ICU MANAGEMENT

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EM/Trauma

PLUS

Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Infection

Acute Brain Dysfunction During Critical Illness

Neuromonitoring in Critically Ill Patients Without Primary Acute Brain Injury

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Providing seamless emergency care is the ideal for those of us who work in emergency medicine and intensive care. In the past, intensive care units were a closed part of the hospital, and admission was strictly controlled. This idea is obsolete now. It is heartening that we are providing more integrated care between emergency and intensive care. Intensivists need to go out of the ICU and take action earlier to stabilise and admit patients — before they are severely affected. We do this for trauma, and we are doing this for sepsis. We talk about the "golden hour", but of course every minute counts. Can we take action even earlier for more conditions?

Our Cover Story addresses some of these issues. Starting with acute ischaemic stroke, Jason Van Schoor, Vivian Sathianathan and David Brealey argue that, when compared with other serious ICU diagnoses such as severe sepsis and long term ventilation, the outcome of AIS patients on ICU compares well. They suggest that this comparison should shake the historical reluctance that surrounds admission of stroke patients to ICU. When treating patients in cardiac arrest, targeted temperature management is the key intervention for improving neurological outcomes after cardiac arrest. Jean Baptiste Lascarrou and Jean Reignier discuss new data on the optimal timing and modalities of targeted temperature management. For burns management, regionalisation of centres has led to improved outcomes, argue Sam Miotke, William Mohr and Frederik Endor. They contend that the complexity of patient care, both in the short- and long-term, requires a well-prepared interdisciplinary team. Such implementation has been made possible by centre regionalisation, which consolidates expert wound care and critical care management, with benefits for patient outcomes.

Next, Aristomenis Exadaktylos and Wolf Hautz provide a snapshot of the pre-hospital emergency system, focusing on Berne. Michael Reade provides a review of blast injury, outlining what to expect in civilian versus military injuries. He observes that mistaken preconceptions of the medical consequences of blast can lead planners and managers to allocate resources incorrectly. Civilian blast injuries are not rare, but most are not due to military explosives, meaning extrapolation from military texts is often inappropriate. Last, Anatole Harrois and Jacques Duranteau focus on the types of fluid available and their respective indications in the course of trauma resuscitation

Our series on Infections concludes with an article on the ICU response to the Middle East Respiratory Syndrome (MERS) Coronavirus by Hasan Al-Dorzi, Hanan Balkhy and Yaseen Arabi. They emphasise that prevention of healthcare-associated transmission should be the main focus of ICU preparedness.

In the Matrix section, Stuart McGrane, Heidi Smith and Pratik Pandharipande discuss acute brain dysfunction during critical illness. They outline risk factors, prevention and treatment, and reason that delirium monitoring and management may help decrease development and duration of delirium in adults and children. Next, Matthew Kirschen and Peter Le Roux focus on the current experience with clinically available neuromonitoring techniques in critically ill patients at risk for neurological compromise, but without overt acute brain injury.

Although finding evidence has got easier with electronic databases and the Internet, translating knowledge into practice can still take time before it has a discernible effect. aC3KTion Net in Canada is a knowledge translation network, and Nicole O'Callaghan and John Muscedere outline its work in quality improvement in our Management section. Next, we feature an interview with Daren Heyland, who directs the Canadian Researchers at the End of Life Network (CARENET), about the network's activities, which includes the development of innovative resources to prompt discussions about end-of-life care, both for patients and for health professionals.

It is fair to describe Michael Pinsky as a true leader of critical care. He is interviewed in this issue about some of the fundamentals of critical care he has been involved in over the years as a researcher, practitioner and leader.

New Year, New Name

In 2016 *ICU Management* changes its title. Since we began publication in 2000, we have always been the Official Management and Practice journal of the International Symposium on Intensive Care and Emergency Medicine (ISICEM). To better reflect the contents of the journal, we will bring practice alongside management to become *ICU Management & Practice*.

Not only are we changing title, but the journal will be even bigger. I thank the Editorial Board for their continuing support, the many authors from around the world who write for the journal, and you, the readers. As always, if you would like to get in touch, please email editorial@icu-management.org

Jean-Louis Vincent

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MANAGEMENT OF ACUTE ISCHAEMIC STROKE

DEFINING THE ROLE OF THE INTENSIVE CARE UNIT

This review article aims to alter the preconceived mindset that surrounds the intensive care unit (ICU) and the patient with an acute ischaemic stroke (AIS). A contemporary body of evidence is emerging that shows that specific interventions can improve outcomes, and this article highlights key evidence-based strategies in AIS management. More importantly, it focuses on the broader management facets such as the standards of AIS care, stroke care pathways and indications for ICU admission. When compared with other serious ICU diagnoses such as severe sepsis and long term ventilation, the outcome of AIS patients on ICU compares well. This comparison should shake the historical reluctance that surrounds admission of stroke patients to ICU.

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Stroke is the second largest contributor to mortality worldwide. Its devastating consequences are also a major contributor to morbidity, especially in high-income countries, where it is a leading cause of years of life lived with disability (Lopez et al. 2006). Historically, acute ischaemic stroke (AIS) was largely seen as an irreversible condition with reports previously suggesting no significant reduction in morbidity and mortality following intensive care unit (ICU) admission (Drake et al. 1973; Kennedy et al. 1970). Modern-day paradigms have changed however with an established, contemporary body of evidence showing that specific interventions can improve outcomes. As a consequence, thresholds for admitting AIS patients to ICU to support these interventions, and their potential complications, are falling. A recent analysis of 31,301 AIS patients admitted to hospital in the eastern half of the United States showed that 26% required ICU admission at some stage (Golestanian et al. 2009). Despite this, there seems to be a lack of widely accepted indications for admission to the ICU and evidence for management thereafter.

Standards of Care and Stroke Care Pathways

Management of acute stroke is complex. Interventions such as prompt diagnosis, consideration for thrombolysis, correction of deranged physiology and secondary prevention must be coordinated in a timely fashion. Care pathways assist healthcare professionals in making clinical decisions according to the best available evidence, thereby improving patient care and reducing variation in clinical practice. Their place in the acute management of AIS has therefore become commonplace. Some of the typical components of an AIS care pathway include (Intercollegiate Stroke Working Party 2012; National Collaborating Centre for Chronic Conditions (UK) 2008):

- If indicated, "immediate" brain imaging (ideally the next slot and definitely within one hour);
- If indicated, thrombolysis with alteplase within 4.5 hours;
- Direct admission to a specialist acute stroke unit;
- Antiplatelet treatment to start as soon as possible, and certainly within 24 hours.

The evaluation of care pathways in acute stroke is complicated however, given regional variability in content and delivery. A recent Cochrane review (Stroke Unit Trialists' Collaboration 2013) looked at the use of care pathways in acute stroke management and rehabilitation. Of the 15 studies, which included more than 4,000 patients, only three were randomised. The primary outcome measures of death and dependency at discharge showed no clear benefit with the use of care pathways. Mindful that non-randomised studies are susceptible to biases and clinical studies of care pathways are open to confounding, this Cochrane review still suggests that the benefits of AIS care pathways are not proven.

If care pathways are to succeed, they are only likely to improve standards of care if implemented in specialised stroke units. Such units confer a clear morbidity and mortality benefit over general medical care and should form the standard of care. This benefit does not seem to be limited by age, sex, type or severity of stroke (Stroke Unit Trialists' Collaboration 2013).

Where such units exist, cohesive multidisciplinary input ranging from paramedics and emergency physicians through to stroke specialists, interventional radiologists and surgeons are key to drive standards set in the care pathway. Intensivists are playing increasing

roles within these teams, ensuring that provision of optimal organ support and specialised nursing care continue in parallel to other ongoing stroke management. The delay in transfer of critically ill stroke patients from the emergency department to the neurointensive care has been shown to be an independent indicator of poor outcome at hospital discharge (Rincon et al. 2010).

Appropriate training tools can also improve standards of acute stroke care. Simulation-based models have been used to improve utilisation of thrombolysis by helping to identify barriers along care pathways (for example picking up delays in ambulance transfers) and provide solutions for these (for example the scoop-and-run protocol) (Lahr et al. 2013). Navarrete-Navarro et al. (2012) also showed that the introduction of a training model (e-learning course, lectures and workshops) focusing on therapeutic and organisational aspects of AIS management led to improved knowledge of emergency and critical care physicians and formed part of the regional strategy on stroke management, leading to increased uptake of thrombolysis in the region.

Indications for ICU Admission

The decision to admit an AIS patient to ICU is often to improve/support blood flow to the ischaemic penumbra. This is achieved through reperfusion therapies, optimisation of neuroprotective strategies and the support of other organs during neurological recovery. Other indications include prevention, early detection and treatment of complications and the need for close monitoring. Before making a final decision on appropriateness for admission, prior co-morbidity, cognitive and functional status and personal wishes should also be taken into consideration.

Accurate neurological prognostication is central to the decision to admit, but is notoriously difficult. Detailed history taking, thorough examination and appropriate imaging are key, but may not predict for all. Stroke mimics such as psychogenic disorders, hypoglycaemia, seizures, complicated migraine, encephalopathy, central nervous system mass lesions and drug toxicity need to be excluded. Neurological prognostication is near to impossible during the acute phase and is more accurately determined through repeated assessments temporally, involving regular discussion between ICU and stroke physicians (Kirkman et al. 2014). Therefore the American Stroke Association recommends aggressive treatment and postponement of "Do Not Attempt Cardiopulmonary Resuscitation" (DNACPR) orders for at least the first 24 hours (Jauch et al. 2013).

Table 1. Indications for the Intensive Care Unit Admission Following Acute Ischaemic Stroke: Our Recommendations (Kirkman et al. 2014)

Need for intubation and/or mechanic ventilation due to: • Decreased conscious level (GCS <8) or evidence of brainstem dysfunction or any other cause of a threatened airway • To prevent aspiration pneumonia in any of the above • Adjuvant therapy for intracranial hypertension or significant cerebral oedema • Acute respiratory failure, for example, due to pulmonary oedema (neurogenic or cardiac) • Generalised tonic-clonic seizures or status epilepticus • Apnoeic episodes
Severe stroke (National Institute of Health Stroke Score > 17)
Reperfusion therapy (intravenous or intra-arterial) • If multi-organ failure present • To manage complications of therapy (haemorrhagic transformation) • In those undergoing local intra-arterial therapy
Large middle cerebral artery infarct (145cm^3 on MRI) that predicts a malignant course
Persistent extremes of blood pressure, including: • systolic > 220 not undergoing thrombolysis or • systolic > 185 undergoing thrombolysis or • systolic < 90, that are difficult to manage in a ward setting
Management of organ support, particularly renal replacement therapy and noninvasive ventilation — needed either due to previous underlying condition or acute pulmonary oedema (for example) and cardiac dysfunction
Postoperatively following decompressive craniectomy
Management of the patient with massive stroke and high risk of mortality in whom organ retrieval/harvesting is planned

Reproduced with kind permission from Springer Science+Business Media: Intensive Care Medicine, The intensive care management of acute ischemic stroke: an overview, 40, 2014, 644, Matthew A. Kirkman, Giuseppe Citerio, Martin Smith, Table 1.

Kirkman et al. recently reviewed current AIS guidelines and produced recommendations on indications for ICU admission as shown in Table 1 (Kirkman et al. 2014). While patients with AIS, decreased level of consciousness and a National Institutes of Health Stroke Score (NIHSS) > 17 on admission are thought to have a poor prognosis, exceptions exist, such as the response seen by cerebellar infarcts to sub-occipital craniectomy (Kirkman et al. 2014; Wijdicks et al. 2014). The relationship between stroke severity and outcome should be observed with caution as patients with more severe deficits will inherently have the most to gain from treatment, especially when compared with mild strokes where death or severe disability have been used as the primary outcomes of research (Stroke Unit Trialists' Collaboration 2013).

The need for respiratory support is one of the more common causes for ICU admission in patients with AIS. While the literature is not clear, a few small trials indicate that patients who are intubated and ventilated for neurological deterioration (coma) and respiratory deterioration do not do as well as those who are intubated and ventilated for potentially reversible causes such as seizure management or prevention of aspiration pneumonia (Burtin et al. 1994; Leker and Ben-Hur 2000; Meyfroidt et al. 2014; Steiner et al. 1997; Wijdicks and Scott 1997).

Therapeutic Strategies in AIS Management

The initial supportive management of AIS is not complex and should not intimidate the ICU practitioner. Even in ICU, the simple task of ensuring that all the small facets of stroke care are done well can have the greatest benefit to our patients by avoiding secondary brain damage. Supplemental oxygen therapy targeted to oxygen saturation (to avoid both hypoxia and hyperoxia), avoidance of fever and glucose control are paramount. Both high and low blood pressure during an AIS are independent

poor prognostic factors for outcome (Leonardi-Bee et al. 2002). It is necessary to acutely lower blood pressure to less than 185/110mmHg to enable thrombolysis. If treatment does not include thrombolysis, only blood pressures greater than 220/120mmHg should be gently reduced by no more than 15% per 24 hours, except if co-morbidities such as severe cardiac failure, aortic dissection or hypertensive encephalopathy occur (European Stroke Organisation (ESO) Executive Committee and ESO Writing Committee 2008). AIS patients with very high or labile blood pressures, or patients who are being mechanically ventilated should have continuous invasive arterial blood pressure monitoring. Intravenous labetalol is most commonly recommended, but intravenous nicardopine or glycerine trinitrate may all be used to cautiously lower blood pressure. A recent trial has shown that more aggressive systolic blood pressure lowering to around 140mmHg is safe but confers no benefit (He et al. 2014).

Early aspirin therapy (within 48 hours) seems to confer a small benefit with fewer deaths and less stroke recurrence without an increase in haemorrhagic complications (CAST (Chinese Acute Stroke Trial) Collaborative Group 1997). Aspirin therapy should not however be used within 24 hours of thrombolysis (Jauch et al. 2013). Although immediate treatment with subcutaneous heparin is associated with less recurrent ischaemic strokes, it is associated with more haemorrhagic strokes and therefore AIS patients are not therapeutically anticoagulated for at least the first two weeks after their stroke and preferably after liaison with a haematologist.

AIS patients are at high risk of deep vein thrombosis (DVT) and pulmonary embolus (Jauch et al. 2013). This risk may be reduced through hydration and early mobilisation. However, the use of prophylactic subcutaneous low molecular weight heparin should be avoided for at least 24 hours after thrombolysis, and is commonly withheld for 2 weeks following an AIS for fear of potentiating a haemorrhagic transformation. The exact timing of initiating low molecular weight heparins is unclear and further research in this area is underway. The use of intermittent pneumatic compression is an effective method of reducing DVTs and shows a trend to reduced mortality, while graduated compression stockings do not reduce thromboembolic events and may cause skin tears and are therefore best avoided (CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration et al. 2013).

