (White et al. 2012).

As another example, the role of the intestine in patients with AKI is also the intense focus of research. Here, alterations in the microvascular milieu result in increased epithelial permeability, effecting changes in the interaction between the host and the pathogens in the intestinal lumen (White et al. 2011). Toxins may reach the lymphatic channels more easily, and reach the systemic circulation easily through lymphatic flow. Aldosterone is noted to upregulate a potassium channel regulator in the colon, and may explain the increased colonic potassium excretion that is seen in patients with AKI (White et al. 2011).

Conclusion

Modern polytrauma care draws on the recent developments in the understanding of the complex pathophysiology of inflammation, though the situation remains incompletely understood. The current definition of polytrauma acknowledges that there be presence of significant injuries in multiple anatomical areas, but also stresses the incidence of a systemic inflammatory response in these patients. This definition reflects the central role that inflammation plays in polytraumatised patients. The inflammatory phenomenon is a whole body process, with complex interactions between multiple organs. Integral to this inflammatory response is a well-coordinated system of communication, by neural and endocrine means, involving tissues of all sizes, from individual cells to entire organs. It appears that where a certain threshold of initial injury is exceeded, the inflammatory pathways may become overwhelmed and dysfunctional, no longer facilitating the normal healing response and returning to physiological homeostasis for which they are designed.

These new understandings have led to a paradigm shift from the focus on individual anatomical injuries to an appreciation that the patient's pathophysiology is centre-stage. To minimise the impact of these inflammatory processes, that may become overwhelmed and detrimental to the patient's health, careful coordination of surgical procedures alongside the intensive medical therapies in resuscitation is required. As more understanding of these complex pathways is obtained, we hope novel therapeutic strategies will emerge to assist modulation of dysfunctional inflammation. ■

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HOW TO UNDERSTAND ORGAN-ORGAN INTERACTIONS

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A compartment syndrome (CS) is defined as increased pressure in a closed anatomic space which threatens the viability of enclosed and surrounding tissue (Malbrain et al. 2006). Within the body there are four major compartments: the head, the chest, the abdomen and the extremities. Within each compartment, individual organs can be affected by a CS. As such, orbital CS, cardiac CS, hepatic CS, renal CS and pelvic CS have all been described separately within this paper. This review will discuss the different aspects of PCS and the interactions between individual compartments.

Introduction

A CS can have many causes and can develop within many disease processes, but most importantly it is often related to massive fluid loading in the setting of capillary leak leading to second and third spacing of fluids. This fluid accumulation will lead to organ oedema and organ dysfunction. The abdominal compartment has unique anatomical properties because it is "up-stream" from the extremities and "down-stream" from the chest. Therefore, it may influence the pathophysiology of other compartments as well. The presence of a CS often plays a role when we are dealing with therapeutic dilemmas or conflicts. A therapeutic conflict is a situation where each of the possible therapeutic decisions carries some potential harm. In high-risk patients, the decision about fluid administration is taken within this context. Therapeutic conflicts are the biggest challenge for protocolised cardiovascular management in anaesthetised and critically ill patients, where our decisions can make the most difference (Kavanagh and Meyer 2005; Malbrain et al. 2012).

Scalea, with colleagues, was the first to introduce the term multiple CS in a study of 102 patients with increased intra-abdominal (IAP), intrathoracic (ITP), and intracranial pressure (ICP) after severe brain injury (Scalea et al. 2007). He suggested that different compartments within the body are not isolated and independent entities but instead are closely connected. Because the term multiple CS is nowadays mostly used in relation to multiple limb trauma with CS, needing fasciotomy, the term polycompartment syndrome (PCS) was finally coined in 2007 and proposed in order to avoid confusion (Malbrain and Wilmer 2007). Organ-organ interactions, and thus also the presence of a PCS, may occur more often than we realise in real life. Table 1 lists some possible scenarios.

Table 1. Clinical Examples of Organ-Organ Interactions and Polycompartment Syndrome.

	Polycompartment syndrome presence	Treatment
Case scenario 1	A patient who was in a car accident and has blunt abdominal trauma develops ICH and worsening neurologic function due to spleen rupture with ACS.	Neurologic improvement after abdominal decompression and splenectomy.
Case scenario 2	A patient with burns develops ACS after placement of a subclavian central venous line (IAP → 20 mmHg on continuous tracing). This is followed by acute respiratory failure due to tension pneumothorax and ACS.	Respiratory and haemodynamic function improve after placement of a chest tube; moreover, IAP returns to normal.
Case scenario 3	A haematologic patient with graft versus host disease of the bowel develops abdominal hypertension related to infection with clostridium difficile and toxic megacolon.	
Case scenario 4	A haematologic patient with chronic myeloid leukemia and splenomegaly develops signs and symptoms of dyspnea related to pulmonary hypertension on transthoracic cardiac ultrasound.	After splenectomy, abdominal hypertension normalises and the pulmonary hypertension disappears.
Case scenario 5	A patient with a ventriculoperitoneal shunt develops headache in relation to shunt dysfunction because of obstipation and abdominal hypertension.	
Case scenario 6	A patient with morbid obesity has signs and symptoms of ideopathic ICH (pseudotumor cerebri).	The symptoms disappear after bariatric surgery and weight loss.
Case scenario 7	A patient with COPD is treated with non-invasive ventilation via mask interface. When the physiotherapist puts him into the upright position the patient has a cardiac arrest. This was related to aerophagia and gastric distension.	Only after placement of a nasogastric tube and evacuation of the air from the stomach could return of spontaneous circulation (ROSC) be obtained.
Case scenario 8	A patient with head trauma develops ICH during colonoscopy.	

ACS: abdominal compartment syndrome, **ICH:** intracranial hypertension, **IAP:** intra-abdominal pressure, **COPD:** chronic obstructive pulmonary disorder

Pathophysiology of the Four Major Compartment Syndromes

An increased compartment pressure (CP) will increase venous resistance and decrease perfusion pressure in the implicated compartment, but will also affect other compartments (Figure 1). The resulting impact on end-organ function and viability can be devastating.

• 1. Intracranial Compartment Syndrome

Any change in volume in the head leads to a reciprocal change in the size of the remaining components, and results in an increase in ICP and a decrease in cerebral perfusion pressure (CPP), defined as mean arterial pressure (MAP) minus ICP (CPP=MAP–ICP). Treatment options for intracranial hypertension (ICH) either focus on lowering ICP or raising CPP. However, fluid therapy used to support CPP may exacerbate visceral oedema, promote ascites and increase IAP, which in turn can further increase ICP (De Laet et al. 2007). In patients with severe traumatic brain injury, treatment decisions may

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result in a vicious cycle that increases pressures in various compartments (Scalea et al. 2007). Therefore, PCS should be considered present in patients with multiple injuries, with increased ICP, who do not respond to conventional therapy (Scalea et al. 2007).

• 2. Thoracic Compartment Syndrome

Thoracic CS (TCS) has traditionally been described in patients undergoing cardiac surgery (Kaplan et al. 1996; Rizzo and Sample 2003). TCS is rare in patients with thoracic trauma due to the limited survival when injuries are significant enough to result in massive tissue oedema after resuscitation. In the ICU, increased intrathoracic pressure (ITP) is most commonly related to sepsis, capillary leak, fluid resuscitation, positive pressure ventilation with high positive end-expiratory pressure (PEEP) or dynamic hyperinflation, pneumothorax, COPD with auto-PEEP, diminished chest wall compliance (e.g. morbid obesity or eschars), lung fibrosis and ARDS. Rising ITP and mean or peak inspiratory pressures during thoracic wall closure may serve as an early warning that a patient is at risk for TCS. Since increased ITP, like raised IAP, is most commonly related to excessive fluid resuscitation, both frequently coexist (Talmor et al. 2006; Valenza et al. 2007). Some key issues to remember are: best PEEP should be set to counteract ITP and IAP whilst at the same time avoiding over-inflation of already well-aerated lung regions (best PEEP (cmH_2O)=IAP (mmHg)). During lung-protective ventilation, plateau pressures (Pplat) should be limited to transmural plateau pressures (Pplattm) below 35 cmH_2O (Pplattm=Pplat–ITP=Pplat–IAP/2<35 cmH_2O). Increased ITP and IAP facilitate lung oedema. Therefore, monitoring of extravascular lung water index (EVLWi) could be beneficial (Quintel et al. 2004). Spontaneous respiration and mechanical ventilation increase inspiratory and decrease expiratory IAP. Therefore, ΔIAP may indirectly predict abdominal wall compliance (Figure 2) (Malbrain and Wilmer 2007; Sturini et al. 2008).

• 3. Abdominal Compartment Syndrome

The abdomen can be considered as a closed box with partially rigid sides (spine, pelvis and costal arch) and partially flexible sides (abdominal wall and diaphragm). Since the abdominal cavity can be considered as a relatively non-compressible and primarily fluid-containing compartment, behaving in accordance to Pascal's law, the IAP measured at one point can be assumed to represent the IAP throughout the entire abdomen (Malbrain 2004; Malbrain and Jones 2006). In normal conditions, IAP ranges from 0–5 mmHg (Sanchez et al. 2001; De Keulenaer et al. 2009). The gold standard IAP measurement method is via the bladder, either by a transurethral FoleyManometer (Holtech Medical), or coupled to an AbViser valve (ConvaTec), or any homemade system (Malbrain 2004). The term abdominal CS (ACS) was first used by Fietsam and colleagues in the late 1980s to describe the pathophysiologic alterations resulting from

Figure 1. Interactions Between Different Compartments of the Body

Arrows indicate interactions between different compartments. Solid lines show direct effects by mechanical pressure forces. Dotted lines show indirect distant effects between compartments.

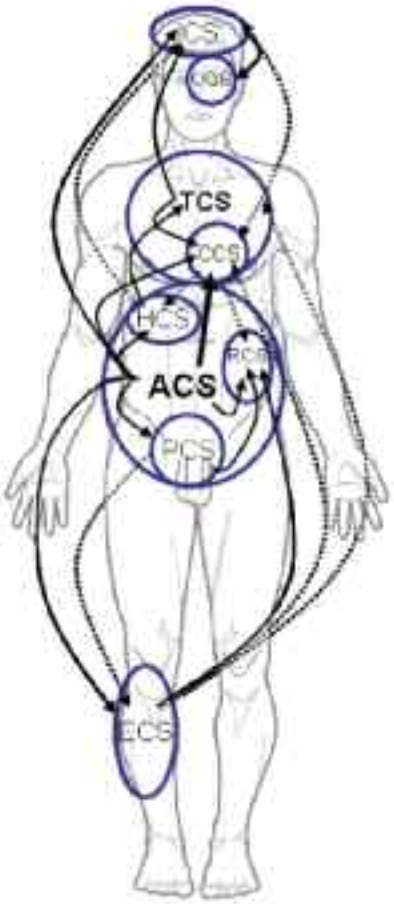
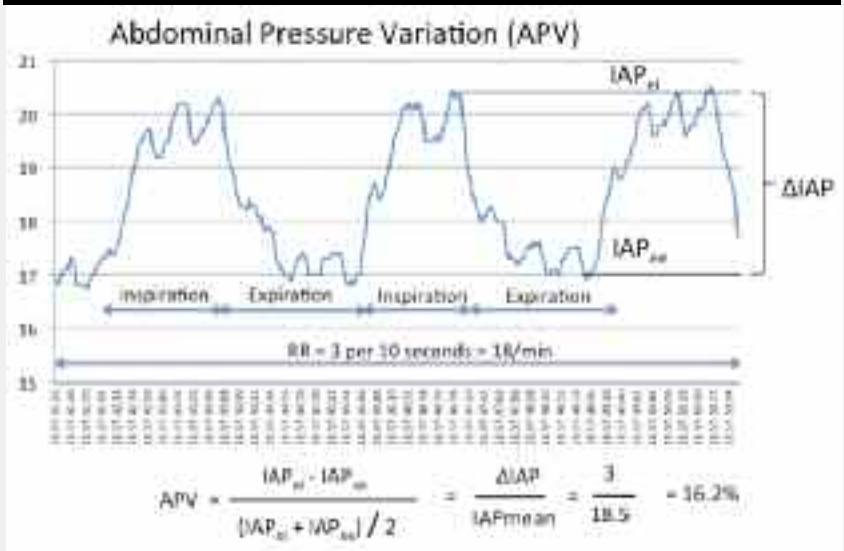


Table adapted from Malbrain and De Laet 2008.
ACS: abdominal compartment syndrome, **CCS:** cardiac compartment syndrome, **ECS:** extremity compartment syndrome, **HCS:** hepatic compartment syndrome, **ICS:** intracranial compartment syndrome, **RCS:** renal compartment syndrome, **OCS:** orbital compartment syndrome, **PCS:** pelvic compartment syndrome, **TCS:** thoracic compartment syndrome

Figure 2. Respiratory Variations of IAP are an Indirect Measurement of Abdominal Wall Compliance



A RAW data tracing of continuous IAP monitoring with CiMON (Pulsion Medical Systems, Munich, Germany) is showed in a mechanically ventilated patient showing breath-to-breath variations in IAP. Ventilator settings were: IPAP=25 cmH_2O and PEEP=5 cmH_2O. Mean IAP was 18.5 mmHg with IAP=17 mmHg at end expiration and IAP=20 mmHg at end inspiration (ΔIAP=3 mmHg). The abdominal pressure variation (APV) can be calculated as ΔIAP divided by mean IAP (i.e. 3/18.5=16.2%). Higher APV values for a given ventilator setting correspond to lower abdominal wall compliance..

IAH secondary to aortic aneurysm surgery (Fietsam et al. 1989). The World Society on Abdominal Compartment Syndrome (WSACS – www.wsacs.org) recently published consensus definitions (Malbrain et al. 2007). Analogous to the widely accepted and clinically utilised concept of CPP, abdominal perfusion pressure (APP) has been proposed as a more accurate predictor of visceral perfusion and a potential endpoint for resuscitation by considering both arterial inflow (MAP) and restrictions to venous outflow (IAP) (APP=MAP–IAP) (Cheatham et al. 2000; Malbrain 2002; Deeren et al. 2005; Cheatham and Malbrain 2006).

- **4. Limb or Extremity Compartment Syndrome**

Extremity CS (ECS) is a condition in which the pressure within a closed muscle compartment increases to a level that reduces capillary blood perfusion below the level necessary for tissue viability. Permanent loss of function and contracture may occur. Extremity CP can be measured by a needle connected to a fluid-filled pressure transducer system. Normal CP values should be <20 mmHg. This technique can be used to guide the need for surgical intervention: tissue perfusion pressure should be equal to capillary pressure minus extremity CP. ECS is especially common in obese patients and mostly results from trauma with fractures (especially of the tibia), tight plaster casts, muscle contusions, bleeding disorders, burns (with eschars), venous obstruction and arterial occlusion with post-ischaemic swelling. ECS will result in muscle compression and rhabdomyolysis, which may cause hypovolemia, acute kidney injury (AKI), coagulopathy, acute lung injury (ALI) and shock. Therefore, ECS may also have distant effects on other organs (Figure 1). In case of established ECS, the only definitive treatment is decompressive fasciotomy with muscle debridement in case of necrosis. Apart from its influence on other distant organs, extremity CP is influenced itself by increased IAP related to ACS or Pelvic CS, as both conditions diminish venous return from the extremities, promoting further limb swelling.

Pathophysiology of Subsidiary Compartment Syndromes

- **1. Orbital Compartment Syndrome**

Acute orbital CS (OCS) is a rare complication of increased pressure within the confined orbital space. An increased intraorbital pressure (IOP) may cause decreased orbital perfusion pressure (OPP) by a mechanism similar to mass lesions (OPP=MAP–IOP). OCS presents with typical signs and symptoms (eye pain, reduced ocular motility, pro-optosis, diplopia) and progressive visual deficits. Recognition and prompt treatment is of paramount importance to prevent blindness. A recent study in burn patients showed that increased IOP was significantly associated with the amount of fluids given during the first 24 hours of hospitalisation and with the presence of peri-ocular burns (Singh et al. 2008).

- **2. Cardiac Compartment Syndrome**

Within the thorax, cardiac tamponade can be considered as a specific CS. Strikingly, as little as 250 ml of fluid can cause acute cardiac tamponade. However, under chronic conditions, much greater amounts of fluid can accumulate as the cardiovascular system can slowly adjust. A similar condition arises when either ITP directly (in case of TCS), or IAP indirectly (in case of ACS) compresses the cardiac chambers. The latter is due to an upward movement of the diaphragm. In case of increased ITP or IAP, coronary perfusion pressure (CoPP) is lowered (CoPP=DBP–PAOP=DBP–ITP) (where DBP is diastolic blood pressure and PAOP is pulmonary artery occlusion pressure). Increased ITP also results in a more difficult preload assessment because invasively measured filling pressures will be falsely increased. Transmural filling pressures, calculated as the end-expiration value minus ITP may better reflect preload (Valenza et al. 2007; Ridings et al. 1995) (CVPtm=CVPee–ITP or PAOPtm=PAOPee–ITP). A quick estimate of transmural filling pressures can also be obtained by subtracting half of the IAP from the end-expiratory filling pressure (Wauters et al. 2007) (CVPtm= CVPee–IAP/2 or PAOPtm=PAOPee– IAP/2). "Volumetric" preload estimates such as right ventricular end diastolic volume index (RVEDVi) or global end diastolic volume index (GEDVi) are useful alternatives for pressure-based measurements in conditions of ITP (Malbrain and Cheatham 2004; Schachtrupp et al. 2003; Michard et al. 2003).

- **3. Hepatic Compartment Syndrome**

Because the liver is an encapsulated organ, local haematoma formation caused by trauma or bleeding diathesis (oral anticoagulants, liver cirrhosis, and so on) may compromise tissue perfusion by causing hepatic CS (HCS) (Goldman et al. 2003; Pearl and Trunkey 1999).

> *"The abdominal compartment could play a key role in the pathophysiology of acute decompensated heart failure and cardiorenal syndrome"*

- **4. Renal Compartment Syndrome**

The association between IAH and renal impairment has been known for over 150 years (Schein 2006). However, the exact (patho)physiological interplay between IAP and kidney injury has only been studied intensively in recent years (Biancofiore et al. 2003; Sugrue et al. 2006; De Laet et al. 2007). Elevated IAP significantly decreases renal blood flow and causes renal venous hypertension through pressure transduction, leading to renal dysfunction and failure (Kirkpatrick et al. 2006; Wauters et al. 2009). Oliguria develops at IAP>15 mmHg and while values >25 mmHg are associated with

anuria in the presence of normovolemia. Within the capsule of the kidney itself, local haematoma formation (caused by trauma or bleeding diathesis) may have a further adverse effect on tissue perfusion, causing a local renal compartment syndrome.

• 5. Pelvic Compartment Syndrome

In the pelvic region, three major compartments—gluteus medius-minimus, gluteus maximus, and iliopsoas—can be distinguished from the smaller compartment of the tensor fasciae latae muscle. Pelvic CS (PCS) is rare and a clear history of trauma is often lacking (Bosch and Tscherne 1992; Hessmann and Rommens 1998). It is often associated with drug and alcohol abuse, infections (necrotising fasciitis) and the use of anticoagulant therapy (Hessmann and Rommens 1998). Increased PCP may eventually increase IAP and affect kidney function due to bilateral ureteral obstruction. Moreover, massive intrapelvic haematoma with increased retroperitoneal pressure can cause renal failure. Decompressive fasciotomy of the gluteal compartment is the treatment of choice.

• 6. Cardio-Abdomino-Renal Syndrome

The abdominal compartment could potentially form a missing link in the pathophysiology of acute decompensated heart failure (ADHF) and cardiorenal syndrome. Only recently, it was shown that raised IAP is prevalent in cases of advanced heart failure with reduced ejection fraction, and that it correlates with impairment of renal function (Mullens et al. 2008). Importantly, medical treatment resulting in a decrease of IAP ameliorates renal function, and in cases of persistent high IAP, ultrafiltration might be beneficial (Mullens et al. 2008). Notably, while organ dysfunction in intensive care literature has only been described when IAP exceeds 12 mmHg, patients with ADHF already develop worsening renal function with a much lower IAP (Mullens et al. 2008). This might suggest that the underlying reserve of the kidneys to counteract increased IAP is limited in this setting. Therefore, we would like to define Cardio-Abdominal-Renal Syndrome (CARS), to emphasise the potentially important role of the abdominal compartment and splanchnic vasculature in the pathophysiology of ADHF and cardiorenal syndrome.

Table 2. Treatment Options for Compartment Syndrome

1. Improvement of compartment wall compliance
• Sedation
• Pain relief (not fentanyl)
• Neuromuscular blockade
• Body positioning
• Negative fluid balance
• Skin pressure decreasing interfaces
• Weight loss
• Percutaneous abdominal wall component separation
• Escharotomies
2. Evacuation of intracompartmental contents
• Gastric tube and suctioning
• CSF, ascites, pleural or pericardial drainage
• Rectal tube and enemas
• Chest tube and suctioning
• Endoscopic decompression of large bowel
• Colostomy or ileostomy
• CT- or US-guided aspiration of abscess
• CT- or US-guided aspiration of haematoma
• pericardectomy
3. Correction of capillary leak and positive fluid balance
• Albumin in combination with diuretics (furosemide)
• Correction of capillary leak (e.g. antibiotics, source control)
• Colloids (Hypertonic-Voluven® instead of cristalloids)
• Dobutamine (not dopamine)
• Dialysis or CVVH with ultrafiltration
• Ascorbic acid in burn patients
4. Specific therapeutic interventions
• Continuous negative external pressure (VAC®)
• Targeted compartment perfusion pressure
5. Rescue therapy
• ICS: decompressive craniectomy
• ACS: decompressive laparotomy
• TCS: decompressive sternotomy
• ECS: decompressive fasciotomy
• PCS: decompressive gluteal fasciotomyy
• RCS: renal decapsulation
• HCS: hepatic decapsulation
• CCS: decompressive pericardiotomy
• OCS: orbital decompression

CSF: cerebrospinal fluid, **CT:** computed tomography, **US:** ultrasound, **CVVH:** continuous veno-venous haemofiltration; **ICS:** intracranial compartment syndrome, **CCS:** cardiac compartment syndrome, **RCS:** renal compartment syndrome.

Clinical Management

The management of patients with PCS is based on three principles (Mayberry 2006; Parr and Olvera 2006):

1. Specific medical and surgical procedures to reduce CP (Table 2), including:
   - Improvement of compartment wall compliance;
   - Evacuation of intracompartmental contents;
   - Correction of capillary leak and positive fluid balance;
   - Specific treatments; and
   - Rescue treatments.
2. General and organ support (intensive care) of the critically ill patient.
3. Optimisation and prevention of specific adverse events after surgical decompression (ischaemia/reperfusion).

Take Home Message

While PCS is uncommon, its consequences can be significant. The abdomen plays a central role, and the effect of IAH on different organ systems has been described, along with recommendations to compensate for these effects. The abdominal compartment could play a key role in the pathophysiology of acute decompensated heart failure and cardiorenal syndrome. The ultimate treatment goal of PCS is not only to decrease CP, but also to improve organ function and to decrease mortality. ■

For references, please send a request to editorial@icu-management.org

DIAGNOSIS AND MANAGEMENT OF CRITICAL LIMB ISCHAEMIA

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Critical limb ischaemia (CLI) represents the most advanced state of peripheral disease within the spectrum of chronic limb ischaemia. Rest pain, ischaemic ulceration, and gangrene attributable to vascular disease define the range of findings within CLI. Although dwarfed by the prevalence of asymptomatic peripheral vascular disease and intermittent claudication, CLI carries substantial social and economic costs.

The frequency of cases of critical limb ischaemia—estimated at 500 to 1000 cases per million—and high morbidity and mortality are under appreciated (Norgren et al. 2007). Consider, as an example, the expected outcome at one year: 25% mortality and 30% amputation, leaving only 45% alive with both limbs (Norgren et al, 2007). It is worth emphasising that critical limb ischaemia is a subset of chronic limb ischaemia and therefore distinct from acute limb ischaemia, with which it is sometimes confused. Clearly there is some overlap and patients with critical limb ischaemia will on occasion develop so-called acute-on-chronic limb ischaemia (e.g. the patient whose limb is entirely dependent on collateral flow and has had symptoms of rest pain may develop acute limb ischaemia from sudden occlusion of the collaterals), but the overall distinction is important because of its implications for approach and management.

It is self-evident that any number of non-vascular conditions may mimic rest pain or ischaemic ulceration, ranging from neurologic conditions (e.g. spinal stenosis) to malignancy and vasculitis. As such, all diagnoses must be confirmed to have a vascular aetiology. The most basic technique relies on ankle-brachial index, which is typically of a value lower than 0.4. Alternative confirmatory tests include ankle pressures less than 50 mmHg and toe pressures less than 30 mmHg. Note that meeting the precise cutoffs for objective testing listed above is not technically necessary (e.g. a patient with an ABI>0.4 may still have CLI), but measurements that deviate substantially should raise the possibility of a non-vascular aetiology. Nevertheless, the evaluation of the diabetic patient is more challenging as objective pressure measurements can be falsely elevated due to calcification within the arteries, a finding which is common in the diabetic with vascular disease.

> *"Revascularisation, undertaken via open surgery or endovascular intervention, remains the foundation of therapy for CLI"*

Diagnosis

The cornerstone of diagnosis is a patient history consistent with rest pain or the presence of ulcerations or frank gangrene. Patients with rest pain typically describe pain in the toes or over the metatarsal heads in the absence of any exertion. Placing the feet in a dependent position, which is believed to augment blood flow, may partly or fully resolve these symptoms. Nighttime calf and thigh cramps and discomfort (common in the elderly population) do not represent rest pain. Many of these patients will also report a history of claudication in the past, as this is often a precursor to critical limb ischaemia. It is important to note that a significant percentage of patients with peripheral arterial disease have diabetes as well. For example, in the prospective PREVENT III trial by Conte and colleagues, 64% of patients with critical limb ischaemia who were undergoing vein bypass had diabetes. The associated neuropathy may make it very difficult to determine whether the patient has true critical limb ischaemia (Conte et al. 2005).

After diagnosis, it is imperative to define the extent and distribution of disease. Digital subtraction angiography (DSA) is widely held to be the "gold standard" test.

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The advantages of high imaging quality and the ability to simultaneously intervene must be balanced against the possibility of complications from the test itself (e.g. access site injury, distal embolisation, dissection, and so forth), renal toxicity, and radiation exposure. Carbon dioxide angiography mitigates the risk of renal injury, but at the cost of imaging quality. Computed tomographic angiography (CTA) is the noninvasive analogue to standard angiography and also involves iodinated contrast administration and radiation exposure. CTA imaging quality is comparable to angiographic images and in some respects better with the use of 3-D reconstructions, which can provide significantly more information than 2-D angiography. Small vessel calcification and metal may produce significant artifact. Magnetic resonance angiography (MRA) avoids radiation and iodinate contrast; however, it often overestimates the degree of stenosis. Furthermore, not all patients are eligible for MRA: many implants (e.g. pacemakers) may not be compatible, and gadolinium is still contraindicated for those with severe renal insufficiency because of the risk of nephrogenic systemic fibrosis. Arterial duplex is a noninvasive modality that does not involve contrast or radiation. It is most useful in infrainguinal imaging. Obesity or significant limb oedema, painful ulcers, and dense vascular calcification may degrade image quality, however. Although blanket recommendations regarding imaging selection are impossible to make given the varying advantages and disadvantages of each modality, we generally prefer CTA or DSA.

Management

In contradistinction to the management for intermittent claudication, revascularisation remains the mainstay of CLI therapy. This should not be misconstrued to imply that medical management is irrelevant. In fact, optimisation of cardiovascular risk factors is an essential adjunct, without which any vascular reconstruction is bound to fail. Smoking, hypertension, dyslipidemia, diabetes, and hypercoagulable states should all be optimally controlled. Specifically, goals of blood pressure less than 130/80, low-density lipoprotein (LDL) less than 100 mg/dl (or less than 70 mg/dl for higher risk patients), and haemoglobin A1C less than 7% should be sought. Three classes of medication have been shown to reduce cardiovascular morbidity and mortality associated with peripheral vascular disease: antiplatelet agents, angiotensin-converting enzyme inhibitors (ACEI), and statins (Mangiafico 2011).

Table 1. TASC II Classification of Aortoiliac Disease

A
• Stenosis of the CIA
• Unilateral or bilateral single ≤3 cm stenosis of EIA
B
• Single ≤3 cm stenosis of infrarenal aorta
• Unilateral CIA occlusion
• Unilateral single or multiple EIA stenoses with a total length of 3-10 cm without involvement of the CFA
• Unilateral EIA occlusion without IIA or CFA involvement
C
• Bilateral CIA occlusion
• Bilateral Single or multiple EIA stenoses with a total length of 3-10 cm without involvement of the CFA
• Unilateral EIA stenosis extending into the CFA
• Unilateral EIA occlusion extending into the IIA or CFA
• Heavily calcified unilateral EIA occlusion
D
• Infrarenal aortoiliac occlusion
• Diffuse aortic and bi-iliac disease
• Multiple stenosis of the unilateral CIA, EIA, CFA
• Unilateral CIA and EIA occlusion
• Bilateral EIA occlusion
• Iliac stenosis in patients with abdominal aortic aneurysm requiring open repair or other lesions demanding open aortic or iliac repair

CIA: common iliac artery, EIA: external iliac artery, IIA: internal iliac artery, CFA :common femoral artery

Vascular reconstruction may be undertaken through an open, endovascular, or hybrid approach. The Trans-Atlantic inter-Society Consensus II (TASC II) classification provides a basic framework for understanding the approach. All disease distributions in the aortoiliac and femoropopliteal regions are divided into four categories, A-D. Generally, endovascular therapy is recommended for categories A and B, while open therapy is the treatment of choice for categories C and D (Tables 1 and 2).