Two interventions that alter the natural course of AIS, which are both backed by level 1 evidence, are worthy of discussion and should be actively facilitated and supported where necessary with ICU admission. First, thrombolysis with intravenous recombinant tissue plasminogen activator (rTPA), after clinical and radiographic diagnosis of AIS. This should be given within a four-and-a-half-hour window and be instituted as soon as possible. Endovascular alternatives (e.g. clot retrieval, stenting) are gaining in popularity. New evidence suggests that some patients with AIS and moderate to severe neurological impairment, with very proximal occlusions, benefit from clot retrieval and stenting, demonstrated by improved outcomes beyond that possible by thrombolysis alone (Prabhakaran et al. 2015). Time to reperfusion seems to be the most crucial factor, irrespective of the method used. However, this field is moving fast and indications and preferences are likely to change.

Secondly, patients with large infarctions who are at risk of malignant cerebral oedema should be monitored closely, and early referral to a unit with neurosurgical capabilities should be discussed as soon as possible. Patients under the age of 60 with malignant MCA infarcts and cerebral oedema have improved outcome if decompressive craniectomy is achieved within 48 hours (Vahedi et al. 2007). The recent Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY) II trial has illustrated increased survival, but some survivors are often left with substantial disability (Jüttler et al. 2014) and surgery should be considered with caution especially in advancing age.

Comparing Outcomes – Is it Worth it?

One of the main reasons for refusing an AIS patient admission to the ICU is the perceived futility of the admission. Navarrete-Navarro et al. conducted a multicentre, prospective observational study in 28 Spanish hospitals that recorded the mortality and disability of 132 ICU-admitted severe stroke patients. Patients with AIS had the highest inpatient survival rate of 78%, but this decreased to 34% after one year and only 25% of patients had minimal or no disability at one year (Navarrete-Navarro et al. 2003). This data is similar to critical care outcomes at one of the largest acute stroke units in London, which followed up 144 patients over two years and found an ICU survival rate of 62% and a one-year survival rate of 30% in patients with AIS. Importantly over 60% of these survivors had a favourable neurological outcome (unpublished data).

These outcomes are not markedly different from other groups of critically ill patients. A recent prospective analysis of severe sepsis survivors showed comparable mortality outcomes as well as cognitive and functional disability rates. This large nationally representative cohort of more than 1,194 patients over the age of 50 revealed a 90-day mortality after severe sepsis of 41%. The odds of acquiring a moderate to severe cognitive impairment were 3.3 times more likely following sepsis when compared with a general hospital admission. Furthermore, there was a mean increase of 1.5 new functional limitations following sepsis (Iwashyna et al. 2010). Similarly, studies have shown that only 9% of long-term (median of 27 days) ventilated patients reach independent functioning at one year (Unroe et al. 2010).

Stroke should therefore be viewed in the same light as other severe conditions requiring ICU admission, including severe sepsis and long-term ventilation. Rapidly evolving strategies that aggressively alter the natural course of stroke hope to further improve stroke outcomes in the near future.

Conclusion

Stroke is a major contributor to mortality and morbidity worldwide. Modern-day attitudes and paradigms are shifting as a rapidly growing body of evidence emerges. As a result, there is generally less reluctance to admit AIS patients to ICU, and outcomes compare well with other serious ICU conditions. Effective management of the critically ill stroke patient requires proactive, rapid and coordinated decision-making by a multidisciplinary team, including stroke physicians and nurses, intensivists and radiologists. This teamwork does not always come naturally; education, regular training, systems and support need to be put in place to ensure that the correct resources are rapidly bought to bear on one of the most time-critical medical emergencies. It is hoped that future trials will identify further medical interventions and better ways to structure stroke units to facilitate better outcomes. ■

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THERAPEUTIC HYPOTHERMIA FOR CARDIAC ARREST

Targeted temperature management is the key intervention for improving neurological outcomes after cardiac arrest. We discuss new data on the optimal timing and modalities of targeted temperature management.

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It took nearly half a century, from 1957 to 2002, for therapeutic hypothermia to acquire its current status as a key intervention for improving neurological outcomes in survivors of cardiac arrest. Despite growing interest from healthcare workers and researchers, many questions remain unanswered regarding this treatment tool. Recent large multicentre trials raised as many questions as they provided answers. In this review, we will try to reconcile new and old data, explain discordant results, and discuss future trials of therapeutic hypothermia and other aspects of the management of cardiac arrest survivors.

Indications of Therapeutic Hypothermia

Cardiac Arrest in Shockable Rhythm

For the past 12 years, treatment decisions for cardiac arrest survivors have relied largely on two trials reported in 2002 (Hypothermia after Cardiac Arrest Study Group 2002; Bernard et al. 2002). Both trials showed improved neurological outcomes with hypothermia between 32° and 34° compared to normothermia after cardiac arrest in shockable rhythm. The vast majority of observational, retrospective, and propensity-adjusted cohort studies support this finding. The landmark Targeted Temperature Management (TTM) trial reported in 2013 (Nielsen et al. 2013) failed to demonstrate any difference in neurological outcomes or survival between hypothermia at 33° and hypothermia at 36°C. The results of the TTM trial complicate the interpretation of another preliminary study showing better outcomes with hypothermia at 32°C compared to 34°C (Lopez-de-Sa et al. 2012).

These data have generated active controversy. The International Liaison Committee on Resuscitation (ILCOR) issued the following statement:

Pending formal consensus on the optimal temperature, we suggest that clinicians provide post-resuscitation care based on the current treatment recommendations. We accept that some clinicians may make a local decision to use a target temperature of 36°C pending this further guidance (ILCOR 2013).

The European Resuscitation Council (ERC) new guidelines issued in October 2015 specify: "maintain a constant, target temperature between 32°C and 36°C for those patients in whom temperature control is used" (Nolan et al. 2015).

Several considerations may help to reconcile new data from trials of TTM and older results. First, TTM at 36° is not normothermia [37°]. The difference in neurological outcomes between two groups depends on the temperature difference: for instance, a 3° difference [e.g., 33° vs. 36°] may produce a 33% smaller benefit than a 4° difference [e.g., 33° vs. 37°]. Second, the control groups were not comparable between the trials reported in 2002 (Hypothermia after Cardiac Arrest Study Group 2002; Bernard et al. 2002) and 2013 (Nielsen et al. 2013). Interest in the management of cardiac arrest increased massively during this interval, leading to marked improvements in outcomes, due not only to TTM, but also to changes in the management of heart disease, notably the use of coronary angiography (Dumas et al. 2012), haemodynamics and gas exchange. The benefits from these other interventions may decrease the relative effects of TTM to levels detectable only in large sample sizes. Third, 10% to 20% of patients survived without marked neurological damage (Cerebral Performance Category 1 or 2) in subgroups with favourable prognostic factors (bystander cardiopulmonary resuscitation and short low-flow time) in the 2002 trials and in patients with poor prognostic factors (no bystander, longer low-flow time and, above all, non-shockable rhythm) in recent trials. Conceivably, patients with more severe brain damage may benefit from lower temperatures, e.g., 33°C instead of 36°C. In several retrospective studies, benefits from TTM at 33°C were more marked in patients with longer no-flow or low-flow times (Testori et al. 2012; Kagawa et al. 2010; Drennan et al. 2014), but this result was not replicated in a post hoc analysis of data from the TTM trial (Kjaergaard et al. 2015).

Cardiac Arrest in Non-Shockable Rhythm

Patients with cardiac arrest in non-shockable rhythms now account for the majority of patients admitted to the ICU after the return of spontaneous circulation (ROSC) (Wong et al. 2014). Their prognosis is considerably poorer compared to that of patients with cardiac arrest in shockable rhythms. Nevertheless, very few data are available on this specific population, which is more heterogeneous than the population with cardiac arrest in shockable rhythm, as causes include heart disease, pulmonary embolism, asphyxia, hanging and many other conditions. Except for a subgroup analysis in the TTM trial (Frydland et al. 2015), no data from randomised trials are available. Guidelines still recommend TTM after non-shockable cardiac arrest. An ongoing trial will provide information on this growing population of cardiac arrest survivors (Lascarrou et al. 2015).

1. Modalities of Targeted Temperature management (Nau et al. 1992)

Induction of TTM

Recent data on conducting TTM, particularly the induction phase, are available. Earlier induction seemed associated with better outcomes in animal experiments and small observational studies. However, no adequately powered trial in humans

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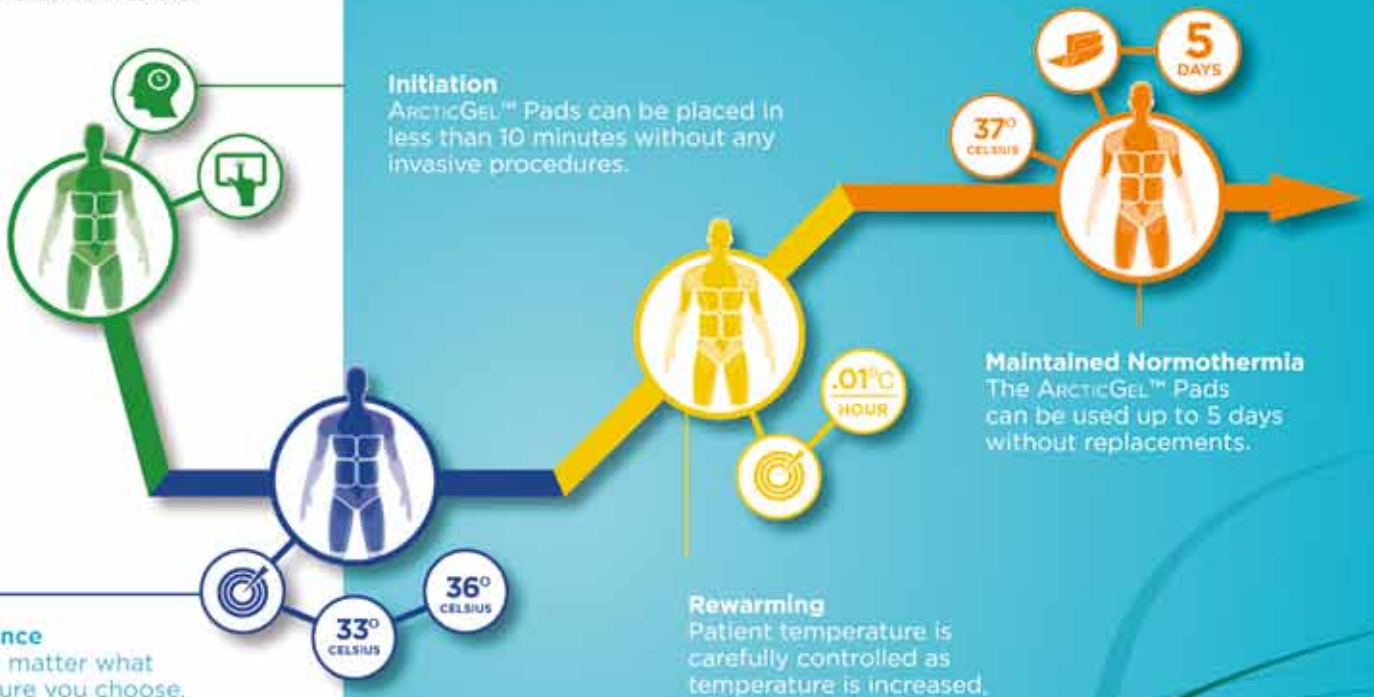

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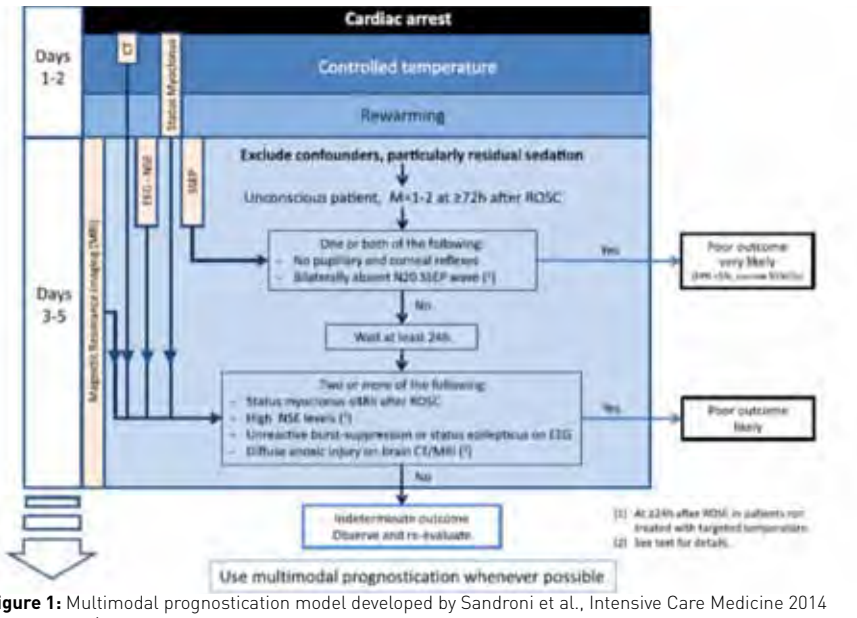

Figure 1: Multimodal prognostication model developed by Sandroni et al., Intensive Care Medicine 2014 (Open Access)

Suggested prognostication algorithm. The algorithm is entered ≥ 72 h after ROSC if, after the exclusion of confounders (particularly residual sedation), the patient remains unconscious with a Glasgow Motor Score of 1 or 2 The absence of pupillary and corneal reflexes, and/or bilaterally absent N20 SSEP wave, indicates a poor outcome is very likely. If neither of the features is present, wait at least 24 h before reassessing. At this stage, two or more of the following indicate that a poor outcome is likely: status myoclonus ≤ 48 h; high neuron-specific enolase values; unreactive EEG with burst suppression or status epilepticus; diffuse anoxic injury on brain CT and/or MRI. If none of these criteria are met consider continue to observe and re-evaluate.

Reprinted from: Sandroni C, Cariou A, Cavallaro F et al. (2014) Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. Intensive Care Med, 40(12): 1816-31.

has confirmed this possibility. Pre-hospital induction of mild hypothermia by infusing 4°C normal saline immediately after ROSC not only failed to improve neurological outcomes, but was also associated with higher rates of re-arrest and acute pulmonary oedema (Kim et al. 2014). However, this trial has several methodological weaknesses: only 77% of patients managed with pre-hospital hypothermia subsequently received hospital maintenance of hypothermia, and oxygenation level was unusually high in the patients diagnosed with acute pulmonary oedema. A major source of bias in studies of TTM is the faster speed of cooling in the sickest patients, due to absence of the hypothalamic response to cooling (Lin et al. 2014). There is probably a need for studies of fluids other than normal saline for inducing hypothermia. In particular, balanced crystalloid solutions (Hartman's solution and others) are generating considerable attention for managing sepsis, and may deserve similar interest in the treatment of cardiac arrest survivors. Finally, an intranasal cooling system for inducing hypothermia in the field, with no fluid infusion, is under investigation (Nordberg et al. 2013).

Maintenance of TTM

Hypothermia can be maintained using a specific internal or external device equipped with a temperature control driver or using non-specific means, such as a makeshift tent and conventional ice packs. Studies of specific devices, including a recent randomised trial (Deye et al. 2015), showed no improvement in neurological outcomes compared to nonspecific means, although nurse workload was lower.

Duration of TTM and Rewarming Phase

No adequately designed trial is available for guiding decisions about the duration of hypothermia or the speed of rewarming. Based on the trials reported in 2002, TTM is usually maintained for 12-24 hours. However, the longer duration used in the TTM Trial may have beneficial effects, notably on the inflammatory response (Bisschops et al. 2014). Another trial addressing hypothermia duration is under way [NCT02035839] (Zoll Circulation Inc 2015). Last, findings from observational studies support a slow pace of rewarming, and further information on this point will be provided by an ongoing trial [NCT02555254] (Centre Hospitalier Departemental Vendee 2015).

2. Patient Management During Therapeutic Hypothermia

A specific protocol adapted to local conditions must be developed and applied to optimise neurological outcomes after TTM (Sunde et al. 2007). All healthcare workers must adhere to guidelines (Orban et al. 2012; Camp-Rogers et al. 2013). Sedation and analgesia are necessary during TTM induction, maintenance and rewarming, but interfere with the neurological examination, thereby hindering outcome prediction. The predicted neurological prognosis is a major consideration when deciding whether treatment limitation decisions are in order. There is some evidence that drugs with short half-lives, such as propofol and remifentanil, may deserve preference over drugs with longer half-lives, such as midazolam and fentanyl (Bjelland et al. 2012). TTM is often associated with shivering. The first-line treatment of shivering is adjustment of the sedation and analgesia. If shivering persists, surface counterwarming, dexmedetomidine, or neuromuscular blockade may be used depending on the local protocol. Recent data suggest beneficial effects of neuromuscular blockade on neurological outcomes (Lascarrou et al. 2014; Salciccioli et al. 2013), but the level of evidence is low and further studies are needed.

3. Side Effects

Recent trials have improved our understanding of the risk/benefit ratio of TTM. Most adverse effects are well-known and have no effect on mortality or morbidity; examples include changes in the electrocardiogram or in serum potassium levels. A few are more serious and can lead to increased morbidity. The pathophysiological effects of hypothermia explain the increased risk of bacterial pneumonia associated with TTM in all studies. This risk is particularly high in cardiac arrest patients, whose upper airways are unprotected until endotracheal intubation is performed. Nevertheless, no effect of pneumonia on neurological outcomes was found in recent studies, regardless of their design (observational, observational with propensity-adjusted analysis) (Gagnon et al. 2015; Perbet et al. 2011).

4. Prognostication: Early and Late

Large strides have been made in neurological prognostication since the trials reported in 2002. The two main advances are the clear definition of situations warranting treatment limitation decisions in the most recent trials and the availability of validated and accurate prognostication criteria that can be used at the bedside. These tools consist of clinical tests (Glasgow motor score and brainstem reflexes), serum assays of neuron-specific enolase and S-100B, evoked potential recordings and electroencephalography and magnetic resonance imaging (MRI). Neurological prognostication now relies on a combination of findings

obtained using these tools. It cannot be performed accurately until 72 hours after the arrest, except when the prognosis is catastrophic, defined in the TTM trial for instance as "the patient becomes brain dead, has an early myoclonus status or, if there are strong ethical reasons to withdraw intensive care" (Nielsen et al. 2013). Recent European guidelines (see Figure 1) provide clinicians with useful guidance (Sandroni et al. 2014). However, according to a recent survey intensivists vary widely regarding the tools they use for neurological prognostication, and their decisions may be based as much on beliefs as on science (Friberg et al. 2015).

Predicting a poor neurological prognosis is important to determine whether life-sustaining interventions should be withheld or withdrawn. There is growing evidence that factors predicting a good prognosis can be assessed during TTM. Thus shivering (Nair and Lundbye 2013) and bradycardia (Staer-Jensen et al. 2014; Thomsen et al. 2015) during TTM are associated with better outcomes. Furthermore, although the use of specific cooling devices does not affect patient outcomes, they indicate how much power is needed to cool the patient, and greater power is associated with better outcomes (Murnin et al. 2014).

Predictors of neurological outcomes must be well characterised both for designing trials of individualised treatment strategies and to provide accurate information to the family. Attention to cognitive impairments and emotional difficulties in cardiac arrest survivors may improve outcomes even in the medium and long term (Moulaert et al. 2015).

Conclusion

Although recent efforts have chiefly targeted the first three links in the chain of survival (Becker et al. 2015), we must keep in mind that TTM is the only intervention proven to favourably affect the fourth link. Huge knowledge gaps still exist regarding all aspects of patient management during TTM. Further trials are needed to fill these gaps and to provide the information needed to develop individualised treatment strategies. ■

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

NEWS

SURVEY: IN-HOSPITAL CARE OF CRITICALLY ILL PATIENTS IN FRANCE

When patients present with organ failure to French teaching hospitals, the receiving hospitals have very varied staffing and organisation, according to a survey by the French Society of Anaesthesia & Intensive Care - Société française d'anesthésie et de réanimation (SFAR). The results have been published in the Society's journal, *Anaesthesia Critical Care & Pain Medicine*.

Lead author, Dr. Hervé Quintard, University Hospital of Nice, told ICU Management that the management and role of intensivists and anaesthesiologists in this situation has never been assessed before in France. This survey was intended as the first step to describe effective organisation for patients with a life-threatening condition.

The questionnaire was sent to 32 university hospitals that admit patients with organ failure, and had a 75% response rate. These hospitals admitted between 700-1400 patients to emergency units per week, of which 10 to 20 were admitted for critically ill conditions.

The criteria for receiving patients with a life-threatening condition were highly variable, as were staffing and organisation. In 18% of hospitals, such patients were treated in a specialised room in the ICU; in 40% of hospitals they were treated in a specialised room in the emergency department (Service d'admission des urgences vitales [SAUV]) Intensivists were involved in 50% of hospitals, emergency physicians in 26% and staffing was mixed in 24% of hospitals.

Dr. Quintard said that the most surprising finding was the heterogeneity of organisation of in-hospital primary care, which could have an impact on patient prognosis. He noted: "These observations underlined the fact that the same patient could have different care according to his geographic situation. For example, a thoracic trauma could be treated directly by intensivists in ICU whereas in another hospital it could be treated by physicians, not always trained to manage trauma, in an emergency room not always dedicated for unstable patients."

The specialist physicians could be reached in 20 (84%) of hospitals, but a formal network was efficient in only 11 (45%) of the hospitals. Dr. Quintard observed that most teaching hospitals had specialist physicians in their organisation, but a network to develop direct contact with specialists is essential to improve prognosis.

They recommend that consensus be sought to homogenise and improve practice. The authors conclude that the logical and most efficient approach is to favour direct hospitalisation of patients with several organ failures in an ICU rather than in a salle d'accueil des urgences vitales (SAUV). Dr. Quintard said that "The right patient in the right place " is essential for improving prognosis of patients. A better interaction between prehospital care and intra hospital orientation is essential for improving procedure. They plan to investigate non-teaching hospitals in due course.

In an accompanying editorial, Dr. Pierre Bouzat, Dr. Pierre-Géraud Claret and Dr. Jean-François Payen write: "Improving the morbidity and the mortality in these pathologies is undoubtedly linked to networking that provides the perfect path from initial symptoms to definitive treatment. They add: "The heterogeneity of leadership in French ERs only illustrates heterogeneous local expertise. Everyone should follow the leader in the ER and the leader is the one who knows!" ■

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Bouzat P, Claret P-G, Payen J-F (2015) Management of life-threatening emergencies in France: follow the leader! Anaesth Crit Care Pain Med, 34(4):189-90. doi: 10.1016/j.accpm.2015.07.001 - See more at: https://healthmanagement.org/c/icu/news/survey-in-hospital-care-of-critically-ill-patients-in-france#sthash.Mirv3wbL.dpuf

BURN CARE

REGIONALISATION, ORGANISATION AND TRIAGE

The interdisciplinary nature of burn care has driven centre regionalisation. The role of burn centres in the national trauma system cannot be overstated.

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Burn centres, essential components of any trauma system, serve a broad base of patients, including potentially those injured in mass casualty events. Over the past fifty years, the field of burn care has made dramatic improvements in patient outcomes following severe burns, attributable to advances in all aspects of patient management. The complexity of patient care, both in the short- and long-term, requires a well-prepared interdisciplinary team. Such implementation has been made possible by centre regionalisation.

Regionalisation of Burn Care

Specialised burn care has been in place in the United States since 1947 (Brigham and Dimick 2008). While still a source of significant morbidity and potential mortality, outcomes of burn injury have improved greatly; fire-related deaths fell from 2.9 per 100,000 population in 1970 to 1.5 per 100,000 in 2000 (Gibran et al. 2005). Currently, only 3% of burn centre admissions result in fatality, and almost 88% of patients are discharged to home (American Burn Association (ABA) 2015). This unprecedented survival and functional recovery was brought about through fluid (Baxter et al. 1973) and nutritional (Curreri et al. 1974) resuscitation protocols; early burn wound excision and closure (Desai et al. 1990); expanded graft coverage products and techniques (Jeschke et al. 2013); topical antimicrobials; and the pharmacologic modulation of the hypermetabolic response (Demling and DeSanti 2003). As important was the recognition that such patients require a team of experts to optimise their outcomes. These teams, led by burn surgeons but involving professionals across multiple disciplines, could likely not exist without the regionalisation of care, i.e. the hierarchical consolidation of patients with similar diagnoses in a geographic catchment area. Similar groupings have demonstrated benefits in many other complex surgical conditions (Mackenzie et al. 2006; Luft et al. 2007; Birkmeyer 2000; Birkmeyer et al. 2002). That these benefits would extend to burn patients is unsurprising.

With the physiologic damage that results from thermal injuries often comes significant physical and psychosocial rehabilitation requirements necessary to facilitate reentry into society. As such, successful and cost-effective burn management requires not only a surgeon experienced in burns and critical care, but a skilled nursing staff, physical and occupational therapists, social workers, nutritionists, pharmacists and chaplains. Paediatricians and child life specialists are commonplace when caring for younger patients (Kastenmeier et al. 2010). Representing multidisciplinary care in its truest sense, this care extends well beyond the initial treatment, with burn serving as a hub for necessary aftercare as well (Sheridan et al. 2000). It would be difficult to provide this level of expertise in a non-regionalised fashion, and the benefits are mutual to patients and providers — providers stay busy enough to maintain their skills, patients benefit from the derived expertise (Warden and Heimbach 2003).

This approach has proven benefits. Mortality has been improving for decades (Wolf et al. 1997; Sheridan et al. 2003; Palmieri et al. 2008). Verified burn centres in California were shown to have comparable mortality rates to non-verified burn centres, despite admitting more patients per centre and caring for more severely injured patients (Palmieri et al. 2008). Delayed transfer to a burn centre was shown to have deleterious effects on risk of infection, renal dysfunction, wound sepsis and bacteraemia, and was also associated with a longer time to 95% wound closure and a longer hospital stay in paediatric patients (Sheridan et al. 1999). While multidisciplinary treatment has been shown to have significant impact on patient quality of life after discharge (Sheridan et al. 2000), patients treated in high-volume centres have been shown in multiple studies to be more likely to discharge home, rather than to skilled nursing facilities, implying better functional outcomes at discharge (Pacella et al. 2006; Klein et al. 2008).

Regionalisation has prompted appropriate concerns that with a reduction in centres most equipped to treat burns would come morbidity associated with a delay in care. These concerns have not been borne out. If injuries occur at a significant distance from a burn centre, patients are triaged at an outside hospital and resuscitation is begun, often under remote guidance from a burn centre. Patients are then transported for definitive management. Transfer itself, even over substantial distances, has been shown to be safe (Klein et al. 2007). Transfer from an outside facility has not been shown to increase

length of stay, operations, hospital charges or mortality (Klein et al. 2006; Bell et al. 2012).

The consolidation of expert wound care and critical care management has benefits extending beyond burn treatment. Clinically, highly morbid conditions such as toxic epidermal necrolysis, necrotising fasciitis and frostbite are routinely referred to burn centres acting as 'wound intensive care units' for definitive management with excellent outcomes (Barillo et al. 1989; Faucher et al. 2001; Palmieri et al. 2002; Endorf et al. 2005). From an educational perspective, these centres drive the outreach in their respective areas, and serve as excellent training grounds for clinicians, whether students, residents, fellows, nurses, therapists, pharmacists or nutritionists. Burn centres are also at the forefront of clinical and basic science research pertaining to all facets of burn and wound care (Gibran et al. 2005).

The concept of burn care regionalisation has been around for decades (Praiss et al. 1980). However, despite documented improvements in outcomes and easily accessible ABA transfer criteria, the adherence to such criteria remains fairly low, with studies demonstrating that significant numbers of patients meeting ABA referral criteria are not transferred to ABA-verified burn centres (Zonies et al. 2010; Holmes et al. 2011). The responsibility for educating outside hospitals and arranging transfer agreements falls on such facilities to ensure that burn patients benefit from the expertise and resources that they are uniquely able to offer.

Staffing Guidelines

In North America, approximately 60% of acutely injured burn patients are hospitalised at the 128 burn centres, with the remainder spread across the other 5,600 acute care hospitals. This results in a 200:1 ratio of admissions in favour of the dedicated burn centre (Healthcare Cost and Utilization Project 2010). Of these 128 centres, only 63 have achieved external verification by an outside agency, the American Burn Association (ABA). The guidelines for providing optimal care of severely burned patients were set forth initially in the *Resources for Optimal Care of the Injured Patient* (American College of Surgeons, Committee on Trauma 2006), and are now refined on the ABA website (ABA 2014). Where possible, numbers are listed, reflecting average values derived from a cross-sectional biopsy of verified burn centres.