> *"there is clearly a need for better data to assist in decision-making regarding therapy"*

Clearly, however, decisions must be tailored to individual circumstances. Other salient characteristics that influence the final decision include lesion morphology, including eccentricity and calcification, presence of

Table 2. TASC II Classification of Femoropopliteal Disease

A
• Single stenosis ≤10 cm
• Single occlusion ≤5 cm
B
• Multiple stenoses or occlusions, all ≤5 cm
• Single stenosis or occlusion ≤15 cm without infrageniculate popliteal artery involvement
• Single or multiple lesions without continuous tibial vessels with the objective of improving inflow for a distal bypass
• Heavily calcified occlusion ≤5 cm
• Single popliteal stenosis
C
• Multiple stenoses or occlusions with a total length >15 cm
• Recurrent lesions requiring therapy after two prior endovascular interventions
D
• Chronic CFA or SFA occlusion (>20 cm with popliteal artery involvement)
• Chronic popliteal artery and proximal trifurcation occlusion

CFA: common femoral artery, SFA: superficial femoral artery

significant tissue loss in the limb, and disease across a joint, all of which would favour open intervention.

There is a dearth of high-quality evidence for revascularisation, a fact that is reflected in the absence of firm guidelines for intervention. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial is the only major randomised trial to compare surgical bypass and percutaneous intervention. Briefly, the BASIL trial examined the primary endpoints of overall survival and amputation-free survival in 452 patients with severe leg ischaemia, defined as rest pain or tissue loss with an arterial aetiology of greater than two weeks in duration, who were randomised between bypass surgery-first and angioplasty surgery-first strategies (Adam et al. 2005). Patients were enrolled from 1999 to 2004, and the trial concluded that patients with a life expectancy greater than two years benefited from open bypass while in those with a lower life expectancy and those in whom vein conduit was unavailable, percutaneous intervention should be preferred. Although a seminal trial in vascular surgery, the BASIL trial design has been widely criticised (Clair 2012) and there is clearly a need for better data to assist in decision-making regarding therapy.

Conclusion

Critical limb ischaemia—as indicated by rest pain, ulceration, or gangrene, and confirmed by objective testing to have a vascular aetiology—carries a high near-term rate of mortality or amputation. Medical management of cardiovascular risk factors is a necessary element of successful therapy. Specific medications that have been demonstrated to improve outcomes include antiplatelets, ACEI, and statins. Revascularisation, undertaken via open surgery or endovascular intervention, remains the foundation of therapy for CLI. ■

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HEALTHCARE-ASSOCIATED BACTERIAL INFECTIONS:

COMMON SOURCES OF SEVERE SEPSIS AMONG PEOPLE WITH HIV

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In this article, we discuss the emergence of healthcare-associated bacterial infections as a major source of severe sepsis among people with HIV, and recommend treatment and prevention guidelines to be heeded by clinicians and healthcare practitioners.

The long-term prognosis for people with HIV has improved since the advent of highly active antiretroviral therapy (HAART). Over this time period, in-hospital survival for critically ill people with HIV has improved as well. Surprisingly though, studies have not consistently found HAART use prior to critical illness to be a predictor of intensive care unit (ICU) survival (Huang et al. 2006). Instead, ICU outcomes have improved mainly because admission patterns for people with HIV have changed with the development of HAART (Casalino et al. 2004; Pacheco et al. 2009). Patients are now less likely to be admitted for respiratory failure from Pneumocystis jirovecii pneumonia (PCP), which carries a particularly high mortality. They are more frequently admitted for sepsis and exacerbations of chronic illnesses, which have better short-term prognoses (Akgun et al. 2011). Continuing to improve outcomes for members of this population necessitates a better understanding of why people with HIV are now requiring ICU care.

At Claude Bernard Hospital, Paris, France, admissions for sepsis increased from 16% to 22% with the advent of HAART (Casalino et al. 2004). In addition to there being a greater number of admissions for sepsis, multiple studies have identified sepsis as a predictor of short and long-term mortality after ICU admission. Patients with HIV who are admitted to an ICU with sepsis have a two to four times greater risk of death than people with HIV who are admitted to an ICU for a different reason. (Mrus et al. 2005; Croda et al. 2009; Japiassu et al. 2010; Chiang et al. 2011). In one cohort, severe sepsis was the dominant predictor of 28-day and six-month mortality (Japiassu et al. 2010).

In the current HAART era, people with HIV are spending more time in healthcare settings because they are living longer, and they have an increased risk of developing a number of chronic diseases. Specifically, people with HIV have a greater incidence of chronic lung diseases than those without HIV (Crothers et al. 2011). Co-infection with Hepatitis B or C increases the risk of chronic liver disease (Verucchi et al. 2004), and HAART-related medication toxicities may lead to metabolic complications and cardiovascular disease (Friis-Moller et al. 2003). Chronic kidney disease is also more common in people with HIV because of HIV-associated nephropathy and co-morbid conditions such as diabetes and hypertension (Wyatt, 2012). Finally, a number of malignancies have

> *"At San Francisco General Hospital, California, US, the frequency of ICU admissions for sepsis increased from 10% to 20% from 1981 to 2003 (Powell et al. 2009)."*

Shifting Admission Patterns

Recent studies have found that sepsis is a more common reason for ICU admission for people with HIV than it was at the beginning of the AIDS epidemic. At San Francisco General Hospital, California, US, the frequency of ICU admissions for sepsis increased from 10% to 20% from 1981 to 2003 (Powell et al. 2009). At Bichat-

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greater prevalence in the HIV population (Pinzone et al. 2012).

Healthcare-Associated Infection

As people with HIV are receiving more healthcare during their lifetimes, the spectrum of bacterial organisms causing severe sepsis is likely changing. The term "healthcare -associated infection" has been coined to reflect an infection that may be acquired in the community, but has a similar antibiotic-resistant pattern to an infection contracted in the hospital. Patients are at greater risk for antibiotic-resistant bacterial infections if they were hospitalised in the previous 90 days, reside in nursing homes or long-term-care facilities, or receive chronic haemodialysis or intravenous therapy (Kollef et al. 2008). In a study by a public hospital in Atlanta, Georgia, focusing only on ICU admissions for sepsis, there were 194 acute infections among the 125 patients studied (Greenberg et al. 2012). The majority of these infections were nosocomial or healthcare-associated. Respiratory-tract infections accounted for 53% of acute infections and bloodstream infections accounted for 24% of acute infections. Japiassu and colleagues described a similar population of patients with HIV and sepsis in their ICU; the majority of infections were nosocomial and most were pulmonary or primary bacteraemia (Japiassu 2010).

Prevention and Management of Infection

Current recommendations for the prevention and management of healthcare-associated infections do not account for a patient's HIV status (Kollef et al. 2008). The general approach for any patient begins with identifying whether he or she is at risk for a healthcare-associated infection. The strategy then involves early initiation of broad-spectrum antibiotics that are effective against methicillin-resistant Staphylococcus aureus (MRSA) and multidrug-resistant gram-negative bacteria. Empirical therapy for antibiotic-resistant Enterococci or fungal organisms depends on the clinical situation. The purpose of this approach is to ensure adequate antimicrobial coverage against the infecting organism, as mortality increases with delay in appropriate antibiotic administration. As the patient's clinical status evolves in response to therapy and culture results become available, the spectrum of antibiotic coverage should be narrowed to reduce the chance of breeding new antibiotic-resistant organisms (Kollef et al. 2008).

For critically ill people with HIV and severe infections, it is unknown whether initiating HAART in the ICU as adjunctive therapy is of benefit. There are no randomised control trials or consensus guidelines on the use of HAART in the ICU. In fact, clinicians are often hesitant to start a patient on HAART for a number of reasons. Firstly, many antiretrovirals can only be administered enterally and gastrointestinal absorption may be variable in ICU patients. Secondly, drug toxicities may be more likely to occur as antiretrovirals interact with common ICU medications, and resulting organ failure may lead to reduced medication clearance. Finally, there is some concern that beginning HAART may lead to immune reconstitution inflammatory syndrome, which could worsen the patient's condition in the short term (Huang et al. 2006).

There are no recommendations for preventing nosocomial or healthcare-associated infections specifically for patients with HIV. Prior to the development of HAART, it was well documented that people with HIV were at greater risk of developing nosocomial infections than people without HIV (Goetz et al. 1994; Stroud et al. 1997). Thus, clinicians caring for patients with HIV should incorporate measures to reduce the risk for nosocomial infections, such as evidence-based practice bundles and timely removal of unnecessary intravenous catheters and indwelling lines (Berenholtz et al. 2011; Weber et al. 2011). It is also true that immune dysfunction increases the risk of developing bacterial infections. In a large, multicentre epidemiological study, lower CD4 cell counts were associated with increased risk of developing a serious bacterial non-AIDS infection (Sogaard et al. 2013). Utilising resources to improve HAART compliance in patients with advanced AIDS who are frequently hospitalised would likely have a large impact on reducing the number of ICU admissions for nosocomial or healthcare-associated infections.

> *"Utilising resources to improve HAART compliance in patients with advanced AIDS who are frequently hospitalised would likely have a large impact on reducing the number of ICU admissions for nosocomial or healthcare-associated infections"*

Conclusion

In conclusion, the landscape of ICU admissions for people with HIV has changed with the advent of HAART. Sepsis is a more frequent diagnosis for admission to the ICU and is a risk factor for short- and long-term mortality. Patients are now presenting to ICUs with greater amounts of prior healthcare exposure and thus may be more likely to develop severe sepsis from antibiotic-resistant bacterial organisms than from opportunistic infections. Further studies describing the burden of healthcare-associated infections in different HIV communities are warranted. In addition, further investigation into ways to prevent and treat healthcare-associated infections, specifically for patients with HIV, would provide clinicians with more guidance. In the meantime, we recommend that clinicians follow the same guidelines for the treatment of healthcare-

associated infections regardless of a patient's HIV status. We also suggest that clinicians focus on improving compliance with HAART in patients who frequently require healthcare, and that invasive procedures and indwelling catheter use is limited so as to reduce the risk of healthcare-associated infections and improve outcomes for critically ill patients with HIV in general. ■

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THE FUTURE OF GLUCOSE CONTROL IN THE ICU

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Continuous glucose monitoring systems and therapeutic algorithms adapted to the actual insulin sensitivity are needed to prevent hypoglycaemia, hyperglycaemia and high glucose variability, all associated with poor outcome in intensive care unit (ICU) patients.

Introduction

A decade after the publication of the landmark Leuven I trial (Van den Berghe et al. 2001), the issue of glucose control in the ICU is still a matter of intense debate. After the initial enthusiasm inspired when authors of the Leuven I trial reported a 40% relative decrease in mortality by tight glucose control (TGC), several confirmatory trials failed to verify this benefit (Marik and Preiser 2010). A major difference between the Leuven trials and other studies is that a much lower amount of intravenous calories is given in other centres than Leuven. The recent "Impact of Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients" (EPaNIC) trial (Casaer et al. 2011), which was performed in the same centre, demonstrated that administering early parenteral nutrition (PN), as compared to late PN, when enteral nutrition (EN) was not tolerated after one week, was in fact detrimental. In theory, the effects of TGC by intensive insulin therapy should be re-assessed when a lower caloric load is administered, in accordance with these findings.

> *"Regarding the therapeutic impact of inaccuracies in the reading of BG concentrations, error grids adapted to the actual insulin algorithms that are in use in ICUs are needed"*

Not surprisingly, guidelines for glucose control (GC) swung from the recommendation of TGC to a more liberal threshold, i.e. a target range for blood glucose (BG) below 150 mg/dl (Jacobi et al. 2012) or even 180 mg/dl (Dellinger et al. 2013; Qaseem et al. 2011). In fact, a universally acceptable upper threshold for BG is probably elusive (Ichai and Preiser 2010) for several reasons, either related to the patients' underlying condition (diabetes, neurological conditions or trauma, cardiac surgery) or to organisational aspects (nurse staffing, type and accuracy of glucose meter in use).

Very interestingly, this decade of debates brought several advances to the field:

1. Associations between each of the three domains of dysglycaemia—hypo, hyper, high variability—and poor outcome;
2. Technological advances in the monitoring of blood glucose in ICU; and
3. Development of automated, computer-assisted therapeutic insulin-algorithms.

Dysglycaemia Associations with Poor Outcome

Several investigators worldwide reported the associations between each of the three domains of dysglycemia (hypo, hyper, high variability) and poor outcome, with studies often involving a very large database (Badawi et al. 2012; Falciglia et al. 2009; Finfer et al. 2012; MacKenzie et al. 2011; Krinsley et al. 2013). At the very least, these very consistent findings indicate that each of these domains is a marker of the severity of disease. Iatrogenic components, such as insulin therapy, rapid correction of hypoglycaemia, steroids, and catecholamines, were also identified as causes of dysglycemia. The unsolved issue is now whether the prevention and avoidance of hypo, hyper and high glycemic variability is associated with an improved outcome. This key question is very difficult to answer when the achievement and maintenance of BG in a narrow range is precluded by the impossibility to continuously monitor BG. Intermittent BG measures can underestimate glycemic variability, and even episodes of severe hyperglycaemia or hyperglycemia can be missed (Joseph et al. 2009; Rice and Coursin 2012). A board of experts published quality criteria for the desirable per-

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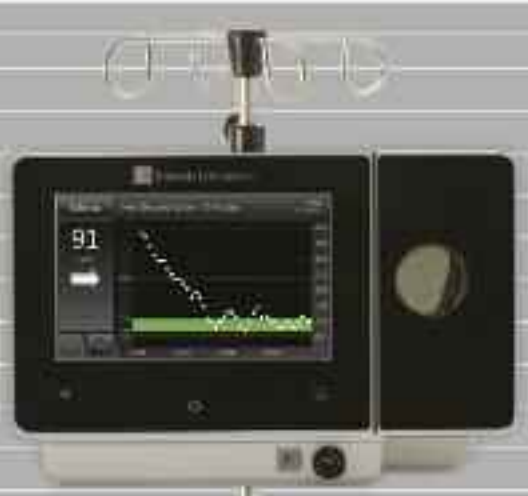

Glycemic management has been shown to improve patient outcomes through reduced morbidity and mortality in the critically ill patient.[1,2]

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1. Van den Berghe, G., et al. Intensive insulin therapy in the critically ill patients. N Engl J Med 2001; 345: 1359 - 1367.