In 1995 the ABA and the American College of Surgeons Committee on Trauma (ACSCOT) developed a verification process to externally validate the quality of care by U.S. burn centres (Gamelli et al. 2007). In addition to its focus on survival, objective review of complications to determine preventability, emotional health, and reintegration in society, this rigorous process sets minimum guidelines for burn centre facilities, volume, staffing, experience, continuing education, dedication to prevention, teaching and research.

The burn centre hospital must maintain a specialised unit, with designated ICU-capable beds dedicated to acute burn care (ABA 2014). There must be a sufficient number of admissions to maintain clinical competency for the staff in the critical care of burn patients (ABA 2006). The minimum number of yearly admissions is 100 for both adult and paediatric programmes (ABA 2014). Overall burn centre admissions number more than 200 (Healthcare Cost and Utilization Project 2010), while verified burn centres (VBC) average 250. The average number of burn centre beds is 17. While the average daily census must be greater than three (ABA 2014), the mean VBC census is eight. If the burn centre is not a designated trauma facility, there must be transfer agreements to provide care for the 5% of burn patients who have associated trauma. Burn surgeons demonstrate expertise in burn treatment by completion of a burn fellowship or by two or more years of mentored experience in the management of patients with acute burn injuries. Each must be involved in the primary decision-making of at least 35 burn patients each year (50 for the burn director). There must be at least one burn surgeon for every 300 admissions.

The burn unit manager must have two or more years of acute burn care experience and six months of managerial experience. A staffing system that adjusts for patient acuity is required. The average VBC has one nurse for every critically ill acute burn admission during the first 24 hours; the ratio can be as high as three nurses per patient during wound care. The patient:nurse ratio decreases to 1.5:1 during the next 24 hours, and stabilises between 2-3:1 during the remaining acute hospitalisation. Burn-specific nursing orientation and ongoing education is required. Due to the extensive learning curve and camaraderie developed through shared experiences, it is not surprising that burn centre nursing teams show an average experience and turnover at VBC of 8 years and 8.5% respectively. The nursing managers are expected to participate in burn-related clinical, education and performance improvement activities.

Because rehabilitation is so important for the functional recovery of burn patients, an organised rehabilitation programme with patient-specific goals is essential (ABA 2006). Both occupational and physical therapists are mandated, with availability seven days a week, and staffing must be one therapist per six patients. Ideally, speech therapy and cognitive therapy are also present. Burn aftercare requirements state that more than 75% of all discharged patients must be followed by the burn programme. Access to appropriate rehabilitation, reconstructive surgery, peer support/survivor groups and vocational counselling must be available (ABA 2014). A dedicated anaesthesia team with burn experience, surgical technicians and nurses who regularly work with the thermally injured patient, and burn specific pre- and postoperative protocols are required. Integration of the critical care pharmacist into daily clinical burn rounds results in improved overall care and significant cost avoidance, and prevents drug-related toxicity (Patel et al. 2006). Respiratory therapists and dietitians with adequate critical care and burn experience should be available on a 24 hour basis (ABA 2014). As with physicians and nurses, all members of the burn team must complete varying amounts of burn-specific education each year. For centres caring for the burn-injured child, child life or recreational therapy personnel are required. Opportunity to continue with school while hospitalised is standard; school re-entry programmes are strongly encouraged. Paediatric intensivists and paediatricians participate in the age-specific care of these young patients.

> "Verified burn centres...essential to the national trauma system"

Triage in Burn Injury

Despite improved regionalisation and staffing of burn centres, there are rare occasions in which mass disasters may overwhelm the resources of

Table 1.

	Burn Size (%TBSA)									
Age, yrs	0 – 10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	91+
0-1.99	Very High	Very High	Very High	High	Medium	Medium	Medium	Low	Low	Low
2-4.99	Outpatient	Very High	Very High	High	High	High	Medium	Medium	Low	Low
5-19.9	Outpatient	Very High	Very High	High	High	High	Medium	Medium	Medium	Low
20-29.9	Outpatient	Very High	Very High	High	High	Medium	Medium	Medium	Low	Low
30-39.9	Outpatient	Very High	Very High	High	Medium	Medium	Medium	Medium	Low	Low
40-49.9	Outpatient	Very High	Very High	Medium	Medium	Medium	Medium	Low	Low	Low
50-59.9	Outpatient	Very High	Very High	Medium	Medium	Medium	Low	Low	Low	Low
60-69.9	Very High	Very High	Medium	Medium	Low	Low	Low	Low/ Expectant	Low/ Expectant	Low/ Expectant
70+	Very High	Medium	Medium	Low	Low	Low/ Expectant	Expectant	Expectant	Expectant	Expectant

Credit: Saffle JR et al. (2005) Defining the ratio of outcomes to resources for triage of burn patients in mass casualties. J Burn Care Rehabil, 26(6):478-82, by permission American Burn Association.

any given burn care facility. In these cases, it is important to triage patients appropriately in order to maximise overall survival.

Burns are a unique injury in that mortality can be very accurately predicted using simply the patient's age and percent total body surface area burned (%TBSA) (Hussain et al. 2013). The ABA adopted a table created by Saffle et al. (2005) that used data from the National Burn Repository to predict outcome to resources ratios for the spectrum of ages and burn severity (see Table 1). The following categories for the possibility of survival and the required resources to care for those patients are used:

1. **Outpatient:** Patients that will have greater than 95% survival and will not need to be hospitalised.
2. **Very High:** Survival greater than or equal to 90%, length of stay (LOS) less than or equal to 14-21 days, 1 to 2 operations needed.
3. **High:** Survival greater than or equal to 90%, LOS 14-21 days, multiple operations necessary, prolonged rehabilitation.
4. **Medium:** Survival greater than 50% but less than 90% even with full treatment.
5. **Low:** Survival greater than 10% but less than 50% despite full treatment.
6. **Expectant:** Survival less than or equal to 10% despite full treatment.

These criteria were reviewed in 2014 by Taylor et al., who added inhalation injury to better reflect true mortality numbers, as updated by newer data from the National Burn Repository.

The ABA has a defined disaster management plan including triage scenarios (ABA Board of Trustees and the Committee on Organisation and Delivery of Burn Care 2005). Primary triage requires burn patients to be sent to a burn centre within 24 hours of a disaster. The incident commander on site should contact the nearest verified burn centre, determine available capacity, and solicit alternative burn centre information if necessary. Secondary triage is the transfer of patients from one burn centre to another when a given centre's surge capacity is reached. This determination should be made by the burn centre director, but is based on a surge capacity of 50% more than the normal maximum number of burn patients at that facility. Transfer is recommended to ABA-verified burn centres when possible and then to other burn centres. Secondary triage should ideally be completed within the first 48 hours following the disaster.

Conclusion

Optimal burn care requires a diverse team of professionals. Consolidation of resources, including staff expertise and availability, has produced a trend towards regionalisation, which has proven beneficial to patient outcomes. Preparedness to handle large-scale disasters is just part of what makes verified burn centres so essential to the national trauma system. ■

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Whole Blood Analyser for Point-of-Care Lactate Testing

The Surviving Sepsis Campaign (SSC) has produced new recommendations titled *International Guidelines for Management of Severe Sepsis and Septic Shock: 2012*. These new updated guidelines call for lactate assays to direct therapy for septic shock. For patients with lactate greater than 4 mmol/L, SSC recommends quantitative resuscitation targeting normalization of lactate levels.

StatStrip Lactate provides a 13 second assay on a whole blood sample to allow rapid, early, goal directed therapy in septic patients. Testing is as fast and easy as bedside glucose testing. The single use StatStrip Lactate biosensor is pre-calibrated, fast and uses a very small whole blood sample (0.6 microliters) yet provides lab equivalent accuracy.

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Switzerland is a country of 8.2 million inhabitants, who mostly live outside one of the six major cities: Zurich (384,786 inhabitants), Geneva (191,557), Basel (174,491), Lausanne (132,626), Berne (128,848) and Winterthur (105,676) (Bundesamt für Statistik 2015). Switzerland is composed of 26 cantons that enjoy a great deal of independence from the federation. The jurisdiction of the emergency service and hospital structure mainly lies with these cantons (Wyss and Lorenz 2000), although smaller cantons collaborate on many aspects. For example, Basel University Hospital (its official name translates as "University Hospital of both Basels") is a joint undertaking of the two cantons Basel City and Basel Country.

Healthcare System

Every Swiss inhabitant, regardless of nationality, is obliged to obtain healthcare insurance that in its base tariff covers the costs of healthcare and medication listed in a legal document. Insurance for accidents, both during work or leisure, is further provided through employers, who insure their employees, usually with one of the few major companies that provide this type of coverage. The government subsidises insurance fees for the needy.

The Swiss healthcare system is among the most expensive in the world. In a 2006 comparison of the costs of healthcare in OECD member countries, Switzerland came second after the United States, with average expenditure of 11.1% of GDP on healthcare (OECD 2010). However, in the most recent comparison of the quality and performance of healthcare systems among the 197 member states of WHO, Switzerland was rated second in the overall quality of its system ("attainment of WHO-goals") and 20th in performance (where quality is compared to costs) (WHO 2000).

Emergency Medicine

As in most western countries, major emergency rooms are usually part of a university hospital, of which there are five in Switzerland: Basel, Berne, Geneva, Lausanne and Zurich. In 2006 there were 138 hospital-based emergency rooms in Switzerland, of which 21 (including the five affiliated to a university) provide care to more than 20,000 patients per year (Sanchez et al. 2006).

As pre-hospital emergency services are largely regulated (and often provided or commissioned) by cantons, there is a great diversity of modes of service. This article therefore focuses on the situation and numbers from Berne.

As the canton of Berne covers a large alpine area and its university hospital is the closest by air to most of the Swiss Alps, patients injured when farming the steep slopes or during sport make up a comparatively large portion of emergency patients here (see Table 1), leading to a relatively young population of patients (see figure 1). This may further explain why caring for hypothermic patients is comparatively common in the Berne University emergency room.

Pre-hospital emergency service in the canton of Berne is mainly provided by Rega and Air Glacier (both providing a physician-staffed helicopter rescue service) and the 'Sanitätspolizei' (translated as 'rescue police') on the ground. The Sanitätspolizei staffs one car with an emergency physician around the clock that can meet the emergency medical service at the scene if

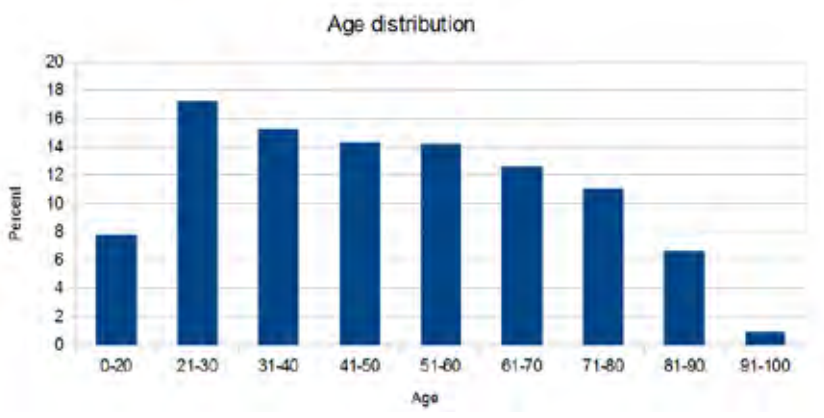

Figure 1. Age distribution of patients admitted to the Berne University Hospital Emergency room, 1 October 2014 - 30 September 2015

needed, but paramedics in the usual rescue operation are fairly well trained and are competent to provide a number of medical procedures and treatments, including administering selected medications or providing advanced airway management.

Once on their way to an emergency room, more seriously ill patients are typically transported to one of the larger hospitals by the Sanitätspolizei. Most patients in Swiss emergency departments, however, are walk-in patients who present themselves (and most of the time are treated and discharged: see Table 1). Around 60% of all patients presenting to the emergency room in Berne are discharged home. Only around 5.7% are admitted to the intensive or immediate care unit. Intensive care specialists can typically expect a complete diagnostic workup of patients transferred to the ICU, including collection of microbial samples, calculated antibiotics, lumbar puncture and the collection of procedural statements from all relevant disciplines. In Berne, almost the only measure we omit in the emergency room is inserting a central venous line into patients before admitting them to the ICU, because doing so could limit the ICU's options for extended haemodynamic monitoring, with either PICO catheters or a pulmonary artery catheter, which is usually inserted together with a central venous line.

> "Intensive care specialists can typically expect a complete diagnostic workup of patients transferred to the ICU"

Emergency Rooms

Most hospitals throughout Switzerland now operate as interdisciplinary units, but there are still some older systems, in which patients are separated along the lines of surgical care or internal medicine (Sanchez et al. 2006). The emergency room at Berne University Hospital is an interdisciplinary unit within the department of emergency medicine, intensive care and anaesthesiology and sees all adult patients with an interdisciplinary team. As in most other emergency rooms throughout the country, patients are classified according to the urgency of their treatment by specially trained nurses using a standardised triage model (Hallas 2006; Hollimann et al. 2011). Urgent treatment (for around 7.5% of our patients) is usually provided within one of the three shock rooms, while patients with minor complaints can be referred to an integrated 'fast lane', staffed with one general practitioner from 8am to 10pm every day. Discharged patients can also be scheduled to revisit within this fast lane concept.

Aside from patients who walk in or who are brought in through an emergency service, the emergency room at Inselspital Berne sees all non-planned patients referred to any of the specialities at the University Hospital from an outside clinic. In total, we see more than 40,000 patients a year, with numbers continually rising for the last five years. Around 18% of these patients are brought in by ambulance or helicopter, slightly below half (46%) present themselves and the remainder are referred to us from various sources, including external hospitals, general practitioners, the police, psychiatric institutes or

Table 1. Characteristics of patients admitted to the emergency room at Inselspital Berne, 1 October 2014 – 30 September 2015. Percentages within each category.

Total number of patients		41007
Gender	female	43.5%
	male	56.5%
Admittance	ambulance or helicopter	17.9%
	external physician or hospital	16.8%
	self	46.1%
	police or detention facility	1.2%
	other	17.9%
Discharge	home	59.6%
	ICU/IMCU	5.7%
	external hospital	5.0%
	ward	26.8%
	other	2.9%
Triage category	1	7.5%
	2	23.0%
	3	58.9%
	4	6.9%
	5	3.6%
Type of emergency	surgical	30.9%
	medical	27.5%
	neurological	9.8%
	other	31.9%

ICU – Intensive Care Unit; IMCU – Intermediate Care Unit

prisons (see Table 1). Those patients presented by the police or referred from prisons are a special feature of Berne, as the university hospital here is the only one in Switzerland that runs a specialised ward for detainees with all medical care available.

Physician Education and Training

Current undergraduate teaching of emergency medicine is rather sparse in Europe (Smith et al. 2007). Education of physicians working in emergency medicine in Switzerland is regulated through the Swiss Society of Emergency and Rescue Medicine (SSERM). It offers two types of degrees, termed 'certificates of ability': one for preclinical and one for clinical emergency medicine. Both curricula are available online (**sgnor.ch/faehigkeitsausweise**). While the certificate for preclinical medicine is available to every physician who has completed the three year curriculum, the certificate for clinical emergency medicine is only available once candidates have completed residency and have obtained a degree in internal medicine, surgery, anaesthesiology, intensive care, orthopaedic surgery, traumatology or cardiology. To obtain the certificate, one further needs to participate in various courses (including Focused Assessment with Sonography in Trauma (FAST), Advanced Trauma Life Support® (ATLS) **facs.org/quality%20programs/trauma/atls** and Advanced Cardiovascular Life Support (ACLS)) and complete an 18-month rotation in an accredited emergency room. The curriculum is based on the curriculum of the European Society of Emergency Medicine (EUSEM), and the catalogue of learning objectives is an adaptation of the English Emergency Medicine specific learning objectives. The degrees in clinical or preclinical emergency medicine further require that the student passes a final assessment. However, emergency medicine is currently not available as a separate residency training in Switzerland (Osterwalder 1998), and the two certificates of ability do not substitute for a residency programme, but may be completed as part of a residency training. Maintenance of certification requires physicians in Switzerland to obtain a predefined number of credits for continuous education activities, but currently does not involve reassessments. ■

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BLAST INJURY

WHAT TO EXPECT IN CIVILIAN VS. MILITARY CONTEXTS

Civilian blast injuries are not rare, but most are not due to military explosives, meaning extrapolation from military texts is often inappropriate. In civilian mass casualty events, emergency departments will see large patient numbers, but few require surgery or intensive care. Survivors of small civilian blasts rarely have blast wave injury and should be treated according to standard trauma principles.

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Blast injuries are uncommonly encountered in civilian practice, but equally are not rare. For example, in the United States from 1983-2002, 36,110 civilian bombing incidents were reported (Kapur et al. 2005). The most common intent was homicide, not terrorism. Nonetheless, between 1991-2000, there were 29 worldwide terrorist attacks in which there were >30 casualties (Arnold 2004). Dwarfing numbers of criminal incidents, but less easily quantifiable, are accidental burns that involve a component of blast (for example from exploding fuel-air mixtures). Frequently, but erroneously, civilian clinicians turn to military texts (such as the *Combat Casualty Care* textbook (Savitsky and Eastridge 2012)), or are misled by civilian news sources that sometimes seek to sensationalise incidents. For example, an initial report in the *New York Post* of the 2013 Boston marathon bombing claimed "12 dead and nearly 50 injured" (Christopher 2013) —atypical for an open air blast. In reality only three were killed, but 264 were wounded, which conforms to historical data. Mistaken preconceptions of the medical consequences of blast can lead planners and managers to allocate resources incorrectly, and clinicians to focus attention away from the most likely pathology.

Blast Mechanisms of Injury

Table 1 and Figure 1 show the traditional classification of blast injuries. Primary blast injury is caused by a high-energy pressure wave. As measured at a single static point, the wave causes an abrupt increase, then decrease, in atmospheric pressure (see Figure 2). Like an ocean wave, there is no mass movement of gas; rather the peak pressure moves while the air molecules stay relatively static. In contrast, the 'blast wind' involves mass movement of gases away from the point of explosion, following the pressure wave by an appreciable delay. 'High explosive' blast is defined as one that causes a supersonic (>340m/sec) pressure wave (see Table 2). Energy intensity dissipates according to the cube of the distance from the blast. The pressure wave can be reflected from solid surfaces, so explosions in closed environments cause more primary blast injury, as shown in Table 3. The potential of the pressure wave to cause injury is a function of its intensity, duration and the orientation of the victim. Military body armour offers no protection to the blast wave. Water propagates a blast wave more efficiently than air, while retarding energised fragments, meaning that underwater explosions are unique in causing injury entirely by primary blast. A particular type of 'enhanced' atmospheric blast involves a prolonged overpressure wave. This increases the chance of primary blast injury, even if exposed in the open. The military application is the thermobaric or fuel-air explosive, in which a vapour cloud of explosive is dispersed by an initial charge and ignited by a second. When they occur in an industrial context, these situations are the exception to the general rule that civilian open-air explosions rarely cause primary blast injury in survivors. Combustion of air/dust mixtures in grain storage silos or coal storage buildings, and boiling liquid-expanding vapour explosions (BLEVEs), which occur upon release of gases stored as liquids under pressure at temperatures above their boiling points (such as might occur when a liquefied petroleum gas (LPG) bottle is engulfed in fire), both mimic thermobaric munitions.

The relationship between blast intensity and effect is well characterised (e.g. in Gibson 1994), but the details are more relevant to weapons engineers than clinicians, as there is almost never sufficient data available upon which to predict injury patterns. The most important points for clinicians are:

a. low energy blast, such as that which accompanies most civilian explosive-burn injuries (see Table 2), does not cause primary blast injury.

> **"Mistaken preconceptions of the medical consequences of blast can lead planners and managers to allocate resources incorrectly"**

b. to suffer primary blast injury from a high explosive device, it is necessary:
   i. to be very close to the explosion, or
   ii. be the victim of an 'enhanced' blast, or
   iii. be exposed to an underwater blast, or
   iv. be in a confined space that reflects the overpressure wave.

Most victims in the open who are sufficiently close to the explosion to experience a primary blast effect will die almost immediately.

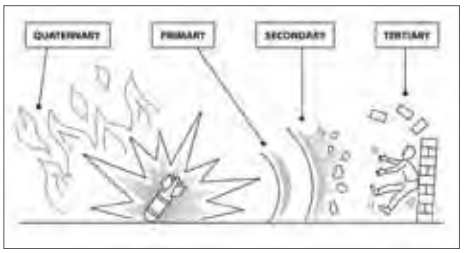

Figure 1. Mechanisms of Injury by Blast
Figure credit: courtesy of Major Anthony Chambers, FRACS RAAMC

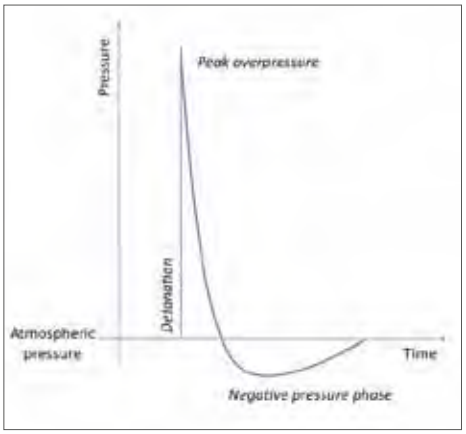

Figure 2. Blast Overpressure

Table 1. Types of Blast Injury

Type	Mechanism	Injuries / Wounds	Notes
Primary	Pressure wave	• Tympanic membrane rupture • 'Blast lung' • Hollow abdominal viscus rupture • Mild traumatic brain injury	Only occurs in high explosive blast. The commonest mechanism of death in many types of explosions. NB: *Survivors* of most types of explosion do not have substantial primary blast injury.
Secondary	Acceleration of projectiles from either the casing of the explosive or from the environment	• Penetrating trauma (in survivors, usually low energy transfer) due to projectiles accelerated by the explosive force or the blast wind	Note that 'shrapnel' is often misused to describe the blast-fragmentation mechanism of injury. A Shrapnel shell is a particular form of antipersonnel device in which preformed objects (e.g. ball bearings) are embedded in the explosive. Shrapnel shells were relatively ineffective in World War I and are no longer in military use. Modern munitions cause penetrating wounds by fragmenting their casing – hence 'blast fragmentation' is preferable to 'shrapnel'.
Tertiary	Mass movement of air causing the victim to be accelerated into fixed structures, or collapse of structures on to the victim	• Blunt and penetrating injury • Traumatic amputation • Crush injury	
Quaternary	All other mechanisms, e.g.: Burns • Oxygen depletion • Cyanide toxicity • Smoke inhalation • Ionising radiation	• Burns • Respiratory injury from inhaled smoke, heat and dust • Asphyxiation	

Table 2. High vs. Low Explosive Blast

	High Explosive	Low explosive
Speed of Detonation	>340 m/sec (i.e. > speed of sound)	<320 m/sec (i.e. < speed of sound)
Examples	2,4,6-trinitrotoluene (TNT) Pentaerythritol (PETN) Cyclotrimethylene trinitramine ("Royal Demolition Explosive" RDX) Cyclotatramethylene tetranitramine (HMX) Nirocellulose Nitroglycerine Ammonium nitrate C4 (RDX, plasticizer, oil)	Dynamite Gunpowder Petroleum
Devices	Military bombs, rockets, grenades, landmines Improvised explosive devices using military munitions or (commonly) ammonium nitrate Industrial explosives	Molotov cocktails Pipe bombs Industrial explosives Domestic fuel-air mixtures
Mode of Combustion	Detonation, in which the explosive almost instantaneously transforms into its expanded volume post-explosion gaseous state, resulting in compression of the surrounding air molecules and the propagation of this compression energy as a supersonic wave.	Deflagration / conflagration, in which the combustion of the explosive propagates relatively slowly through the explosive material, producing little energy to form a compression wave. Energy is primarily transmitted by the mass movement of gas energised by the combustion, and by any solid objects that this process energises.

c. Patients exposed to the same blast event at similar distances may have very different injury patterns, depending on the orientation of their bodies to the blast.

Penetrating ballistic injuries in survivors of blast are usually low energy, causing tissue damage by laceration and crushing rather than the cavitation of high-energy gunshot wounds. Glass debris commonly causes penetrating injuries in urban environments. Injury to multiple body locations is typical. Eye damage is particularly common (10%) (Centers for Disease Control and Prevention 2003), and early on may be overlooked if the eyes are not examined.

Pathogenesis of Primary Blast Injury

Blast pressure waves establish shear forces at tissues of different densities — with the greatest effects at the air-tissue interfaces of the lung, tympanic membrane and gastrointestinal tract. Other than bodily disruption, the arterial gas emboli caused by shear forces at the alveolar-capillary barrier are the main cause of very early death (from stroke or myocardial infarction). Survivors may develop 'blast lung', typically 24-72 hours after exposure, which is clinically indistinguishable from other causes of ARDS. Pneumothorax and haemothorax are also common. The tympanic membrane is even more sensitive to blast, but the influence of head orientation at the time of injury makes this an unreliable screening tool for pulmonary injury: in one study tympanic membrane disruption was present in only 50% of patients with other significant blast injury (Harrison et al. 2009). Gastrointestinal blast injury presents as delayed (up to 14 days) bowel rupture due to ischaemic necrosis. Mild traumatic brain injury is common after high explosive blast (59% in a U.S. military series (Savitsky and Eastridge 2012)), and, while less in civilian trauma (36% in a series of 89), was frequently missed (in 36% of patients who presented with a Glasgow Coma Scale (GCS) of 15) (Bochicchio et al. 2008).

Epidemiology of Civilian Blast Events: Implications for Planning and Response

Civilian blast trauma occurs in one of three

Table 3. Likely Clinical Effects Amongst Survivors of the Three Types of Mass-Casualty Explosive Incident (Arnold 2004)

	Open-Air Blast	Blast in a Confined Space	Blast with Structural Collapse
Immediate mortality, % injured	4 (0-9)	8 (1-14)	25 (6-44)
Late mortality, % injured	1 (0-1)	1 (0-3)	2 (1-3)
Any pulmonary effects, % ED presentations	7 (4-11)	21 (0-46)	5 (2-7)
Blast lung syndrome, % ED presentations	5 (3-9)	16 (0-37)	1 (0-3)
Pneumothorax, % ED presentations	3 (1-6)	9 (0-20)	1 (1-2)
Tympanic membrane rupture, % ED presentations	5 (0-15)	35 (16-54)	2 (1-4)
Intestinal perforation, % ED presentations	0 (0-2)	3 (0-6)	1 (0-6)

Table 4. Characteristics of Civilian Blast Events

	Typical Circumstances	Typical Number of Casualties	Type of Explosive	Typical Wound Pattern
Industrial or domestic accident	Breach of usual safety precautions. Domestic accidents in particular are often associated with misuse of drugs or alcohol.	1-5	Low explosive, e.g. LPG, gasoline	Burns, including respiratory burns from inhalation of hot gases 1° and 2° blast injury is rare; 3° is uncommon except with very large explosions
Terrorist event	High-visibility target with optimised media exposure and recognisable landmarks.	50-500	High explosive, particularly ammonium nitrate	Depends on location of incident; usually conforms to one of the three patterns in Table 3
Homicide / suicide	Attacker known to victim. Explosion used as a mechanism of inflicting trauma without the need for proximity.	1-2	Pipe bomb, usually loaded with low explosive charge	Blast-fragmentation

main patterns (see Table 4). Terrorist explosions injure few people compared to explosive accidents. Most victims either die almost immediately, or do not have life-threatening injuries; only 10-15% require life-saving interventions (Savitsky and Eastridge 2012). The immediate mortality of terrorist blast involving structural collapse (such as the Oklahoma City bombing in 1995, which killed 168 and injured 680) is high (typically 25%; see Table 3), but only 25% of survivors require hospital admission (see Table 5). Most are not directly affected by blast, and are managed as for any other blunt trauma. Blast in an open space is an effective terror tactic if it is caught on film (such as in the Boston marathon bombing in 2013), but immediate mortality is low, and although most victims present to hospital, few need admission. Blast in a confined space (such as the London Underground bombings in 2005 or the Madrid train bombing in 2004) has a lower mortality than that involving structural collapse, but there is a comparatively high chance survivors will be affected by primary blast. While 39% require hospital admission, only 13% require ICU care and 18% require surgery (Kosashvili et al. 2009) The number of patients arriving near-simultaneously is the biggest problem: structural collapse can result in hundreds to thousands (median 359) presenting, while bombings in confined spaces result in a median of 53 presentations and open-air bombings, 76 (Arnold et al. 2004). Effective triage is essential, especially as the least affected patients usually arrive at hospital first (Hogan et al. 1999). A key consideration is to defer non-urgent imaging and manage minor injuries as outpatients. In large cities where terrorist events are most likely, effective prehospital casualty regulation should mean that surgical and critical care capacity is not overwhelmed.