2. Krinsley, J. Glycemic variability: a strong, independent risk factor for mortality in critically ill patients. Crit Care Med 2008; 36: 3008 - 3013.

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formance of intermittent and continuous glucose meters to be used in an ICU (Finfer S, Wernerman J, Preiser JC, Cass T, Desaive T, Hovorka R, Joseph JI, Kosiborod M, Krinsley J, Mackenzie I, Mesotten D, Schulz M, Scott MG, Slingerland R, Van den Berghe G, Van Herpe T. Consensus Recommendations on "Measurement of Blood Glucose and Reporting Glycemic Control in Critically Ill Adults". Crit Care 2013 (in press)).

In relation to the unsolved key question, there are several investigational arguments supporting an improvement in outcome by maintaining BG within a narrow range (Ellger et al. 2006; Behrends et al. 2010) when faced with the potential role of stress hyperglycaemia, as this acts as a component of an adaptive mechanism to survive the initial post-injury phase ((Soeters and Soeters 2012; Dungan et al. 2009). Therefore, the question will remain open until reliable means including continuous monitoring and adapted insulin algorithms to achieve and maintain blood glucose within a narrow range become available.

> *"The question of whether outcome will be improved by maintaining BG within a narrow range can only be answered when rapid, accurate, interference-free, inert, and cost-effective CGM systems are validated for clinical use (Rice and Coursin, 2012)"*

Continuous Glucose Monitoring

The question of whether outcome will be improved by maintaining BG within a narrow range can only be answered when rapid, accurate, interference-free, inert, and cost-effective continuous glucose monitoring (CGM) systems are validated for clinical use (Rice and Coursin 2012). Several techniques are proposed, as well as different sites of monitoring (Table 1). However, technical improvements of these devices are still needed to achieve optimal performance in ICU patients. The different problems reported are related to interferences with drugs, or physico-chemical factors. The reliability of a subcutaneous signal is limited in cases of poor skin perfusion, as in shock, or in obese patients. The use of sensors connected to a peripheral venous catheter can be limited by the quality of venous access. Unfortunately the quality of the signal can hardly be measured and displayed on the screen of these monitoring systems.

An option suggested in case of suboptimal signal is to consider CGM as a warning system, designed to describe a trend of BG rather than actual BG values. In such case, any BG value out of range should be checked on an intermittent glucose meter.

Responding to the numerous limiting factors for the use of continuous or near-continuous monitoring systems in ICUs, manufacturers are working hard to improve the reliability of devices in the very complex and changing environment. In particular, filters for potential chemical interferents (i.e. drugs used in ICU patients) have been incorporated into several devices. The lifespan of some of the disposable equipment has been prolonged over a 24-hour period and time intervals between calibrations have been increased, etc. Nevertheless, most of these devices have not yet been validated for use in a heterogeneous population of medical and surgical ICU patients over relevant time periods. The results of some of the ongoing validation trials should be released soon.

Regarding the therapeutic impact of inaccuracies in the reading of BG concentrations, error grids adapted to the actual insulin algorithms that are in use in ICUs are needed. Indeed, the current Clarke Error Grid was developed to assess the performance of intermittent glucose meters in diabetics, but it is not adapted for use in the ICU. In particular, error grids adapted to the actual target range and insulin algorithms have been published (Ellmerer et al. 2006). Error grids for CGM have also been proposed (Kovatchev et al. 2004) and used to as-

Table 1. Some Continuous Glucose Monitoring systems

Site	Technique	Approval (CE – FDA)	Commercial name (manufacturer)
Peripheral vein	Enzymatic (GO)	CE	Glucoclear (Edwards)
	Microdialysis	CE	Eirus (Maquet)
	Enzymatic (GO)	FDA	GlucoScout (International Biomedical)
Central vein	Mid-infrared spectroscopy	CE	Optiscanner (Optiscan)
	Microdialysis	Pending	Eirus (Maquet)
Subcutaneous	Enzymatic (GO)	FDA	Minimed (Medtronic)
	Enzymatic (GO)	CE	Glucoday (Menarini)
	Enzymatic (GO)	FDA	Dexcom 7 Plus (Dexcom)
	Enzymatic (GO)	FDA	Navigator (Abbott)
Peripheral vein or artery	Quenched fluorescence	Pending	Glucath (Glumetrics) Glysure system (Glysure)
Transdermal	Enzymatic	FDA	Symphony tCGM System (ECHO therapeutics)

GO = glucose oxidase

sess the impact of inaccuracies in the ICU (Brunner et al. 2011). A revision of the criteria required for clearance by the regulatory authorities is currently underway.

> *"When reliable CGM is available, the next advance will be the incorporation of an insulin algorithm that is adapted to actual insulin sensitivity and re-calculated after each BG reading"*

The Future

When reliable CGM is available, the next advance will be the incorporation of an insulin algorithm that is adapted to actual insulin sensitivity and re-calculated after each BG reading. The current glucose intake and rate of insulin are needed for the calculation of insulin sensitivity, which largely varies in critically ill patients (Pretty et al. 2012). The validation of these individualised insulin algorithms can be performed in patients or in virtual cohorts of patients by physiological modelling (Chase et al. 2011; Pielmeier et al. 2010). It seems that computer-assisted insulin delivery systems will be a useful tool in the near future.

Conclusion

In spite of the current uncertainties regarding the optimal BG levels to be achieved in critically ill patients, CGM systems and individualised insulin algorithms are promising tools that will enable us to avoid the three domains of dysglycemia associated with increased mortality. ■

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NUTRITIONAL FAILURE:
AN ADAPTIVE RESPONSE TO CRITICAL ILLNESS?

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For decades, intensive care unit (ICU) physicians have been administering artificial nutrition to improve recovery and outcome. This intensified nutritional support has been associated with a better outcome in several large observational studies (Alberda et al. 2009), though unfortunately, it is impossible to distinguish cause and consequence by association. Large randomised controlled trials (RCTs) comparing feeding with no, or poor, feeding have until recently never been performed. This article will discuss the importance of nutritional intake in critical illness as well as the incidence of nutritional interruption and nutritional loss.

Is Enteral Nutrition The Way to Go?

When simple nutrition by mouth is inadequate, enteral nutrition (EN) has always been preferred above parenteral nutrition (PN) (Martindale et al. 2009; Singer et al. 2009). EN is cheaper, more physiological and probably safer. Indeed, PN provokes metabolic deregulation, particularly hyperglycaemia and perhaps thereby more infections (Peter et al. 2005). The physiologic impact of infusing lipids, amino acids and glucose intravenously has been studied in mechanistic experiments, but remains controversial. PN, in particular intravenous lipids, might worsen pulmonary gas exchange and immune function (Versleijen et al. 2010; Faucher et al. 2003; Smirniotis et al. 1998; Nordenstrom et al. 1979). Meta-analyses of studies comparing EN to PN in the critically ill are conflicting (Peter et al. 2005; Heyland et al. 1998).

Less Than Optimal Enteral Nutrition

The gastrointestinal route seems the way to go. Moreover, most of us believe that EN should be started early: within 24 hours. This is an assumption based on meta-analyses of a few studies comprising 240 patients altogether (Doig et al. 2009). There may, however, be an important discrepancy between the amount of EN we think we are giving and what has really been taken up by the patient (De Jonghe et al. 2001). These EN losses, in the broader sense of the word, are the focus of this contribution. Moreover, should we care about insufficient nutritional intake (early) in critical illness? The importance of hidden micronutrient losses, among others, by renal replacement therapy falls beyond the scope of this overview (Berger et al. 2004).

Enteral Nutrition Simply Not Given

Several papers described the difference between EN prescription, "optimal" intake according to established calculations, and the amount of EN truly administered every day (De Jonghe et al. 2001). EN is interrupted regularly for many reasons, among them airway management, surgical and diagnostic procedures, and fear of regurgitation and pulmonary aspiration of gastric liquids (Cook et al. 1998). Interruptions of EN often go unnoticed, sometimes nutrition simply continues in the patient file while it is stopped in reality. Hopefully EN delivery pumps coupled to a patient data management system will improve the quality of clinical nutrition data (Berger et al. 2006). Also, energy intake is often described as a percentage of target; but in fact no one knows what this target should be. Weight or height based calculations are not dynamic, so indirect calorimetry is assumed the gold standard. The question remains, however, whether amount of endogenous energy being burnt indicates how much exogenous nutrients should be given. Also, the accuracy of indirect calorimeters is questionable (Sundstrom et al. 2013).

Measurement of Gastric Residual Volumes

Many ICUs, including the Leuven Intensive Care Department, interrupt EN twice a day for two hours. Gastric residual volumes are quantified thereafter in order to assess gastric emptying. Whether this practice is useful and prevents complications, in particular aspiration pneumonia, has never been established (Ridley and Davies 2011). Also, the gastric residual volume (GRV) cutoff for the safe increase of the EN

flow rate is unclear. A large Spanish study demonstrated safe administration of EN with an upper GRV limit of 500 ml rather than the classical 200 or 250 ml. This approach allowed enhanced EN delivery (Montejo et al. 2010). Another practical question with GRV is: what should be done with the collected mixture of EN and gastric secretions? If up to 500 ml of GRV is discarded twice every day, this might result in 1000 kcal or more of EN not truly given to the patient. Re-injecting more than one syringe (mostly 50 ml) of gastric fluid requires collecting the liquid in a clean or sterile container before re-injecting it. Therefore, this unpleasant smelling juice is often thrown away in practice. The amount of EN lost when discarding GRV can be measured by refractometry. This simple bedside method has been bench validated (Chang et al. 2005); however, when mixing EN with gastric juice from critically ill patients rather than clear water, we found a somewhat larger inaccuracy with this tool (Stuer et al. 2010). A very simple solution might be to abandon measuring GRV and to instead administer the EN without interruptions (Ridley and Davies 2011).

Bypassing Delayed Stomach Emptying

When the stomach doesn't empty adequately into the duodenum, some pharmacological or mechanic solutions exist. It is not sure if they should be used. Gastroprokinetics improve gastric emptying. Erythromycin is more effective than metoclopramide (Ridley and Davies 2011); moreover, metoclopramide may prolong the QT interval. The promising results of post-bulbar EN tubes in neurosurgical patients have not been confirmed in larger RCTs (Marik and Zaloga 2003), and perhaps such studies should be repeated in particular at risk populations or in patients who failed initially by the gastric route (Berger and Soguel 2010). Systematic introduction of a post-bulbar tube, by gastroscopy or magnetoscopy, in all patients may rather delay feeding than enhance it. Finally, delayed gastric emptying could be a sign that a patient is not yet ready to be fed.

Enteral Nutrition Not Absorbed By the Patient.

Too easily, we consider all nutrition infused into the patient as absorbed by the patient. Recently a Dutch study quantified the amount of nutrients lost in faeces. Despite the patients in this study not being at risk for compromised enteral feeding, the proportion of EN found in faeces was often significant (Wierdsma et al. 2011). Weighing faeces daily might contribute to correct assessment of true enteral delivery. What can be done, however, if EN absorption is inadequate? Several strategies for reducing diarrhea have been tested in practice. Fibre-rich EN reduces the volume and frequency of stools (Spapen et al. 2001), while semi-elemental EN, though physiologically promising, failed as therapy for diarrhoea despite the absence of proteins in the preparations (Mowatt-Larssen et al. 1992). None of these studies, however, have been validated for EN absorption. The endpoint in these studies was instead on volumes or frequency of diarrhoea.

> *"Feeding less than the nutritional target early in critical illness might be harmless and perhaps even beneficial, independent of the route of administration"*

Failure to Deliver Adequate Nutrition: Is it a Problem?

In summary, many patients receive fewer nutrients than what is estimated as optimal; but is this a problem? Most observational studies suggest that it is (Alberda et al. 2009; Dvir et al. 2006). Nevertheless, the "Impact of Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients" (EPaNIC) trial was the first adequately powered randomised controlled trial which tested whether up-to-target feeding really improves clinical outcome (Casaer et al. 2011). Surprisingly, it did not. Patients in this trial were randomised to either receiving early PN, with intravenous nutrition initiated at day three and achieving the nutritional target by the end of day four, if EN was insufficient; or late PN. Here, patients received no PN, no matter how unsuccessful EN was. Patients in the late PN group, despite an important nutritional deficit, recovered faster from critical illness than patients in the early PN group. Also, fewer patients in the late PN group developed a new infection. Duration of organ support was shorter for patients in the late PN group and patients in this group were discharged from the ICU and hospital earlier. This improved outcome from less aggressive therapy resulted in an overall cost reduction of 2.3 million euros (Vanderheyden et al. 2012).

Limitations of the EPaNIC Trial: Wrong Food for the Wrong Patient?

The results of the EPaNIC trial were a wake-up call to the ICU and nutrition community. A long-standing dogma was challenged by the first available clinical data. The first question was: Are these results applicable to patients with true gastrointestinal failure? This was the case. A subgroup of more than 500 patients, who were admitted with a surgical contraindication for EN, benefited even more from late PN than the overall EPaNIC patient population (Casaer et al. 2011). Experts wondered whether early PN would only be beneficial in the most severely ill patients, but harmful in the least severely ill; but a post hoc study of the EPaNIC trial, studying the effect of late PN in subgroups divided by the APACHE II score and cardiac versus non cardiac surgery admission diagnoses, rejected this hypothesis (Casaer et al. 2012). If anything, late PN was found to be even more beneficial in more severely ill patients. Also,

more than 800 patients admitted with the highest nutritional risk scores (NRS: five, six and seven), reflecting a very low body mass index (BMI) or extremely reduced nutrition intake before inclusion in the EPaNIC trial, experienced similar benefit from semi-starvation (Casaer et al. 2011). Recently, an alternative score aiming to predict improved outcome by enhanced nutrition, the Nutrition Risk in the Critically Ill (NUTRIC) score, was developed. Its ability to predict mortality has been established in a large patient population (Heyland et al. 2011). Whether this NUTRIC score truly identifies patients likely to benefit from enhanced feeding remains to be validated. A final aspect of the EPaNIC study that was questioned was that the wrong nutrition had been given, i.e. too much glucose and not enough protein or amino acid. Observational analysis of the relative contribution of glucose versus protein to worse outcome in the EPaNIC study identified protein/amino acids rather than glucose as the culprit (Casaer et al. 2012). The absence of glutamine in the PN therapy administered in the EPaNIC study is no longer an issue. Indeed, a recent large and well conducted RCT, the REDOXS study, reporting increased mortality with glutamine in the ICU, was presented by Dr. Daren Heyland at the Update on Metabolism and Nutrition in Intensive Care Medicine round table discussion, which took place in Rome from 16-19 December 2012. These results torpedoed another ICU-nutrition dogma.