Blast due to criminal acts or accidents is typically not a mass casualty event, therefore presenting more of a problem to clinicians than health planners and managers. A much higher proportion (59%) require surgery and ICU admission (Kulla et al. 2015).

Individual Patient Care

Tympanic membrane rupture requires antibiotic drops (e.g. ciprofloxacin and dexamethasone 4 drops tds [3 times a day]) for 7 days, but only uncommonly (10-20%) requires surgical repair (Chait et al. 1989). Hearing loss is usually not permanent (30% in one series) (Chait et al. 1989). The capillary disruption and diffuse alveolar haemorrhage of blast lung are pathologically different to other forms of ARDS, but

Figure 3. The Three Patterns of Blast Injury
a. Blast in the open air. Note energisation of debris with the potential to cause 2° blast trauma.
Image credit: UK Ministry of Defence
Source: webarchive.nationalarchives.gov.uk/+/http://www.operations.mod.uk/veritas/forces/tlam.htm

b. Blast in a confined space. Bomb blast on a Mumbai train, 2006.
Image credit: Manoj Nair, (originally posted to Flickr as Mahim train blast) [CC BY-SA 2.0 (http://creativecommons.org/licenses/by-sa/2.0)], via Wikimedia Commons
Source: https://commons.wikimedia.org/wiki/File%3AMahim_train_blast.jpg

c. Structural collapse. The Oklahoma City bombing, 1995.
Image credit: Reproduced as a work of the U.S. Federal Government in the public domain

Table 5. Likely Resource Utilisation of the Three Types of Mass-Casualty Explosive Incident
Most survivors do not require ICU operative surgery.

	Open-Air Blast	Blast in a Confined Space	Blast with Structural Collapse
Require ED presentation, %*	94 (89-99)	89 (73-100)	48 (25-70)
Require hospital admission, %*	15 (5-26)	36 (27-46)	25 (6-44)
Require ICU, %**	6.2	13.4	NA
Require operative surgery, %** (Kosashvili et al. 2009)	12.4	17.6	NA
Craniotomy**	1.6	2.7	NA
Thoracotomy**	0.7	1.5	NA
Laparotomy**	4.2	8.4	NA
Orthopaedic**	9.8	9.6	NA

* Of all casualties (Arnold 2004)
** Of patients arriving to hospital (Kosashvili et al. 2009)
NA = not available in the quoted studies

have no specific treatment. Therapy is entirely supportive, involving protective lung ventilation and all other standard measures. Theoretically, high peak airway pressures should be avoided due to the risk of air embolus. Bowel rupture is treated in the same manner as any other form of ischaemic bowel necrosis. The main therapeutic priority in blast mild traumatic brain injury (mTBI) is to reduce the risk of re-exposure, as further insults appear multiplicative rather than additive. Various treatments for the headache, insomnia and mood changes that characterise this syndrome have been attempted, but none is yet supported by large controlled trial evidence.

Penetrating trauma due to secondary blast is usually low-energy transfer and so does not require wide excision of wound tracts. Foreign bodies are often multiple, and should only be removed if lodged in joints or the subarachnoid space (to prevent lead toxicity), if they become the source of systemic infection, if they lie next to an internal organ that presents a risk of subsequent erosion, or if they cause persistent pain. Superficial blast fragmentation wounds only require sharp debridement if they are >1-2cm, present >24 hours after wounding, or are associated with fractures or vascular injury (Bowyer 1997). Otherwise, a simple chlorhexidine scrub is sufficient. All potentially contaminated wounds are left open until it is clear that no further debridement is required.

IV antibiotic prophylaxis should start as soon as possible, ideally in <3hours. Various recommendations exist, but cefazolin 2g IV q6-8hr (+metronidazole 500mg bd for oesophageal, abdominal or central nervous system (CNS) wounds) is accepted by U.S. and allied military hospitals.

Special Considerations

Patients affected by both blast and burn injury should have particularly careful fluid resuscitation. The U.S. military now advocates the 'rule of tens' (10ml/% burn/hr), which is generally a mid-point between the Parkland and modified Brooke formulae (i.e. between 2 and 4 ml/kg/% in the first 24hr). However, this should be titrated to both respiratory function and circulatory adequacy. Traumatic amputation in survivors of terrorist blasts features in popular media reports, perhaps due to its perceived frequency in recent combat. However, of >55,000 US casualties in Iraq and Afghanistan, only 1,645 had major limb amputations (Fischer 2015); civilian bombings only rarely result in traumatic limb amputation. Heterotopic ossification was first described in military casualties 1000 years ago, and is common in substantial trauma caused by blast — for example in 80% of a small sample of London bombing casualties (Edwards et al. 2015). Management involves excision followed by radiotherapy and nonsteroidal anti-inflammatory drugs (NSAIDs).

Conclusion

Most survivors of blast injury do not have clinically significant primary (blast wave) trauma. Civilian terrorist bombing survivors mainly present with penetrating low-energy transfer blast fragmentation wounds, or crush injury due to structural collapse. The main things that distinguish these civilian victims from non-blast trauma patients are the numbers of patients presenting (necessitating triage) and the number of body parts involved in each patient. In the low explosive blasts that typify accidental or homicidal civilian blast wounds, the commonest injuries are burn and low energy penetrating trauma — the management of which follows conventional principles. Treating such patients effectively is well within the scope of civilian trauma hospitals. The principles outlined here have been summarised conveniently by the U.S. Centers for Disease Control in a mobile application (2014). ■

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FLUID CHOICES IN TRAUMA

This article focuses on the type of fluid available and respective indications in the course of trauma resuscitation according to the situation: haemorrhagic shock, trauma brain injury.

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In trauma patients, fluid resuscitation aims at preventing a cardiac arrest due to severe hypovolaemia and at achieving a satisfying level of mean arterial pressure to ensure adequate tissue perfusion. Fluid resuscitation is indicated in trauma patients for traumatic haemorrhage, sympatholysis due to spinal injury or sedation and vasoplegia due to inflammation (tissue attrition and ischaemia-reperfusion).

The perfect fluid for trauma resuscitation should ideally have no interactions with clot formation, have a composition close to that of the extracellular space and be isotonic to avoid cerebral volume variations. It should have a high volume expansion property to avoid excessive fluid volume replacement that could contribute to the development of coagulopathy and complications such as abdominal compartment syndrome. However, no fluid gathers all these properties at one time and fluid choice in trauma resuscitation remains a subject of debate.

Crystalloids

Fluid resuscitation with crystalloid is the first-line therapy to correct haemodynamic instability during blood spoliation due to traumatic haemorrhage. The European guidelines recommend that crystalloids be applied initially to treat the hypotensive bleeding trauma patient (Spahn et al. 2013). Isotonic saline is the reference solution that is mostly used during trauma resuscitation. Its osmolarity is close to the osmolarity of plasma (slightly higher with 308 mmol.L^{-1}) and its believed harmlessness made it a universal fluid for trauma resuscitation. Ringer's lactate, an alternative to isotonic saline, is frequently used in the United States. However, its hypo-osmolarity (273 mmol.L^{-1}) could increase intracellular space volume leading to an increase in intracranial pressure in brain-injured trauma patients. Thus, Ringer's lactate should be reserved for patients devoid of traumatic brain injury. The strong ion difference (SID) of isotonic saline is zero mmol.L^{-1} and the SID of Ringer's lactate is 26 mmol.L^{-1}. Since a solution with a SID inferior to plasma SID (40 mmol.L^{-1}) leads to hyperchloraemic acidosis, the formulation of the lactate Ringer solution proposed by Dr Hartmann in 1930 results in less hyperchloraemic acidosis than isotonic saline. Excessive chloride administration could have renal adverse effects (Yunos et al. 2012), and an association was reported between intravenous chloride load and mortality in intensive care (Shaw et al. 2014). The precise mechanisms explaining these reported side effects of chloride are not well understood at the moment. However, there is growing interest in balanced solutions that were recently proposed to associate a composition and an osmolarity close to that of plasma.

One study randomised 50 trauma patients with haemorrhagic shock to receive either isotonic saline or balanced solution (Plasmalyte with a SID of 50 mmol.L^{-1}) during the first 24 hours of resuscitation (Young et al. 2014). The authors reported a significant increase in base excess in the Plasmalyte group compared to the NaCl 0.9% group (7.5 ± 4.7 vs 4.4 ± 3.9 mmol.L^{-1}) with less severe hyperchloraemic acidosis in the Plasmalyte group. In a recent meta-analysis comparing the administration of low vs high chloride content solution in perioperative and critical care, Krajewski et al. (2015) reported less need for transfusion when using balanced crystalloids instead of isotonic saline. This was confirmed in a study conducted on 60 liver surgery patients by Weinberg et al. (2014), who reported less bleeding during surgery and fewer haematology value disorders after surgery with Plasmalyte than with lactated Ringer's solution. A randomised controlled trial of 2278 patients requiring crystalloid fluid therapy in the ICU compared isotonic saline to Plasmalyte (Young et al. 2015). No difference in severe acute kidney injury (AKI) occurrence (primary outcome) was reported. However, the overall severe AKI (according to Risk, Injury, Failure, Loss and End-stage kidney disease (RIFLE) classification I or F) incidence was only 9.4% and few trauma patients (n=125) were included. It appears that the interest in balanced solutions needs to be investigated in larger randomised controlled trials in trauma patients to explore their effects on coagulation and renal function.

Colloids

The main potential benefit of colloids is that they are able to induce a more rapid and persistent plasma expansion because of a larger increase in oncotic pressure. A ratio of 1:2 to 1:3 between colloids and normal saline has regularly been proposed to obtain the same volume expansion (Mcllroy et al. 2003). However, a recent meta-analysis, including studies in perioperative and criticial care settings, reported an exact mean ratio of 1:1.5 (it was even 1:1.3 in the most recent studies between 2010-2013) (Orbegozo Cortés et al. 2015). Moreover, randomised comparisons of fluid resuscitation with hydroxyethyl starch (HES) 130/0.4 versus NaCl 0.9% in trauma

RAPID PATHOGEN TESTING WITH PCR/ESI-MS IN PRACTICE

Kristoffer Strålin, MD, PhD, is Associate Professor and Senior Consultant at the Department of Infectious Diseases, Karolinska Institute, Stockholm, Sweden. Karolinska Institute is a world-renowned medical university, which has the mission of improving people's health through research and education. Together with Karolinska University Hospital, it is a leader in healthcare developments and medical breakthroughs. The hospital has recently installed the IRIDICA system, a laboratory diagnostic platform that uses PCR/ESI-MS technology, and is now using it for routine testing. Physicians in any part of the hospital can electronically order IRIDICA testing for their patients.

What is your experience with PCR/ESI- MS technology used by the IRIDICA system?

Following two studies on bronchoalveolar lavage (BAL), we are now using the IRIDICA system in routine practice, on blood samples and tissue samples in addition to BAL. In the first BAL study, we looked at the performance of broad-range detection of bacterial DNA with the IRIDICA BAC LRT assay applied on BAL fluid in mechanically ventilated patients with pneumonia (Strålin et al. 2015). We obtained 59 BAL samples from consecutive mechanically ventilated patients in the intensive care unit (ICU). Thirty-two patients (median age 49 years, range 0-79 years) had pneumonia. The median ICU time prior to bronchoscopy was three days. IRIDICA was run on 0.1 mL of BAL fluid. Compared with BAL culture, IRIDICA showed specificities of >87% and negative predictive values of ≥90% for all individual pathogens. The overall sensitivity was 77% (10/13). In patients without prior antibiotic therapy, the method had low additive value. However, IRIDICA was significantly more often positive in patients with prior antibiotic therapy.

In the second study, which we presented at the European Congress of Clinical Microbiology and Infectious Diseases in April 2015 (Ullberg et al. 2015), we compared the performance of the IRIDICA system to conventional culture. During summer and autumn 2014, 0.1 mL from 91 consecutive routine BAL samples received at the clinical laboratory were analyzed using the IRIDICA BAC LRT assay. The results are shown in Table 1. As can be seen, for *S. pneumoniae* and *S. aureus*, considerably more positives were detected by IRIDICA.

Table 1

	Iridica + / Culture +	Iridica + / Culture -	Iridica - / Culture+
Streptococcus pneumoniae	1	10	1
Haemophilus influenzae	9	3	3
Staphylococcus aureus	13	14	0
Klebsiella pneumoniae	3	1	1
Escherichia coli	2	0	0
Enterobacter cloacae	3	0	0
Citrobacter species	0	1	0
Pseudomonas aeruginosa	4	0	0
Stenotrophomonas maltophilia	0	1	0
Legionella pneumophila	0	1	0
Total	35	31	5

Source: Ullberg et al. (2015)

For which additional patient groups are you using the PCR/ESI-MS technology?

We are currently collecting blood samples for IRIDICA to be tested in a study in conjunction with our intensive care unit (ICU). We will collect blood samples from all patients with suspected sepsis. We have collected samples from 12 January 2015 and will continue until 11 January 2016. We are three-quarters of the way through the year and have collected samples from more than 250 patients who have suspected infection on ICU admission.

From the studies you have conducted on the technology to date, what were the key findings?

We found a reasonable amount of samples, as shown in Table 1, where IRIDICA was positive, but the culture was negative. In one of our studies (Strålin et al. 2015), we had 10 cases in which IRIDICA on BAL was positive, where BAL culture yielded negative results, probably due to antibiotic treatment prior to specimen collection.

IRIDICA appears to be a good complement to culture, especially when the patient has taken antibiotics prior to sampling.

In your opinion, what is the key value of the PCR/ESI-MS technology?

It is a key advantage of the PCR/ESI-MS technology that it is more rapid. You can get results at a high speed. More important even than speed is the possibility to detect pathogens that culture does not detect. In particular, if antibiotics are given, culture can give a false negative result; however IRIDICA has the potential to detect the pathogen. IRIDICA is capable

to detect multiple pathogens in those patients with polymicrobial infections. It can also find 'exotic' pathogens, for example the case of Legionella pneumophila (see Table 1).

Would you share and describe for us a patient case where IRIDICA could or has made a difference?

One good example is a 66-year-old woman with breast cancer, who was admitted for fever. She had a systolic murmur at heart auscultation. Samples were collected for blood culture and IRIDICA on whole blood. Since she was clinically stable, she did not receive any antibiotics on the first day. However, the day after she was admitted (day 2), IRIDICA was positive for *Enterococcus gallinarum* and blood culture was positive for Gram positive cocci in short chains. Based on these results, antibiotic treatment with piperacillin/tazobactam was initiated. Ultrasonography showed endocarditis of the aortic valve. On day 3, the blood culture isolate was identified as *E. gallinarum* by standard laboratory methods. For this patient, the IRIDICA findings were used to influence the selection of the antibiotic used to treat the patient.