Benefit of Early Semi-Starvation in the ICU?

Feeding less than the nutritional target early in critical illness might be harmless and perhaps even beneficial, independent of the route of administration. Indeed the "Early Versus Delayed Enteral Feeding to Treat People With Acute Lung Injury or Acute Respiratory Distress Syndrome" (EDEN) RCT, allocating patients to trickle enteral feeding (equivalent to almost no feeding) versus feeding up to target, showed no benefit of the latter (Rice et al. 2012). The population selected in this study, however, might preclude a generalised conclusion. A smaller trial even demonstrated harm by early enteral feeding (Ibrahim et al. 2002). Finally, combining EN and PN, if necessary, to reach caloric target as assessed by indirect calorimetry, induced more infections and prolonged stay in the ICU in "The Tight Calorie Control Study" (TICACOS) (Singer et al. 2011). Starvation-induced autophagy might explain improved outcome by nutrient restriction. The highly conserved au-

tophagy pathway clears cellular damage, toxic protein aggregates, dysfunctioning organelles and intracellular micro-organisms, all typical of early critical illness. Suppressed autophagy compromises cellular integrity (Komatsu et al. 2005). Vanhorebeek and colleagues observed such suppressed autophagy in critically ill patients (Vanhorebeek et al. 2011). Meanwhile, animal experiments identified enhanced PN, and in particular amino acids, as the culprit behind autophagy inhibition and organ damage (Derde et al. 2012). Another notable result from the EPaNIC trial was that early PN compromised muscle integrity and was unable to prevent loss of muscle volume (Casaer et al. 2013).

Other Recent RCTs of Nutrition in the ICU

In two smaller trials, early as opposed to later PN apparently provoked no harm. The answer to this apparent controversy might be that the patients administered with later PN in these trials received too many nutrients to experience any benefit of enhanced autophagy by nutrient restriction. Indeed, the first Swiss trial included no patients with a contraindication for EN (Heidegger et al. 2012). All patients in this trial were therefore relatively well fed via EN by the day of inclusion in the trial. Initiation of PN on day four rather than eight reduced the incidence of infections occurring after day nine, without any impact on clinical outcome. The larger, Australian, early PN trial compared PN administered within one hour after ICU admission to eventual PN started not earlier than day two in the ICU, at the physician's discretion. This intervention—in fact, comparing extremely early PN with early PN—had no impact on hard clinical outcome endpoints, confirmed one of the study's researchers, Dr. Gordon Doig, at The European Society for Clinical Nutrition and Metabolism (ESPEN) congress held in Spain from 8-11 September, 2012.

Why Do RCTs Not Confirm the Hypotheses Generated by Observational Trials?

All the above RCTs—together including more than 6000 patients—agree on one point: tolerating important underfeeding as compared to feeding up to nutritional target does not affect mortality at all. This is in contrast with treatment effect estimates based on large observational trials, which predict excess mortality with every 1000 kcal of energy deficit (Alberda et al. 2009). Should we then distrust RCTs? No, on the contrary; these results point out once more that only adequate RCTs allow the prediction of treatment effect (Peduzzi et al. 2002). Correct trial and endpoint registration; concealed treatment allocation by randomisation; blinding of, at least, the outcome assessors; use of relevant, strong predefined endpoints; inclusion of a sufficient number of patients to achieve adequate credence; and attribution of all events occurring after randomisation to the randomised intervention are needed to provide correct treatment effect assessment. Failure to comply with these requirements increases the risk of the results being distorted by bias. The general bias in nutritional research is that nutrition works.

A specific problem with observational studies in nutritional research is that patients are more easily fed once they are doing better. This mostly results in an increase in average nutritional intake along with ICU stay, while nutritional deficit continues to accumulate. Indeed, many patients never reach nutritional target. The association between nutritional efficacy and recovery will, therefore, depend on the chosen parameter. We recently solved this issue by analysing the effect of nutrition, given over the same time period, on recovery in the upcoming days (Casaer et al. 2012). These analyses revealed delayed recovery with increasing intake, even at very moderate doses. Another problem with observational trials in the ICU is the handling of competing events. What if one treatment shortens ICU/hospital stay, but the outcome of interest is mortality in ICU/hospital? Should patients discharged from the ICU/hospital be censored on the day of discharge, although they are more likely to survive? Doing so is an error named "informative censoring" (Schetz et al. 2013). Certainly, a shorter stay in the ICU/hospital would falsely inflate the mortality in survival analysis (Weijs et al. 2012). In conclusion, more large RCTs are needed to correctly guide nutrition management in the ICU, and observational trials can yield interesting research hypotheses.

So What Should We Do?

Hidden losses and overt failure of EN is common, but failing to reach nutritional targets early in critical illness perhaps isn't that much of a problem. The question now is: how should we manage nutrition until more data is available? Patients able and desiring to eat should do so unless absolutely contraindicated. In all patients, micronutrient status should be assessed and deficiencies, in particular during refeeding, avoided. If nutrition by mouth is impossible or insufficient, initiation of EN shall be attempted. If delayed gastric emptying hampers EN, this can probably be tolerated for several days. PN administration should probably be restricted to patients with intestinal anastomosis leakage or bowel necrosis and even then not be initiated before day eight. Optimal nutritional targets are unknown and are probably much lower than previously assumed. In conclusion: first do not harm! ■

> *"Hopefully EN delivery pumps coupled to a patient data management system will improve the quality of clinical nutrition data"*

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RACING TO IMPROVE EARLY WARNING

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The unique challenges in developing early warning for children have led to a patient-specific early warning approach. The methodology, which is based on the altered patterns of physiological derangement, associated with compensation and decompensation in clinical deterioration rather than population normal distributions, is suitable for patients of all ages. A software platform that is used for Formula One telemetry, which is able to analyse continuous data in real-time and produce predictive models for the future, has been adapted for use in critically ill patients. This enables real-time principal component analysis (PCA) and predictive modelling, which are promising solutions for developmental physiological changes and patient specific variations, whilst avoiding false alarms.

Introduction

Formula One motor racing is all about winning. Healthcare is all about reducing distress and saving lives. Both are most successful when underpinned by detailed knowledge of the context and behaviour involved as well as the drive for safety and quality. In addition, they both require prediction of likely outcomes, pre-planning to mitigate anticipated complications and rapid, real-time decision-making to achieve the best results.

There are, of course, many differences between managing a racing car and managing a sick patient. The most obvious is that while racing cars are relatively predictable, patients have homeostasis with known, but often unpredictable, closed loop feedback systems that aim to compensate for physiological derangement until a point where decompensation is inevitable. The physiological patterns of deterioration prior to respiratory or cardiac arrest are well described in adults and children and underpin the global development of early warning systems (Devita et al. 2006; National Institute for Health and Clinical Excellence 2011; NHS 2011). These systems involve an aggregation of physiological derangement to identify the trend of deterioration and have been shown to reduce avoidable death and life-threatening events. The UK National Early Warning Score (NEWS) is an aggregate scoring system to identify adult patients during the compensation phase before they decompensate to cardiac arrest (Royal College of Physicians 2012). Identification of deterioration triggers a response to generate increased monitoring, management of the cause of decline and a call for more expert help.

> *"Ideally, the changing conditions of the population of individual patients would help inform the most appropriate allocation of nurses"*

Children provide unique challenges in early warning that have led to developing patient specific monitoring. The wide range of "normal" physiology which develops as children grow, and the complex "at risk" patients that have their own specific range of normality, for example pulse oximetry of 75% in cyanotic heart disease, has provided the drive to develop early warning that learns the normal and abnormal physiological patterns for that patient. Once successfully developed, this age-agnostic approach will almost certainly be equally applicable to adult and geriatric patients. We describe an approach where the patterns generated by individual susceptibility, acute physiological response, compensation and decompensation thresholds create early warning.

Early Warning Systems in Adults and Children

Early warning scores are substantially better than relying on chance identification of deterioration, achieving a 25% reduction in life-threatening illness and death

AUTHOR GUIDELINES

ICU MANAGEMENT

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Articles must be written in UK/British English (e.g. organisation, not organization), with short sentences, a clear structure (see above) and no bias. Full stops in numbers may only be used to indicate a decimal place; otherwise use commas as separators.

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Example of within text citation: (Edwards 2004; Edwards and Miller 2002; Miller et al. 2003).

Reference lists should be alphabetised by lead author and included at the conclusion of the submission.

Example of standard journal reference: Sydow Campbell, K. (1999) "Collecting information; qualitative research methods for solving workplace problems", Technical communication, 46 (4) 532-544.

Authors are responsible for the accuracy of the references they cite.

Acceptance

It is always at the discretion of our editorial board to accept or refuse submissions. We will respond to submissions within 8 weeks of receipt. We reserve the right to revise the article or request the author to edit the contents, and to publish all texts in any MindByte Communications journal, on the Internet and to list them in online literature databases.

Thank you,
The ICU Management Editorial Team
editorial@icu-management.org

(Priestley et al. 2004; Tibballs et al. 2009). However, there are two good reasons why we need to explore beyond the current aggregate systems.

Firstly, current early warning systems rely on categorising a patient as normal or increasingly abnormal in comparison to a population normal distribution. Patients have individual normal physiology and resilience and responses to illness are based on their background health or illness, medication and age (Bion 2000; Smith et al. 2008). We need to know what is normal for that specific patient. A well 10-year-old, an immunocompromised 20-year-old with leukaemia and an elderly 80-year-old patient with heart failure will each respond completely differently to abdominal sepsis. Current early warning systems are not tailored to this background-dependent resilience or susceptibility but focus only on the acute, generic physiological changes. In addition, some patients deteriorate and decompensate within the normal range for their age and for them. This is because the effects of deterioration aren't limited to changes in high and low thresholds, but are related to the pattern of variation within physiological parameters. As an example, Figure 1 shows the trends of heart rate, pulse rate, and pulse oximetry. The patient shows a clear change in pattern of variability prior to cardiac arrest, but would not have triggered high or low alarm threshold until the acute life-threatening event. Some of this altered pattern is measured in heart rate variability: a marker that has benefit in identifying sepsis in adults, neonates and foetal distress (Ahmad et al. 2009; Moorman et al. 2011; Van Laar et al. 2008).

> *"Current early warning systems are not tailored to this background-dependent resilience or susceptibility but focus only on the acute, generic physiological changes"*

Secondly, current early warning systems rely on relatively infrequent (every one to 12 hours) and varied vital sign measurements, from a choice of up to 36 parameters. Furthermore, the warning can in some cases be associated with missing measurements (Royal College of Physicians 2012; Duncan 2007; Royal College of Nursing 2011). There is no information on the optimal frequency of observations for a specific patient or population and this decision is often left to relatively inexperienced, busy bedside nurses and healthcare assistants. The assumption is that the bedside staff will recognise a deteriorating change in trends and alter the observation frequency, but this opportunity is often missed. There is also variation in which vital signs should be measured.

In 2008, a paediatric early warning system (PEWS) was introduced in all wards at Birmingham Children's Hospital (Duncan et al. 2006; Parshuram et al. 2011). This is a paper-based aggregate score embedded as colour-coded, age-dependent thresholds on the four standardised observation charts. It is associated with simulation-based training on taking routine observations and appropriate decision-making relating to deterioration. The type and frequency of observations are guided by a comprehensive evidence- and expert-based observation, monitoring and escalation policy. All life-threatening events are tracked, in keeping with international recommendations

Figure 1. Early Warning System Showing Trends of Heart Rate, Pulse Rate, and Pulse Oximetry

An early warning system example showing the heart rate (blue, from ECG), arterial blood pressure (red) respiratory rate (green, from ECG) and oxygen saturation (yellow, SpO_2; from pulse oximetry) frequency time trends, collected with five-second averaging directly from the Philips IntelliVue system. It shows a change in the pattern variability prior to an acute life-threatening event which the bedside clinicians perceived to be unpredictable. The heart rate shows an increase of 20 beats per minute which remained within the alarm threshold settings.

(Devita et al. 2006), and they are classified into timely and untimely for intensive care referral and admission, and whether or not they are predictable and/or potentially preventable for acute life-threatening events. It is this detailed forensic review of all episodes of critical deterioration that has provided the insight into how best to approach early warning.

Since the introduction of early warning systems, in-hospital cardiac arrests have reduced and more patients are receiving optimal pre-intensive care. These are direct indicators of more timely treatment of acute illness. But it could be better: measurements and observations could be more frequent, processing the data could be automated, data entry mistakes could be avoided and warnings or alarms could be tailored more specifically to individual patients.

Birmingham Children's Hospital cares for children from birth to 16 years old, with weights ranging from 450g to 120kg. Our patients are frequently complex with cyanotic heart disease, chronic lung disease, neuro-developmental disorders, multi-organ involvement and they epitomise individuality. Four age-appropriate observation charts are needed to accommodate ab/normal physiological parameters for the age-groups: birth to one year, one to five years, five to 12 years and older than 12 years. Infants, in particular, and older children can deteriorate very quickly; in between infrequent observations. These situations can erroneously be interpreted as unpredictable; however, parents are often adamant that a change had occurred in the child's condition prior to an acute life-threatening event that routine or even enhanced monitoring did not detect. These challenges have led to our exploration of Real-time continuous, Adaptive patient-specific, Predictive Indicators of Deterioration (RAPID).

How Does Formula One Help Solve These Problems?

Based on the problems identified so far, we determined that what is required is a system with the following requirements:

- Real-time analysis - to identify changes in patterns of physiological compensation and decompensation, and predict or form a model for the future;
- Adaptive - to have real-time analytical ability to learn normal for that specific patient;
- Continuous - until an optimal observation frequency can be determined; and
- Scalable and not reliant on expensive individual monitors - to measure as many at risk patients as possible.

A solution is not yet available for medical monitoring, but is routinely used in motor racing telemetry.

You need a fast car, great driver and good strategy to win races in the complex and highly competitive world of Formula One. It is human endeavour at its most extreme, characterised by relentless development with new innovations appearing throughout the year in ever-changing forms. Each must be anticipated, its influence evaluated, and then put into action quickly.