Which additional patient groups may be of interest to test in your institute?

In the ICU, additional patient groups of interest are immunocompromised patients. For inpatients on the wards, we sometimes have unusual pathogens that are difficult to detect. For those populations IRIDICA is a valuable detection and identification method. It is also useful for patients with joint and bone infections and soft tissue infections, because another advantage of IRIDICA is that it can detect multiple pathogens. We are already using IRIDICA with these patients. ■

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patients have not always shown a superiority of HES on the recovery of tissue perfusion (i.e. lactate clearance) and showed no difference in fluid requirements and maximum Sequential Organ Failure Assessment (SOFA) scores (James et al. 2011).

It should be borne in mind that in this latter study patients of the HES group were more severely injured than those in the saline group. As regards to a potential effect on mortality, the Crystalloid Versus Hydroxyethyl Starch Trials (CHEST) study failed to show that a fluid strategy using HES 130/0.4 (vs. NaCl 0.9%) decreased mortality in ICU patients, in particular in the subgroup of trauma patients (n=532) (Myburgh et al. 2012). In addition, there is continuing concern about the effects of HES on coagulation. HES have the potential to decrease the Von Willebrand factor level and to interfere with the polymerisation of fibrinogen and the platelet function. Studies that assessed haemostasis by thromboelastography reported that HES infusion resulted in a weaker clot with a less stable fibrin network and less firm aggregation of platelets than did crystalloid or human albumin (Hartog et al. 2011). This can lead to greater need for red blood cell transfusions (James et al. 2011; Myburgh et al. 2012). Because of these effects, the use of HES is considered at the initial phase of haemorrhagic shock. Alteration of coagulation and potential deleterious kidney effects observed with the last generation of HES prompted the European Medicines Agency (EMA) to drastically limit usage of HES. EMA recommended not to use HES in sepsis patients and to limit their use to haemorrhagic shock patients only when crystalloids alone are not considered sufficient (European Medicines Agency (EMA) 2013). In addition, HES are contraindicated in the case of coagulopathy (EMA 2013).

As regards the other synthetic colloids, coagulation (Niemi et al. 2010) and kidney function alterations (Bayer et al. 2011) have been described with gelatins, but high-quality studies are lacking to know if these recommendations can be extended to them. The Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL) study compared different colloids (including gelatins) to crystalloids in hypovolaemic shock. There were no differences in 28-day mortality (primary outcome) in the whole study population as well as in the subgroup of trauma patients (n=177) (Annane et al. 2013).

On albumin, the Saline versus Albumin Fluid Evaluation (SAFE) study has shown that albumin does not interfere with coagulation and kidney function (Finfer et al. 2004). However, in the subgroup of patients with traumatic brain injury (SAFE TBI patients), the mortality rate was superior with the use of albumin 4% at the initial phase vs normal saline (SAFE Study Investigators et al. 2007). This finding was attributed to the albumin-induced increase in intracranial pressure due to its hypo-osmolarity (Cooper et al. 2013).

Hypertonic Solutions

Hypertonic saline (HTS, 7.5% saline with or without colloids) has long been considered a fluid of interest in trauma patients. Potential benefits of HTS include restoration of intravascular volume with the administration of a small volume, due to its osmotic effect that shifts fluid from the intracellular space to the extracellular space, reduction of intracranial pressure in TBI and modulation of the inflammatory response. However, HTS failed to improve outcomes in patients with haemorrhagic shock or with severe TBI (Bulger et al. 2008; 2010; 2011). Its use in haemorrhagic shock patients was even reported to be associated with an overmortality in the subgroup of patients that was not transfused during the first 24 hours (Bulger et al. 2011). The authors suggest that hypertonic saline masked the clinical haemorrhage signs (hypovolaemia) with subsequent misdiagnosed haemorrhage.

In the setting of life-threatening raised intracranial pressure (ICP), mannitol and HTS are the most frequently used solution to lower ICP. At equimolar doses, HTS and Mannitol led to equivalent decrease in ICP (Francony et al. 2008). Thus, the differences between these two solutions are not related to their brain effects but rather to their haemodynamic properties. Indeed, HTS raises cardiac preload that may have some interest in patients with hypotension and compromised cerebral perfusion (mydriasis) to act on both arterial pressure and ICP at the same time. HTS will not lead to an osmotic diuresis in comparison with mannitol, which implies that mannitol administration should be followed by a fluid bolus (i.e. NaCl 0.9% 500 mL). This property can be an advantage of HTS when a prolonged vascular filling is expected (i.e. hypovolaemic patient), but on the other hand mannitol will be eliminated in the next hours following its administration, inducing a smaller positive fluid balance than HTS for the same brain effect. This can be appropriate for patients needing a transient osmotherapy while waiting for a surgical haematoma evacuation for example.

Lactate solutions have recently been proposed as an alternative to mannitol in trauma brain injury patients. Lactate is an energy substrate for the brain. In one study, equimolar doses of half molar sodium lactate led to more favourable ICP control than mannitol in TBI patients with raised ICP (Ichai et al. 2009). In a second randomised study, the same team compared an infusion of 0.5 $mL.kg^{-1}.h^{-1}$ of half molar sodium lactate to an equivalent infusion of isotonic saline. They reported less intracranial hypertension episodes (36% vs 66% in the half molar sodium lactate and the isotonic saline group respectively) that was not explained by the plasmatic osmolarity, since it was comparable in both groups (Ichai et al. 2013). Sodium lactate could act by increasing chloride extrusion from the cerebral cells associated with a decrease in cerebral water content. This favourable effect needs further investigation to define the therapeutic place of sodium lactate in TBI patients.

Conclusion

Although fluid resuscitation remains the cornerstone of trauma resuscitation, no consensus can be found for a single and ideal fluid. Crystalloid fluid should be administered as a first-line therapy to reverse hypotension. NaCl 0.9% associates an appropriate osmolarity (close to plasmatic osmolarity) with adequate filling properties. Solutions containing less chloride than NaCl 0.9% (i.e. balanced solutions) deserve further investigations to establish a potential benefit on coagulation and renal function. Synthetic colloids, in particular HEA, should be considered as second-line therapy only, since the lack of benefit and their potential nephrotoxicity do not support their use over crystalloids. Hypertonic solutions are indispensable in life-threatening ICP rises to buy time for a life-saving procedure preparation. Mannitol and HTS have the same efficacy. Their use in compromised haemodynamic situations (i.e. haemorrhagic shock) did not demonstrate any benefit. The attractive properties of sodium lactate remains to be investigated to better define its place in neuroICU. ■

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MIDDLE EAST RESPIRATORY SYNDROME CORONAVIRUS (MERS-CoV) INFECTION

THE ICU RESPONSE

Infection with the Middle East respiratory syndrome coronavirus (MERS-CoV), a recently identified virus, has led to several hundred cases of severe acute respiratory illness requiring admission to the ICU (Saad et al. 2014; Arabi et al. 2014). As of 4 December 2015, the World Health Organization (WHO) reported 1,621 laboratory-confirmed cases, including at least 584 related deaths (WHO 2015a). The majority (~80%) of cases occurred in Saudi Arabia (WHO 2015a).

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The disease represents several challenges to ICU management. Although many MERS-CoV cases are community-acquired (Azhar et al. 2014), the disease has great potential for healthcare-associated transmission, and has been associated with several major hospital outbreaks. These include outbreaks in Alahsa (April-May 2013) (Assiri et al. 2013), Jeddah (April and May 2014) (Oboho et al. 2015) and Riyadh (August-September 2015) (World Health Organization 2015). Most outbreaks were triggered by a community case that led to healthcare-associated transmission. Healthcare-associated transmission of MERS-CoV is thought to occur via both droplet and contact routes; in addition to being airborne during aerosol-generating procedures (van Doremalen et al. 2013).

Second, the disease has an indistinguishable presentation from other severe acute respiratory illnesses. The presenting symptoms of fever (71%), cough (68%), dyspnoea (66%) and diarrhoea (32%) (Alsolamy 2015), occurring in older adults with chronic co-morbidities (Alsolamy 2015; Al-Tawfiq et al. 2014), are all common in other forms of pneumonia. The radiologic and general laboratory manifestations also overlap substantially with other causes of pneumonia. Co-infections with other pathogens such as influenza and pneumococcus are not uncommon. Therefore physicians should keep a low threshold for testing by real-time reverse transcription polymerase chain reaction (rRT-PCR) in the appropriate context.

Third, with the infrequent occurrence of the disease, and the unfamiliarity of many staff members with the case definition of MERS-CoV infection, the diagnosis can be delayed or even missed. Delayed diagnosis without taking the proper isolation and infection control precautions leads to exposing many other patients, visitors and healthcare workers to the infection. The latest outbreak in Korea is an example where the diagnosis was delayed in an infected traveller, leading eventually to 186 MERS cases with intra- and inter-hospital transmission (Ki 2015).

Fourth, from the ICU healthcare provider standpoint, caring for these patients represents a substantial exposure risk, in terms of the 'dose' of viral exposure, duration of exposure per day and the total exposure duration. ICU MERS-CoV patients probably have the highest viral load among all MERS-CoV patients and therefore the 'dose' of exposure is probably high. ICU MERS-CoV patients are very ill and often require extended time of bedside care. Many patients develop ARDS and multiorgan failure requiring organ support such as mechanical ventilation, vasopressor therapy or continuous renal replacement. Patients with severe hypoxaemia may need prone positioning and extracorporeal membrane oxygenation (ECMO), which add to the duration of bedside care. Aerosol-generating procedures, such as noninvasive ventilation, suctioning and bronchoscopy further add to the risk for healthcare-associated transmission. ICU stays can last for weeks, with prolonged viral shedding in respiratory sections, urine and stool that may persist for more than 30 days (Memish et al. 2014).

Fifth, severe infection and even death have occurred in young healthcare workers (Memish et al. 2013). The impact of such occurrences on the ICU workforce can be devastating.

In this article, we discuss key issues related to ICU preparedness for managing a MERS-CoV outbreak.

ICU Preparedness for MERS-CoV

Early identification and diagnosis

Early identification and diagnosis is critical in interrupting the chain of transmission in the healthcare setting. In order to facilitate early identification and prompt isolation, healthcare providers need to become aware of the MERS-CoV case definition and be promptly informed of any updates (see Table 1). Effi-

Table 1. World Health Organization interim case definitions of the Middle East respiratory syndrome coronavirus (MERS-CoV) infection (as of 14 July 2015)

Probable case	• An acute respiratory illness with fever and clinical, radiological, or histopathological evidence of pulmonary involvement AND Direct epidemiologic link with a confirmed MERS-CoV case AND MERS-CoV testing is unavailable, negative on a single inadequate specimen or inconclusive • An acute respiratory illness with fever and clinical, radiological, or histopathological evidence of pulmonary involvement AND The person lives in or travelled to Middle Eastern countries or countries where MERS-CoV is known to be circulating in dromedary camels or where human MERS-CoV infections have recently occurred AND MERS-CoV testing is inconclusive • An acute febrile respiratory illness of any severity AND Direct epidemiologic link with a confirmed MERS-CoV case AND MERS-CoV testing is inconclusive
Confirmed case	A person with laboratory-confirmed MERS-CoV infection irrespective of clinical signs and symptoms

Source: World Health Organization (2015a)

cient triage systems, within the emergency department and ambulatory care areas, are needed for early identification of respiratory illness among patients. Once identified with pertinent risk factors healthcare staff need to be provided with proper protective equipment to prevent transmission. Once such patients are classified as suspected, probable or confirmed MERS CoV, proper patient placement according to hospital policy is needed.

When to Suspect MERS CoV

The disease should be suspected in patients with an acute febrile respiratory illness with clinical or radiologic evidence of pneumonia, who have a direct epidemiologic link with a confirmed MERS-CoV case, or live in or have travelled to a Middle Eastern country or countries where MERS-CoV is known to be circulating in dromedary camels or where human MERS-CoV infections have recently occurred. It is important to note that fever may not be present in up to 30% of cases on presentation (Alsolamy 2015).

The diagnosis is confirmed by rRT-PCR. Commonly tested samples are nasopharyngeal and throat swabs, sputum, tracheal aspirates and bronchoalveolar lavage. Lower respiratory tract specimens have a higher sensitivity than upper respiratory tract specimens for detecting MERS-CoV and are preferred (Lee et al. 2015). However, nasopharyngeal swabs have low yield compared to lower respiratory tract samples, and a negative rRT-PCR, even from lower respiratory samples, should not exclude the diagnosis in the presence of clinical suspension. Standardising the workup of patients presenting with lower respiratory tract infections is recommended.

Proper Use of Personal Protective Equipment while caring for MERS CoV

The Centers for Disease Control and Prevention (CDC) recommend that droplet precautions should be added to the standard precautions when providing care to all patients with symptoms of acute respiratory infection (National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases 2015), and that airborne precautions are applied for all suspected and confirmed MERS-CoV cases or during aerosol-generating procedures. These precautions have been shown in the severe acute respiratory syndrome (SARS) epidemic to prevent transmission of infection to healthcare workers (Seto et al. 2003). On the other hand, the WHO recommends droplet and contact precautions (World Health Organization (WHO) 2015b). Airborne precautions should be additionally instituted when performing an aerosol-generating procedure (i.e., aspiration or open suctioning of the respiratory tract, intubation, bronchoscopy and cardiopulmonary resuscitation) (WHO 2015b).

It is recommended that healthcare providers, and in particular those exposed to patients with respiratory illness, including the ICU staff, should be fit tested for the proper respirator, preferably as part of an institutionally-based respiratory protection programme. Powered air-purifying respirators (PAPR) should be made available for staff who fail fit testing, and proper training for use and cleaning should be provided. An accurate record of individuals accessing rooms of suspected and confirmed MERS CoV cases needs to be established to assist proper contact tracing processes.

Additionally, staff should be trained on proper hand hygiene technique and PPE application, including how to don and doff personal protective equipment without self-contaminating. Their competency should be tested and documented. Policies to ensure 100% compliance with proper donning and doffing of personal protective equipment (PPE) should be in place. A buddy system, similar to what is recommended for monitoring healthcare workers' (HCWs) compliance with PPEs while managing Ebola may be used. Housekeepers should also be trained in proper cleaning techniques and the use of PPE.