The cars are changing continually to make them faster, stronger and safer, and they go into intense competition every two weeks between March and November. Hence, it is unsurprising that the world of Formula One is underpinned by data. Quickly making sense of what you see and hear is often the difference between winning and losing (Figure 2). In this respect, healthcare is little different. Recognising problems quickly is the first step towards effective treatment, but each patient is different and early signs can be subtle and complex. Nonetheless, they are

> "The importance of the prediction is that it enables quite tight margins to be applied in testing for divergence from normality"

Figure 2. McLaren Electronic Systems' telemetry data is used during Formula One car development and strategic, time-critical decision making during races

usually there to be found in the data. Recognising deterioration early provides a real opportunity for reducing distress and saving lives.

McLaren Electronics Systems provides telemetry for all Formula One teams so they can measure, visualise and respond to changes during development of the cars as well as during the time-critical race situation. The Formula One real-time data system comprises SQL-Race, an application processing interface (API) that manages a large population of individual sources of time-series and associated data; vTAG server, a data logging and processing platform upon which real-time models run; and ATLAS, the data analysis and viewing software used by teams and engine makers throughout Formula One.

Each car is fitted with over a hundred sensors. Live health and performance data is sent back via telemetry to the garage and over the Internet to the team's factory, often on the other side of the world. Over 750 million numbers from each car are processed in real-time during a two-hour race. Over the race weekend the data is used to make the cars better and faster. The data tells the engineers how much life remains in the engine, how quickly the tyres are degrading and how much fuel is being used (as well as how much is left in the tank). The data tells them whether set-up changes are effective or not, and the system has the ability to run thousands of models simultaneously to predict the consequences of different treatment strategies.

In healthcare, it is not feasible to have the equivalent of a Formula One team's engineers focusing on just two patients, but it is possible to use the data platform to analyse patient-specific data in real-time, and to predict the future. If such analysis of changing physiology and variation could be visible to bedside or remote clinicians, then a much higher incidence of subtle signs of compensation and decompensation could trigger more sophisticated alerts, and we could see the predicted consequences of treatment and observation strategies.

Saving Young Lives

In 2011, Birmingham Children's Hospital and McLaren Electronic Systems installed a real-time data system to gather and process live physiological data from all beds in paediatric intensive care and from the trolley in one of the specialist child transport ambulances. Through the "Young Lives" project, supported by the Health Foundation SHINE programme and applied mathematics academics from Aston University, we developed a system that would stream data from all of the bedside monitors and quickly tease out patterns in the data, with a purpose of alerting doctors and nurses to changing conditions.

The reason for starting in paediatric intensive care was twofold: it is where the sickest children are treated with 1:1 nursing and it is where the physiological data was already routinely collected (but previously overwritten after 96 hours). In the first twelve months of running the system, we collected physiological data from more than 1000 different patients. By streaming the data into the Formula One data system, we have been able to provide a richer display and manipulation of data and store it longer for the purposes of clinical review and research.

The bedside instruments provide data from a range of sensors, but initial focus was placed on pulse oximetry (SpO_2) because it is readily measured and is rich in information about respiration and cardiac activity. The real-time data platform can gather and process data from a large population of individual patients. The data processing can be applied to any of the physiological sensors and uses principal component analysis (PCA) to extract the characteristic patterns from the data as it changes with time. This technique is used for analysis and prediction in financial, environmental, military and aeroplane engineering applications. A patient who is stable exhibits patterns that change little over time. Plotting two principal components against each other creates a model "distance". Deterioration is reflected in an increase in the model "distance", a parameter which characterises how well the principal components correlate with the evolving data.

The PCA approach not only teases out characteristic patterns, but also provides the means to predict how the data should look in the future. It does this by extrapolating and then reconstructing the physiological data for a later time. Currently, we predict about two minutes ahead. The importance of the prediction is that it enables quite tight margins to be applied in testing for divergence from normality. This can lead to much earlier reliable detection of change for individual patients.

We are testing the PCA model distance alongside an automated version of a modified paediatric early warning score (mPEWS). Early indications show that changing conditions are apparent in the PCA distance and scatter plots well before the mPEWS or raw data are seen to change. Further clinical interpretation is needed before changes may be characterised in terms of deterioration (Figure 3).

What Does the Future Hold?

Formula One has been using telemetry data to develop and race cars for over 25 years. The engineers and drivers believe and act upon the information they see, using it to understand and continually improve their cars and race-craft. Analytical techniques and fidelity checking between parameters has managed false alarms out of the system. Much of the work done in setting up the race car and developing a winning strategy takes place away from the track using live data sent across the world via standard fibre and wireless networks. It is no longer always necessary for the engineer and car to be in the same location in order to make a difference.

However, exploiting this approach in healthcare involves more than simply transferring technology. The healthcare environment is less structured, people can be more complicated and less predictable, clinical interventions can be frequent and varied and the culture in secondary (and primary) health is not always one that is immediately receptive to change. The next

Figure 3. RAPID System Showing the Model Distance Increasing Before the Modified Paediatric Early Warning Score and Before the Event

stages of development at Birmingham Children's Hospital will be to:

(1) Establish more rigorous clinical interpretation of the changing patterns;
(2) Ensure that false detection of deterioration cannot happen;
(3) Move the system beyond the walls of intensive care and into the high dependency and general wards through-out the hospital; and
(4) Create new patient pathways and resourcing models that make use of the better clinical cues.

A lot has been achieved, but there is much more to do (Nangalia et al. 2010; Bion 2008). Embedding knowledge into the system of what constitutes normality, how characteristic changes in patterns relate to treatment and outcomes, and how alarm thresholds could and should be set, will all come with detailed clinical scrutiny of the data. Properly engineered, our approach will present physiological data clearly, immediately and in context, so that every patient, regardless of age, might be seen by the right people, in the right place and at the right time. Ideally, the changing conditions of the population of individual patients would help inform the most appropriate allocation of nurses throughout the hospital and direct doctors and other clinicians to the sickest patients. There is no reason, however, why an approach like RAPID should be confined to the hospital. Once developed, the applications that detect deterioration could operate remotely or be embedded in local devices, such as smart phones or tablets. Patients with acute and chronic conditions could be monitored at home with the reassurance that expert help could be informed quickly should a condition suddenly worsen.

Acknowledgements

The real-time Principal Component Analysis application that is used to extract and display changing patterns was developed by Dr. Rajeswari Matam of Birmingham Children's Hospital. She also liaised directly with the software and support engineers from McLaren Electronic Systems throughout the development and commissioning of the system. The development of the analysis approach, and ensuring that it was both practical and relevant to this new application, was supported strongly by Prof. David Lowe of Aston University. ■

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THE KIDNEY AS THE **PROTAGONIST**

AN INTERVIEW WITH **DR. SEAN BAGSHAW**

Doctor Sean Bagshaw, Clinician Scientist and Associate Professor in the Division of Critical Care Medicine at the University of Alberta, Canada, supported by a Canada Research Chair in Critical Care Nephrology, has played an active and influential role in the research of clinical, epidemiological and translational issues related to acute kidney injury (AKI), and was this year elected as a Scientific Advisor for ISICEM. With AKI proving to be a hot topic of discussion and area of development of late, we asked Dr. Bagshaw to share his opinions on recent research as well as provide an insight into which organ interactions he thinks are posing the greatest challenge to physicians.

Following your widespread research related to AKI, what guidance can you provide for diagnosing the condition, predicting worsening injury, and assessing the need for renal replacement therapy?
Acute kidney injury (AKI), occurring in the context of critical illness, continues to take a heavy toll on patients, presenting a high risk of death and long-term morbidity in survivors. It remains a common and challenging clinical problem for clinicians, is often iatrogenic, has virtually no recognised interventions to modify or improve outcome once well established, and clearly burdens our health systems with added expenditures.

One of the most important initiatives in AKI research has been to improve the capacity for early recognition and diagnosis. This has repeatedly been set forth as a top priority. While the recognition of established consensus-driven criteria, such as the RIFLE or AKIN criteria that are based on detection of changes to serum creatinine and urine output, has been a monumental advance in the field, we also recognise that these criteria that emphasise the use of serum creatinine as the driving marker for AKI are clearly inadequate and may contribute to not only delays in diagnosis but also missed episodes of important declines to glomerular filtration in our critically ill patients.

Recently, a number of studies, including those from Macedo and colleagues as well as myself and coinvestigators, both in 2011, have focused on time-honoured clinical parameters, such as urine output and urine microscopy, to inform on not only the diagnosis of AKI, but also predicting worsening AKI. These studies confirm suspicions that an episode of oliguria (urine output <0.5 ml/kg/hr) is not banal. While short episodes of oliguria (<4 hours) are not sensitive for predicting subsequent overt AKI when defined by serum creatinine based criteria, longer episodes of oliguria are very specific and show higher likelihood for worsening AKI. They also correlate with the risk for initiation of renal replacement therapy (RRT) and death, as Prowle and colleagues found. Importantly, clinicians should recognise that the risk of overt AKI with even short episodes of oliguria, of one to two hours, is probably context-specific, implying that critically ill patients with greater haemodynamic instability, characterised by metrics such as tachycardiac, hypotension, elevated central venous pressures and ongoing vasoactive support, are more likely to worsen. Similarly, recent studies, from Perazella and coinvestigators in 2010, and my own team in 2012, have shown that an evaluation of the urine sediment for evidence of cellular debris and casts correlates with AKI severity and can predict worsening AKI.

> *"The discovery, characterisation and validation of a number of novel biomarkers specific for kidney damage have also brought the promise of a new era in AKI"*

The discovery, characterisation and validation of a number of novel biomarkers specific for kidney damage, including a large multi-national team that I was a contributor towards, have also brought the promise of a new era in AKI. While numerous studies are ongoing, with the aim of better understanding how best to apply information gained from these novel biomarkers at the bedside, the belief is they will enable improved diagnostics (i.e. aetiology and severity of AKI), prognostics (i.e. risk of worsening AKI, need for RRT, non-recovery of kidney function) and inform risk prediction and decision-making for kidney-specific interventions (i.e. protective strategies, novel therapeutics).

Additional novel methods for the early detection of AKI in critically ill patients include the use of integrated clinical in-

formation systems and automated electronic alerting (i.e. the AKI sniffer). A recent prospective single-centre before and after interventional study in a mixed medical/surgical ICU, by Colpaert and coinvestigators, utilised an AKI sniffer to send automated e-alerts to responsible physicians when a patient had developed AKI, based on the RIFLE criteria. The AKI sniffer was sensitive to the diagnosis of AKI. During the three-month intervention phase, 1,416 e-alerts were sent to 616 patients, 92.3% of which were issued for oliguria. Importantly, patients who were issued an e-alert for AKI were more likely to have a faster assessment and more likely to receive an intervention—most commonly a fluid bolus, a diuretic or initiation of a vasopressor—when compared with the pre- and post-alert control phases. This translated into a higher proportion of patients in the e-alert phase showing kidney function that had returned to baseline within eight hours.

It is believed, collectively, that these innovations in the diagnosis of AKI will greatly improve our capacity to identify risk and triage patients to interventional strategies that lead to improved outcomes.

What do you consider to be the prime factors related with the initiation of renal support in critically ill patients?

The optimal time to start RRT in critically ill patients with AKI, in the absence of immediate life-threatening complications such as hyperkalaemia or diuretic-resistant pulmonary oedema, is currently unknown; unfortunately, there is little consensus to guide clinicians on this issue. This is an important knowledge gap in how we care for critically ill patients with AKI, considering that RRT is one of the core technologies we use to sustain life. Furthermore, survey data would suggest that there is considerable variation in practice as to why and when RRT is utilised. This is clearly suboptimal and there is belief that this may in and of itself contribute to less favourable outcomes.

Survey data we collected in 2012, as well as data collected by Thakar and colleagues in 2012, also show that the perception of life threatening complications is an absolute trigger for starting RRT. However, observational studies have shown that these complications account for a minority of the prime indications for RRT in critically ill patients. Indeed, a recent study found that of all critically ill patients started on RRT, hyperkalaemia (K+ >6 mmol/l) was present in only 8%, severe acidaemia (pH<7.15) in 11% and azotaemia (urea >36 mmol/l) in 21%, respectively. Instead, the most common indications in studies led by myself in 2012, were related to fluid overload or accumulation and oligoanuria, with most patients having multiple indications. Moreover, worsening illness severity correlates with a decreased threshold for starting RRT, which may account for the low incidence of classic life-threatening complications in critically ill patients. Fortunately, there are ongoing randomised trials that are evaluating the optimal timing and circumstances for starting RRT in the critically ill, which should better inform on this issue (ClinicalTrials.gov NCT01557361).

What new findings can you report on haemofiltration and haemodialysis for acute kidney injury, and what future studies are required in this area?

In critically ill patients with AKI, who are supported by continuous renal replacement therapy (CRRT), there has been uncertainty whether a particular mode of clearance, either in the form of continuous haemodialysis (CVVHD) or haemofiltration (CVVH), is more efficacious and associated with better outcomes. The lack of certainty in this area has also likely contributed to a wide variation in clinical practice in how CRRT is prescribed. Theoretically, continuous haemofiltration, whereby solute is cleared by convection, should better enable clearance of middle molecular weight molecules, including inflammatory mediators, and accordingly translate into improved clinical outcomes when compared with continuous haemodialysis. In a small phase II randomised trial (2012) comparing CVVH to CVVHD, we found a trend for improved organ dysfunction in those allocated to CVVH, driven largely by a reduction in vasoactive requirements. In a systematic review, including 19 unique studies with variable data available to allow evaluation of clinical outcomes, there was no clear suggestion of superiority of haemodialysis or haemofiltration; however, the risk of bias across these studies was high. These data imply that a further large, high quality randomised comparison of CVVH versus CVVHD is not only feasible, but necessary, to better shape best practice for the delivery of renal support in critically ill patients with AKI.

Which interactions between organs or compartments do you think are posing the greatest challenge to physicians, ICUs and medical establishments worldwide, and where is further research most warranted?

The kidneys' contributions to physiologic homeostasis are often under-appreciated. The kidney receives a considerable proportion of all cardiac output and is vital for several regulatory processes, including nitrogenous waste excretion/detoxification, fluid balance, electrolyte (i.e. sodium, potassium) and acid-base homeostasis and neuro-hormonal regulation (i.e. renin angiotensin, erythropoietin). Importantly, when the kidneys fail, renal replacement therapy does not in fact "replace" kidney function, but merely supports limited aspects of the kidneys' normal function (i.e. fluid, acid-base, azotaemic, potassium control). This could, in essence, only be accomplished by a kidney transplant. Indeed, as shown by Duranton and his study team in 2012, there are literally dozens of uraemic toxins that have the potential to interact with, and cause disruption of, other vital organs. In the critically ill patient, multi-organ dysfunction may herald the final common pathway of many inciting events (i.e. sepsis); however, without question the kidney is an active pro-inflammatory participant, if not protagonist in this process. The failing kidney has implications for numerous vital organs, whereby specific organ interaction may instigate and exacerbate bi-directional dysfunction, including the brain, heart, lung and liver, as described by Grams and Rabb, 2012. The challenge to clinicians is to understand key strategies and develop interventions that interrupt organ crosstalk pathways and lead to improved outcomes for patients.

What are your most significant research findings regarding elevated cardiac-specific troponin (and related cardiac complications) following emergency repair of ruptured abdominal aortic aneurysms?

With local collaborators, and those at other centres, a number of investigations have focused on the prognostic implications of cardiac-specific troponin leak and outcomes among patients undergoing non-cardiac surgery and in critically ill patients. In the VISION study published in 2012, Devereaux and coinvestigators found that peri-operative peak troponin elevation was independently associated with a graded increase in 30-day all-cause mortality after non-cardiac surgery. Elevation in cardiac-specific troponin has also been shown to be common in critically ill patients and correlates with myocardial infarction and increased risk for death.

We recently (2012) explored the incidence and significance of perioperative troponin elevation in a retrospective population-based cohort of patients with ruptured abdominal aortic aneurysm surviving to receive emergent operative repair. In this cohort, we found 55% had elevated troponin levels in the first 72 hours after surgery, of which 43% had acute changes on their electrocardiogram (ECG) that were consistent with ischaemia. Troponin positive patients had a higher baseline prevalence of coronary artery disease and greater illness severity; also, importantly, these patients received a greater intensity of support (i.e. vasopressor or inotopic support), used greater health resources and were at a higher risk of in-hospital death. Moreover, elevated troponin associated with acute ECG changes was linked to an increased risk for complications, including heart failure and cardiogenic shock. We also found that fewer than two-thirds of troponin positive patients were investigated using the echocardiogram, despite a high incidence of myocardial dysfunction and wall motion abnormalities; and fewer still received an interventional procedure. We believe our data imply uncertainty in how to ideally manage troponin elevation in perioperative critically ill patients, to mitigate less favourable outcomes.

> *"In the critically ill patient, multi-organ dysfunction may herald the final common pathway of many inciting events (i.e. sepsis); however, without question the kidney is an active pro-inflammatory participant, if not protagonist in this process"*

What studies do you currently have underway? What is the significance of this research?

At the University of Alberta Hospital, there is a large liver failure population and a large transplant programme. We have shown in preliminary studies (2009; 2011) that the use of continuous RRT during liver transplantation is safe and feasible in carefully selected patients. We are now performing a phase II randomised trial investigating the optimal method for intraoperative renal support during liver transplantation for patients with high illness severity and kidney dysfunction (ClinicalTrials.gov: NCT01575015). This trial is evaluating the impact of intraoperative CRRT, compared with usual care, on the occurrence of intraoperative and early postoperative adverse events, fluid management, and graft function. We believe this trial will help inform best perioperative practice for critically ill liver failure patients referred for liver transplantation. In addition, with local colleagues, we have had interest in exploring the clinical significance and the potential modifying impact of frailty in critical illness. Frailty is described as a multi-dimensional syndrome characterised by the loss of physiologic and cognitive reserves that gives rise to heightened vulnerability to adverse events. We have hypothesised (2011) that frailty may be an important determinant of survival and recovery from an episode of critical illness. We have recently finished a large multi-centre prospective observational cohort study evaluating the prevalence and outcomes associated with frailty in older patients admitted to the ICU.

What problems in critical care management do you think warrant the most consideration in developing and well as developed countries?

My belief is that there are considerable challenges ahead for critical care, both for developing and developed countries. Some of the challenges in developing countries are related to inadequate primary care, a mechanism that could be seen as able to prevent critical illness in many respects, as studied by Adhikari and colleagues in 2010. However, the challenges are far more complex and have to consider the critical illnesses seen in developed countries as well as the added burden related to conflict and natural disasters, as expressed by Vanholder and his team in 2010. So while demand in developing countries is likely to expand, critical care services are expensive, and this capacity to pay for them will be limited. In developed countries, in particular in those with publicly funded models, one of our most significant challenges will be how to judiciously respond to the growing demand and societal expectation for critical care services amid limited ICU bed capacity and resource availability, in particular in the context of a growing older population. ■

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TRACHEOSTOMY IN THE INTENSIVE CARE UNIT: AN ITALIAN SNAPSHOT

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Optimisation of percutaneous and surgical tracheostomy techniques is one of the challenges of modern intensive care unit (ICU) management. Different percutaneous tracheostomies (PTs) have been developed worldwide over the years. Ciaglia, in North America, described the multiple-step dilational tracheostomy; Griggs, in Australia, defined the guidewire dilating forceps (GWDF) technique; while, in Italy, Fantoni and Frova described the translaryngeal method and the rotational dilating technique, respectively. Different techniques may produce different results. For this reason, the current literature on tracheostomy shows a huge heterogeneity in procedures, outcomes and complication of the techniques currently performed in ICUs. Tracheostomy heterogeneity is also responsible for the different approaches developed in Europe. In Italy, a recent national survey (Vargas et al. 2012) tried to take a snapshot of the current practice concerning PT in critically ill patients. The aim of our work is to analyse the results of the Italian experience, matching them with the European context. (Table 1).

Current Practice of Percutaneous Tracheostomy in Italy

Tracheostomy has many potential advantages over endotracheal intubation and is now used in ICUs worldwide (De Leyn et al. 2007). In the past years, many percutaneous dilatational tracheostomies (PDT) have been proposed for critically ill patients (Kluge et al. 2008).

Italy holds great and antique tradition regarding the tracheostomy procedure. In 1546, Antonio Brasavola, an Italian physician of Ferrara, performed the first successful tracheostomy in a patient with a peritonsillar abscess; at the same time, at the University of Padua, two surgeons and anatomists described a detailed tracheostomy technique using a different cannula and different equipment (Rajesh et al. 2006). In Italy, PDT techniques are indifferently performed. A national report—Promoting Patient Safety and Quality Improvement in Critical Care (PROSAFE)—assessed the amount of interventional procedures performed in ICUs, and reported a case series of 5,555 tracheostomies performed in 167

Table 1. Recent European National Surveys Analysed in this Paper

Country	Year	Authors	Journal	ICUs (n°)	Most common tracheostomy technique
Italy	2012	Vargas M et al.	Minerva Anestesiol	131	Ciaglia Blue-Rhino®
UK	2008	Veenith T et al.	Int Arch Med	198	Ciaglia Blue-Rhino®
Germany	2008	Kluge S et al.	Anesth Analg	455	Modified Ciaglia Techniques
France	2005	Blot F et al.	Chest	152	Surgical
Spain	2004	Anon JM et al.	Intensive Care Med	100	Griggs GWDF and Ciaglia Blue-Rhino®
Netherlands	2003	Fikkers BG et al.	Intensive Care Med	55	Ciaglia and Surgical

ICUs. According to this report, the PDT more frequently performed was Ciaglia single step dilator (29.7%), followed by surgical tracheostomy (ST) (26.7%), PercuTwist® (13.6%), Griggs (11.6%), Ciaglia multiple dilator (8.1%) and the translaryngeal technique (TLT) (6%). Unfortunately, this report did not provide any information about clinical attitudes and management of PDTs performed in national ICUs. In order to obtain this information, we conducted an Italian mail survey to investigate the clinical practice of PDTs performed in Italian ICUs.

A National Survey

Our aim through conducting this survey in Italy was to describe the current situation regarding different techniques, indications, main procedural features, early and late complications, as well as timing of tracheostomy in ICUs (Vargas et al. 2012). This survey, approved by the Italian Society of Anesthesia, Analgesia and Intensive Care (SIAARTI), referred to the tracheostomies performed in 2011. We received questionnaires from 131 ICUs; this number covers about 30% of Italian ICUs, according to a recent statistical report (Italian Department of Health 2012). We collected data on 5,960 tracheostomies, which were mainly performed in medical-surgical ICUs. According to our data, the estimated total number of tracheostomies performed in Italy in 2011 was approximately 17,880.

Tracheostomy Techniques

Our survey allows deeper analysis of the national approach to the tracheostomy procedure, as compared with the approach to the procedure on a European scale. According to previous surveys carried out in Germany (Kluge et al. 2008) and the UK (Veenith et al. 2008), Ciaglia Blue-Rhino®(CBR) is the most common technique (32.8%) performed by Italian intensivists in the ICU, demonstrating the presence of a common European trend. The surgical approach seems to show a constant decline, except in France (Blot et al. 2005); in Italy, its use represents about 11% of tracheostomies in the ICU, with higher use indicated in large ICUs which have more than eight beds (Vargas et al. 2012). Large ICUs were also shown to be more likely to choose GWDF techniques rather than other percutaneous techniques in the same study. These facts could be explained in terms of the further time and resources needed by both surgical and GWDF tracheostomy procedures, as compared to other percutaneous commercial kits (Ambesh et al. 2002; Anon et al. 2004). Since their introduction, PDTs generated an intense debate in the scientific community. Even large meta-analyses show contrasting results in the comparison between surgical and non-surgical tracheostomy techniques, with some authors finding better outcomes and safety profiles in the former (Dulguerov et al. 1999), and others in the latter (Freeman et al. 2000). Despite these contrasts, for its simplicity and low incidence of serious complications, PT seems nowadays to be the choice of most ICU physicians worldwide.

The Translaryngeal Technique

The translaryngeal tracheostomy (TLT) technique plays a particular role in Italy. Antonio Fantoni developed TLT in the 1990s, with the aim of reducing potential posterior tracheal wall damage (Fantoni et al. 1997). TLT is universally recognised to require longer training. Our survey showed that TLT was the technique performed in a case series of 905 patients (15.2%) in Italy, in line with Germany (13%) (Kluge et al. 2008) and France (20%) (Blot et al. 2005), but significantly higher than that shown in the UK survey (Veenith et al. 2008), where TLT is included among "other techniques", accounting for less than 5% of total PT. The overall Italian situation as indicated by the survey is shown in Figure 1.

Figure 1. Distribution of Tracheostomy Techniques in Italy

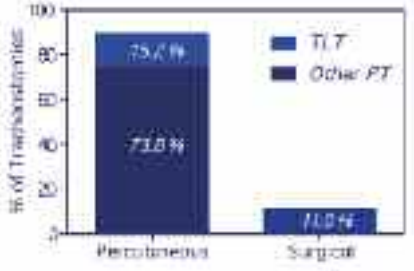


Figure adapted from Vargas et al. 2012

It is quite difficult to compare the impact of TLT methods on complications and outcome, since most of the studies worldwide use CBR or GWDF as a reference for percutaneous techniques.

An Italian randomised trial, with a one-year double-blind follow-up, tried to compare complications and outcomes of Fantoni's TLT with those of ST (Antonelli et al. 2005). The results showed a reduction of time-consumption and major bleeding in TLT, whilst no difference was shown in development of severe infections or survival (Antonelli et al. 2005).

Although less used than before, TLT still animates discussions in literature. Also of interest are the results of controlled trials. TLT was compared to forceps dilational PT in a French study (Cantais et al. 2002), and to CBR in an Italian trial (Divisi et al. 2009), which each showed that TLT had a lower safety profile. It is of interest how both studies concluded that most of the complications with TLT are due to its complexity. This suggests that they might be reduced by appropriate training, since the learning curve for Fantoni's TLT is known to be slower than that for other PTs. Despite this, many centres still elect TLT as their choice for PT due to the very low incidence of bleeding and tracheal sequelae when it is performed by trained physicians, as exposed in large case studies, e.g. in Germany (Konopke et al. 2006) and Canada (Sharpe et al. 2003). On the basis of this inhomogeneity and unanimous concern about the fact that TLT complexity might mask its advantages over other PT techniques, a Greek team (Katsaragakis et al. 2007) proposed a modified translaryngeal method that combines the retrograde TLT with a blind needle puncture of the trachea. Further studies are necessary to validate such method.

Indications and Timing

Our Italian survey confirmed prolonged mechanical ventilation or difficult weaning as the leading indication for tracheostomy (74.3%), as in the French survey (Blot et al. 2005). Germany and the UK's surveys did not explicitly investigate PT or ST indications. A recent Spanish prospective, observational cohort study investigated patients receiving ST or PT under this indication,

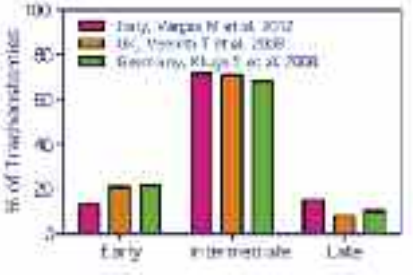
and showed that a longer time-to-decannulation was associated with male gender, age >60 years and high suctioning frequency (Hernandez et al. 2012). On the other hand, the same study found that among patients whose tracheostomy indication was impaired level of consciousness or inability to manage secretions, the main factors predicting a long time-to-decannulation were Glasgow Coma Scale and high suctioning frequency.

Timing is a widely discussed parameter of tracheostomy. It is well known that tracheostomy ratio, defined as incidence of tracheostomy per ICU patient, shows a wide intra- and inter-country variability (Nathens et al. 2006). Many ICUs use guidelines that include a specific time window (Scales et al. 2008). To optimise patient care and outcome, different studies investigated whether a specific timing was effectively associated with an improvement in patient survival or complication rates. The two arguments most commonly used to support early tracheostomy are that it could reduce infectious complications and promote early weaning. A recent Italian multicentric prospective observational study randomised more than 400 intubated patients without preexisting lung infection to early (<7 days) or late tracheostomy (Terragni et al. 2010), and showed slightly higher incidence of ventilator-associated pneumonia (VAP) in the latter group, though without reaching statistical significance (Terragni et al. 2010). Regarding the effects on weaning, retrospective studies showed an association between early tracheostomy and early weaning (Freeman et al. 2005) confirmed by randomised trials (Rumbak et al. 2004) that suggested a causal link between the two. A more recent, larger study that tried to reduce bias in patient selection concluded that no advantage on weaning time was presented by early tracheostomy (Blot et al. 2008).

Figure 2 compares the results of the cited surveys in Italy, Germany and the UK. For methodological issues, French and Spanish studies could not be included in this analysis.

A two-way analysis of variance between groups (ANOVA) was conducted to analyse differences between timing in countries; no differences between countries were indicated (P>0.9). Analysed data conclude that among such countries there is a homogeneous preferential use of intermediate (7-14 days) tracheostomy (mean 70.3%) compared to early (<7 days, mean 18.6%) or late (>14 days, mean 11.1%). Early tracheostomy was more likely to be performed in small or non-teaching hospitals' ICUs in both Italian and French surveys.

Figure 1. Distribution of Early (<7 days), Intermediate (7-14 days) or Late (>14 days) Tracheostomies Across Three European Countries, According to Recent Peer-Reviewed National Surveys



Procedural Features

Past studies suggest that the adoption of locally developed guidelines could decrease the incidence of PT associated complications (Cosgrove et al. 2006). In our survey, a protocol for sedation during tracheostomy was used by 83.2% of participating ICUs, while only 58.8% of ICUs used a protocol for mechanical ventilation during the procedure. Tracheostomy was performed mainly with the endotracheal tube already present in patients (83.2%). Furthermore, 62.6% of ICUs declared having a specialised tracheostomy team. There is an increasing interest in understanding mechanisms that can enhance the efficacy of tracheostomy procedures while consolidating collaborative teamwork between physicians and nurses (Mitchell et al. 2012).

Continuous bronchoscopic guidance was routinely used in 93.1% of ICUs in Italy (Vargas et al. 2012), 80% in the UK (Veenith et al. 2008), 98% in Germany (Kluge et al. 2008), 36% in the Netherlands (Fikkers et al. 2003) and 16% in Spain (Anon et al. 2004). Note that the comparison between those percentages might be biased due to differing years of publication, since it is known that fibroscope use in ICUs dramatically increased in the last decade.

Complications

Our Italian survey ranked "minor bleedings" as the most frequent early complication, whilst the French survey identified a more generic group of "tracheal complications", more notably underlining the risk perceived by the physician rather than the real incidence of complications.

The complication rate is the most difficult parameter to be distinguished by a survey study, and prospective controlled trials are more suitable for such purpose. An already cited study, while investigating another endpoint, reported an overall incidence of early plus late complications of 39.0%, which lowers to 23.9% if non-suppurative stoma inflammation is excluded (Terragni et al. 2010).

Conclusions

Tracheostomy is nowadays a procedure frequently performed in ICUs. Tracheostomy techniques, procedural features as well as complications are markedly heterogeneous among European ICUs (Veenith et al. 2008). Our national analysis can be considered a snapshot of the Italian way of performing tracheostomy in the ICU. Our study found that:

1) CBR was the preferred technique among PT;
2) Prolonged mechanical ventilation and difficult weaning were the leading indications for PT or ST;
3) Tracheostomies were mainly performed within seven and 14 days of mechanical ventilation;
4) PTs and STs were mainly performed by a specialised team with the use of sedation and ventilation protocol;
5) Most of the PTs were performed under continuous bronchoscopic guidance; and
6) Minor bleeding was the most frequent early and late complication. ■

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ENSURING OPERATING ROOM SAFETY: THE ITALIAN APPROACH

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Policies for the management and control of risks associated with healthcare constitute one of the priorities of the modern health systems. Like most European countries, the Ministry of Health in Italy has recognised the importance of assessing quality and safety on all levels of the system, taking into account patient expectations and enhancing the role and responsibility of health professionals.

Through the establishment of a ministerial working group dedicated to patient safety, there have been many clinical governance initiatives, the most significant being the Information System for Monitoring of Sentinel Events (SIMES). SIMES allows the collection of information on the spread of sentinel events in healthcare facilities needed for the analysis of contributing factors and determinants, and develops specific recommendations for the safety of patients. The major care priorities are identified and the systematic use of best practices for patient safety is promoted.

Operating Room Safety

Particular attention has been placed on safety in the operating room in the light of guidance and awareness initiatives launched by the WHO in the World Alliance for Patient Safety and the Safe Surgery Saves Lives programme in particular. Surgical activity, the volume of surgical activity and the inherent complexity of all procedures related to it, even the simplest, is one of the areas with the highest probability of error. The many critical points of each surgical procedure have the potential to cause serious harm to the patient and that is why safety in the operating room is a challenge and a priority for health systems and the management. Using risk assessment we can implement the best solutions for organisational and logistical security so that they constitute an effective barrier system for errors.

In Italy, operating room safety is often the centre of attention due to the occurrence of particularly severe adverse events.

> *"The many critical points of each surgical procedure have the potential to cause serious harm to the patient and that is why safety in the operating room is a challenge and a priority for health systems and the management."*

In Sicily, for example, the emergence of a number of incidents in the operating room, in different contexts and over a relatively short period of time, led to the establishment of a regional commission of experts for a large scale verification of safety procedures. The survey was completed in a few months and resulted in the closure of several facilities operating without safety requirements. This confirmed the role of the organisation and maintenance in causing adverse events and has led to increased risk control and dissemination of a safety culture. The next step is a special plan for modernisation and increase the safety of the medical devices.

The Italian Ministry of Health considered it essential to launch a major campaign to raise awareness among health professionals on the issue of safe surgery. This was done through the creation of a manual for safety in the operating theatre derived from the WHO Guidelines for Surgery and centred on 16 goals for the safety of the perioperative process including 10 derived from the cited WHO document.

Within the scope of the manual for safety in the operating room, a ministerial working group has also developed an Italian adaptation of the WHO OR checklist including controls on the most important aspects of the surgical safety, such as the confirmation of the identity of the patient and type of surgery, the verification of systems for monitoring and maintenance of vital parameters and confirmation, within the team, of the knowledge of the procedure that they are going to perform. Compared to the 19 items of the original version, the Italian checklist presents an additional item to control the prophylaxis of venous thromboembolism, which is considered essential for the prevention of adverse events in the postoperative period.

The checklist should not only allow for the verification of the process and a reminder mnemonic for the proper performance of a particular task, but also fa-

cilitate communication within the team, especially with regard to critical information about the patient and intervention, with better identification of roles within the team and a more optimal exchange of critical information regarding the clinical condition of the patient and the type of work that he is going to perform. The Ministry has also recommended that the health facilities in the National Health Service also take into account the recommendations of the WHO. The checklist will be adapted locally based on the characteristics of each healthcare organisation or particular procedures used. Altered versions could include the addition of further control or elimination of items of routine use and therefore unnecessary.

Promoting the Checklist

In order to raise awareness among health professionals and promote the use of the checklist, the Ministry of Health has developed some explanatory videos to explain the correct procedures for carrying out checks during the course of surgery.

A working group composed of influential figures in the Italian health system took the WHO video as a starting point along with other similar experiences in different countries and adapted the scenes and content to the Italian situation. Particular attention was paid to the choice of surgical procedures on which to apply the checklist, to ensure they are consistent with the local situation.

In order to create a tool that can positively influence the behaviour of the operating team it was also decided to include testimonials from prestigious figures in the national health system, including presidents and members of scientific societies and organisations for the protection of patients: Francesco Basile, Dean of the Faculty of Medicine, University of Catania; Louis Conte, Italian Hospital Surgeons Association (ACOI); Giorgio Della Rocca, the Italian Society of Anaesthesia and Intensive Care (SIAARTI); Giuseppe Greek, chairman of the Standing Conference of regions Cittadinanzattiva Tribunal for Patients' Rights; Giuseppe Mancini, President of Operating Room Nurses (AICO); Barbara Mangiacavalli, Secretary of the Central Committee of the Federation of Colleges IPASVI; Walter Mazzucco, national president of the Italian Secretariat of Postgraduate Doctors; Gianluigi Melotti, President of the Italian Society of Surgery (SIC). Famous faces from the world of culture, Maestro Nicola Piovani and actress Mariella Lo Giudice created the soundtrack and narrated the video. In order to facilitate the sharing of the video within the international scientific community, scenes filmed in the Italian language were captioned in English.

The ministerial working group also considered strategies to highlight the key role of managers as facilitators of the use of the checklist. At the beginning and end of the video a short presentation was inserted to draw attention to the purpose and the importance of corporate policies of clinical risk management in preventing error. Stefano Cencetti, Director General of the Hospital Policlinico of Modena and Gianfranco Finzi, Medical Director of Presidio dell'Azienza University Hospital S. Orsola Hospital in Bologna and president of the National Association of Doctors of Hospital Management (ANMDO) described the purpose of the initiative. These statements put in proper perspective the role that health managers play in the governance of healthcare organisations and emphasise the importance of the organisational aspects at all stages of surgery in which important decisions are made or activities that require high attention especially in terms of communication between the team members and the exact identification of the tasks assigned to the operators.

The video, made in 2009, was presented to health professionals as part of a dissemination campaign launched at the annual Risk Management Forum of Arezzo; one of the main Italian events in training and updating clinical risk. The key strategy was the involvement of scientific societies including ANMDO to stress the important role of doctors as facilitators of the adoption of the checklist.

There is a risk that the use of a large-scale national checklist, although highlighting sensitivity to the issues of clinical risk, is likely to remain a bureaucratic formality with no added value for safety. Particular attention has therefore been paid to the verification of the use of the checklist on a regional level. This was implemented by the Ministry of Health through a questionnaire to gather information on the adoption of the manual and checklist and local training initiatives. The first results of the national survey, although still incomplete, already show a high level of adherence by all health facilities across Italy thus confirming the important role that health policies play in the construction of an error proof system. It is significant that the ministerial handbook for safety in the operating room and related checklist has favoured the creation of a national network for safe surgery. Evidence of this success can be seen through the large number of reports on the theme presented during the last Risk Management Forum of Arezzo.

> *"The ministerial working group also considered strategies to highlight the key role of managers as facilitators of the use of the checklist"*

For a comprehensive approach to safety, which covers all aspects of structural, technological and organisational management, the contribution of the professionals involved is of paramount importance. Strategic synergy is needed to ensure seemingly minor aspects, which may be fundamental to the prevention of the error, are not ignored. A logical system of safety and quality assurance is decisive for the prevention of error.

In this context, of particular importance is the role of the medical director and medical management. Acting as the pivot and facilitator of the process and as a reference for the establishment of a proactive vision for safety, management can ensure error analysis is used as a tool to learn how the same error can be avoided in the future. ■

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worldcongress.com/events/HR13000/index.cfm?confCode=HR13000

25-26 10th Annual Critical Care Symposium
Manchester, UK
www.critcaresymposium.co.uk

MAY

8-11 2nd Annual EuroELSO Congress
Stockholm, Sweden
www.euroelso2013.com

22-25 5th European-American Anesthesia Conference
Rovinj, Croatia
www.hdail.hr/2013

JUNE

1-4 Euroanaesthesia 2013
Barcelona, Spain
www.euroanaesthesia.org

JULY

12 – 14 2nd Singapore-ANZICS Intensive Care Forum 2013
Singapore, Singapore
www.sg-anzics.com

AUGUST

28 – 1 11th Congress of the World Federation of Societies of Intensive and Critical Care Medicine
Durban, South Africa
www.criticalcare2013.com

28 – 1 ESPEN
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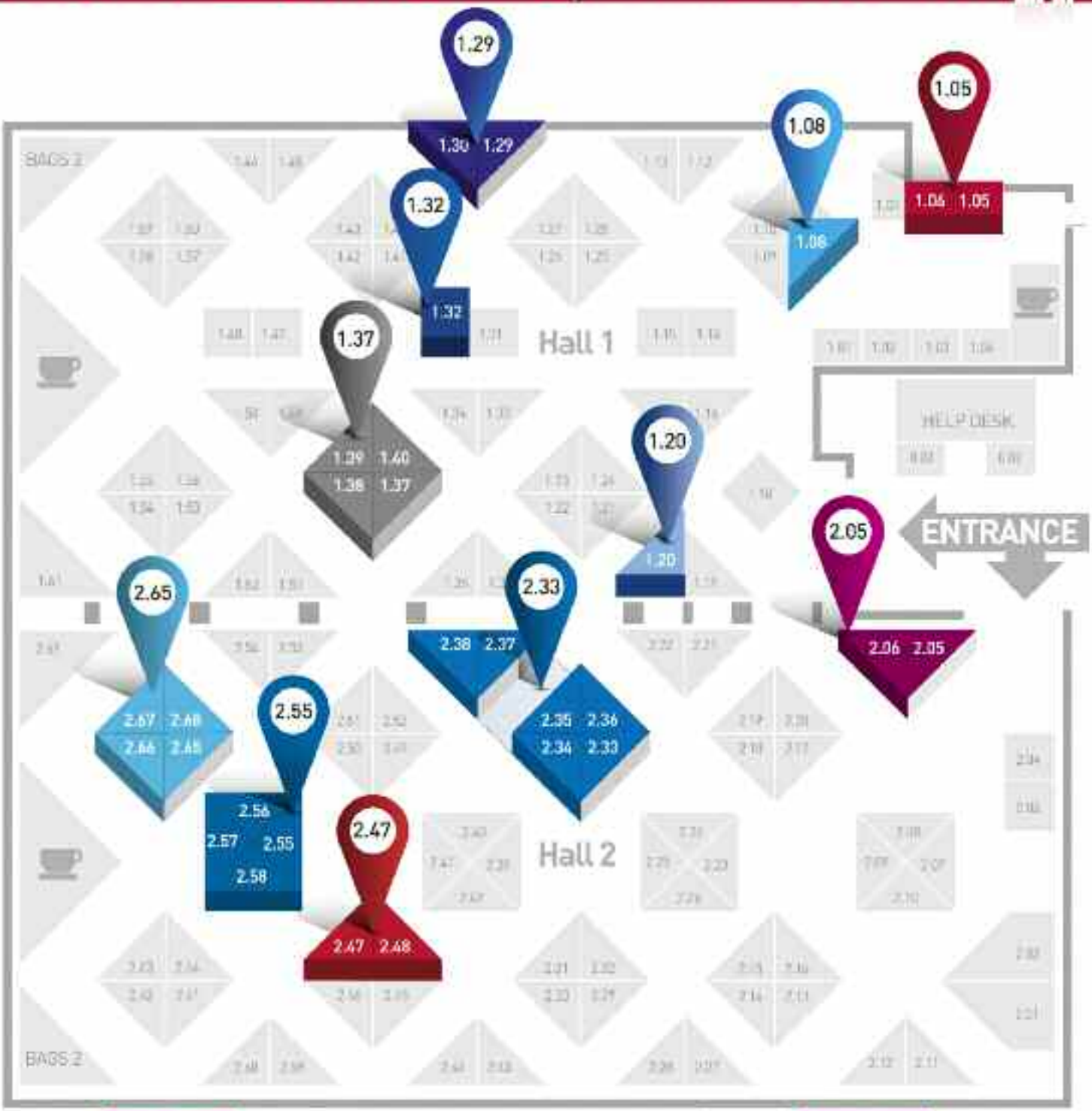

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stand 1.20	BioPorto Diagnostics
stand 1.29-1.30	European Society of Intensive Care Medicine
stand 1.32	Nova Biomedical
stand 1.37-1.40	Edwards Lifesciences

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stand 2.05-2.06	Alere
stand 2.33-2.38	Orion Pharma
stand 2.47-2.48	Thermo Scientific
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