The implementation of such infection control measures requires having adequate stocks of PPE, such as respirators, goggles, face shields, gowns and scrub suits. During an outbreak, the consumption of PPE supply increases substantially and logistic plans should be in place to ensure constant supply.

Placement of Patients with Suspected and Confirmed MERS-CoV Infection

The CDC recommends that a suspected or confirmed MERS CoV case should be isolated in an airborne infection isolation room that is constructed and maintained according to the current guidelines (National Center for Immunization and Respiratory Diseases, Division of Viral Diseases 2015). For example, the negative pressure room should have a minimum of six air changes per hour, with the air from these rooms exhausted directly to the outside or filtered through a high-efficiency particulate air (HEPA) filter before recirculation (National Center for Immunization and Respiratory Diseases, Division of Viral Diseases 2015). Until such placement, a facemask should be placed

"Prevention of healthcare-associated transmission should be a major focus of ICU preparedness"

on the patient, who should be isolated in a room with the door kept closed (National Center for Immunization and Respiratory Diseases, Division of Viral Diseases 2015). If the housing ICU does not have an adequate number of such rooms, clinical engineering should have a plan to convert standard rooms to negative pressure rooms. Additionally, the proper negative pressure function of these rooms should be monitored and documented.

Cohorting of MERS patients in one ICU is recommended to facilitate care and monitoring. Other units should be identified prior to any increase in the number of cases beyond the capacity of the first unit. Transferring patients without MERS to other units or hospitals may be needed to increase bed capacity.

Medical Management of Patients with MERS-CoV Infection

To date, there are no clinical trials in humans for virus-specific therapies for MERS-CoV infection. Therefore, the medical management of patients is largely supportive. The WHO has issued interim guidance for the management of suspected and confirmed MERS-CoV infection (WHO 2015b). For patients with worsening hypoxaemia, early endotracheal intubation and mechanical ventilation using a lung-protective ventilation strategy are indicated (WHO 2015b). Early prone positioning and neuromuscular blockade may be considered in patients with moderate-to-severe acute respiratory distress syndrome (WHO 2015b). Systematic corticosteroids should probably be avoided unless there is another indication. Certain aerosol-generating procedures, such as high-flow oxygen and noninvasive ventilation, should be avoided or used with caution (WHO 2015b). A systematic review found the following procedures to be associated with an increased risk of respiratory pathogen transmission: endotracheal intubation, noninvasive ventilation, tracheotomy and manual ventilation (Tran et al. 2012).

Staffing

Care for these patients can be demanding. It is not unusual for the nurse-to-patient staffing ratio for MERS patients to increase to 2:1 nursing for some patients, similar to what has been described in the SARS epidemic (Hawryluck et al. 2005). ICU healthcare providers are frequently given additional tasks such as monitoring and correcting infection prevention practices of other healthcare workers. Infectious outbreaks in hospitals can lead to staff shortage due to the fear of working in a contagious setting, quarantine and illness (Hawryluck et al. 2005). Staff who develop fever, respiratory or gastrointestinal illness should be asked not to present to work, and to report to the emergency department or the employee health service depending on the severity of illness. Each institution should define the algorithm for managing staff exposure such as the required testing and isolation.

On the other hand, unnecessary exposure of healthcare workers to infected patients should be avoided, and limiting the number of medical and nursing staff caring for these patients is recommended.

Communication with Families

Family visits to patients with MERS-CoV infection should be restricted to a minimum. Family members with symptoms of acute respiratory illness should not be allowed to visit and should be tested for MERS-CoV. However, the treating intensivist should have a mechanism to communicate with the next of kin regularly, for example by phone.

Infectious Disease Emergency Preparedness Plan (IDEPP)

The ICU should be part of a hospital-wide infectious disease emergency preparedness plan (IDEPP). The University of Texas at Brownsville has published an example of such a plan (2012), which provides the basic structure and guidance on how and by whom the different activities of the plan will be managed and coordinated. In addition the plan requires monitoring and assessment, to ensure all elements are in place. The IDEPP establishes a command centre that oversees all responses to the outbreak and is typically phased depending on the level of threat. For the ICU, plans for surge capacity should be described.

Conclusion

Prevention of healthcare-associated transmission should be a major focus of ICU preparedness to MERS-CoV. Early diagnosis and isolation of suspected cases, proper use of personal protective equipment, staff management, surge capacity for negative pressure rooms and integrating ICU plans with the hospital IPEPP are key elements of this response. ■

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ACUTE BRAIN DYSFUNCTION DURING CRITICAL ILLNESS

- Delirium (acute brain dysfunction) can be a complication of critical illness.
- Brain organ dysfunction can manifest as a continuum of psychomotor behaviors that are categorised as hyperactive or hypoactive.
- Delirium can be diagnosed using validated and reliable bedside tools.
- Implementation of delirium monitoring can be enhanced by scheduled in-depth discussions about brain organ dysfunction via multidisciplinary rounds with the medical team.
- Delirium may be managed with use of non-pharmacologic and, if necessary, pharmacologic interventions thereafter.

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Acute brain dysfunction is common in the critical care setting, presenting as delirium or coma. Delirium is a clinical syndrome of brain dysfunction characterised by an acute change or fluctuating course of altered mental status, inattention, and a disturbance of consciousness, cognition, or perception, such that a patient's ability to receive, process, store, and recall information is impaired (American Psychiatric Association 2013).

Prevalence

The prevalence of delirium among adults varies among different adult ICU populations: 20-30% in the cardiac ICU (McPherson et al. 2013; Pauley et al. 2015; Zhang et al. 2015), and 50%-80% in mechanically ventilated medical, surgical, trauma ICU (Bryczkowski et al. 2014; Pandharipande et al. 2008) and burn ICU (Agarwal et al. 2010) patients. The clinical presentation of delirium is expressed as a continuum of psychomotor behavior. Hypoactive delirium is characterised by apathy and decreased responsiveness (Meagher et al. 2007; Pandharipande et al. 2007). Conversely, patients with hyperactive delirium may exhibit mild restlessness to severe agitation. Among critically ill adults, hypoactive delirium (43.5%) is extremely prevalent versus the less common hyperactive subtype (1.6%) (Pandharipande et al. 2007), and unless routine monitoring is used, delirium will be missed.

Delirium does occur in critically ill children, although the true epidemiology has yet to be well described. Small case series report paediatric delirium rates of between 10-30% (Smith et al. 2011; Traube et al. 2014; Schieveld et al. 2007). Most recently, Smith and colleagues reported delirium prevalence of 36% in critically ill infants and young children, with rates as high as 46% in patients between 6 months and 2 years of age (Smith et al. 2014). Critically ill children are more likely to present with the hypoactive delirium subtype (81%) than hyperactive delirium (19%) (Goben et al. 2014).

Measurements

Delirium in the adult ICU can be diagnosed by using the validated Confusion Assessment Method for the ICU (CAM-ICU) (Ely et al. 2001a) or the Intensive Care Delirium Screening Checklist (ICDSC) (Bergeron et al. 2001). Given the fluctuating course of delirium, it is recommended that patients be screened at least once per shift to increase the chance of detection (Pun et al. 2013). The use of screening tools is superior to subjective assessment by providers and ideally should be part of routine modern ICU practice.

The first step in delirium diagnosis is assessment of level of arousal. Only patients who are responsive to voice can be evaluated for delirium, while those who are unresponsive are considered comatose. The Society of Critical Care Medicine (SCCM) guidelines recommend the use of either the Richmond Agitation-Sedation scale or the Sedation Agitation Scale for the assessment of the level of arousal (Barr et al. 2013). Patients who are arousable by voice can then be assessed for delirium with the CAM-ICU or the ICDSC, as shown in Figure 1 and Table 1.

Delirium monitoring in paediatric patients is equally as important, especially during critical illness. Similarly to adult patients with delirium, paediatric patients demonstrate the core features of delirium, such as alteration of mental status, fluctuation and inattention. Additionally, infants and children with delirium may exhibit more subtle neuropsychiatric symptoms, such as inconsolability, purposeless actions, autonomic dysregulation, unexplained lethargy and even regression of previously attained developmental skills (Leentjens et al. 2008; Turkel et al. 2006).

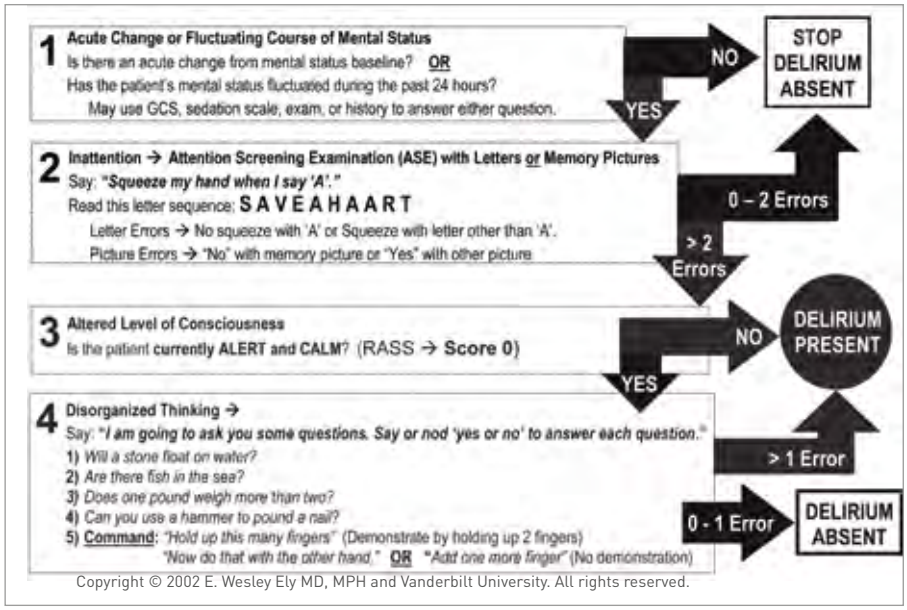

Figure 1. Confusion Assessment Method for the ICU (CAM-ICU)

The confusion assessment method for the ICU (CAM-ICU) is a highly valid and reliable delirium assessment tool. The CAM-ICU requires inattention for presence of delirium as the cardinal feature of delirium. Delirium is present when Feature 1 and Feature 2 are present, plus either Feature 3 or Feature 4.

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Table 1: The Intensive Delirium Screening Checklist (ICDSC)a

Altered Level of consciousness	Yes or No
Inattention	Yes or No
Disorientation	Yes or No
Hallucination, delusion, or psychosis	Yes or No
Psychomotor agitation or retardation	Yes or No
Inappropriate speech or mood	Yes or No
Sleep-wake cycle disturbance	Yes or No
Symptom Fluctuation	Yes or No

[b]Delirium present with 4 or more symptoms present
Source: Bergeron et al. 2001

[a]Each component is assessed and noted as 'yes' (1 point) or 'no' (0 points).
[b]Delirium is present when a patient's score is ≥ 4 points.

Recently, there has been progress in the development and validation of paediatric-specific delirium tools. The paediatric confusion assessment method for the ICU (pCAM-ICU) was the first valid and reliable delirium tool created for use in critically ill children over 5 years of age, including those on mechanical ventilation, demonstrating a specificity of 99% and sensitivity of 83% for delirium diagnosis (Smith et al. 2011).

Children under 5 years of age pose challenges for delirium diagnosis due to vast changes in their cognitive and developmental skills from infancy to early childhood. The Cornell Assessment for Pediatric Delirium (CAPD) is largely an observational delirium screening tool with a reported specificity of 79% and sensitivity of 94% (Traube et al. 2014). Unlike DSM-5 criteria (ed American Psychiatric Association 2013), the CAPD does not require inattention to be present for delirium diagnosis. More recently, the preschool CAM-ICU (psCAM-ICU) was created and validated for use in critically ill infants and preschool-aged children. The psCAM-ICU is a largely objective and interactive, developmentally-targeted, 'in the moment' delirium assessment tool for children under 5 years of age. In preliminary validation study reports, the psCAM-ICU demonstrated a specificity of 91% and sensitivity of 84%, with excellent reliability (Smith et al. 2014).

Risk Factors

Critically ill adult patients are predisposed to multiple risk factors, and it has been shown that the presence of more risk factors is associated with increased delirium (Francis et al. 1990; Inouye et al. 1996). The SCCM guidelines state that the most consistent risk factors are preexisting dementia; history of hypertension and/or alcoholism; and a high severity of illness at admission (Barr et al. 2013). Other risk factors are sedative and analgesic medications (Bryczkowski et al. 2014; Pandharipande et al. 2008), mechanical ventilation (Pandharipande et al. 2005), restraint use (Bryczkowski et al. 2014; Mehta et al. 2015), age (Pandharipande et al. 2005) and specific medical conditions necessitating ICU care, e.g. sepsis (Agarwal et al. 2013; Lin et al. 2008).

Much work has been done on identifying modifiable risk factors of delirium. One of the most important is the use of analgesic and sedative drugs, drugs that are commonly prescribed to adults in the ICU. For example, patients receiving lorazepam have an increased risk for transitioning to delirium (Pandharipande et al. 2006). Follow-up studies have confirmed that the use of non-benzodiazepine drugs for sedation is associated with improved outcomes including delirium (Pauley et al. 2015; Riker et al. 2009). In the most recent sedation guidelines published by the SCCM there is a recommendation to use non-benzodiazepine sedatives and to consider dexmedetomidine in patients with delirium to potentially reduce the duration of delirium. (Barr et al. 2013).

Sedation protocols are now commonplace within modern adult ICU practice. Whilst there is conflicting evidence of the overall benefit of protocols (Sevransky et al. 2015), there is evidence that the use of sedation protocols leads to improved patient outcomes by reducing over sedation (Brook et al. 1999; Sessler et al. 2011). Other studies have included spontaneous awakening trials with sedation protocols, and showed decreased overall sedative use and decreased incidence of acute brain dysfunction (Girard et al. 2008; Khan et al. 2014). With the growing use of spontaneous awakening trials, it has also come to light that a small subset of patients will have rapidly reversible sedation-associated delirium. While seen in less than 10% of patients with sedative-associated delirium, these patients tend to portend better outcomes than those with more persistent forms of delirium associated with sedation (Patel et al. 2014). Protocols which optimise sedation and then have physical therapy added to the management practice significantly reduce the duration of delirium in critically ill patients (Schweickert et al. 2009).

Risk factors for the development of paediatric delirium have not been thoroughly studied. A recently published small cohort study demonstrated that developmental delay, need for mechanical ventilation and age were associated with delirium (Silver et al. 2015). The exposure to benzodiazepine administration

has been associated with the development of delusional memories and subsequent development of post-traumatic stress disorder in children who survive critical illness (Colville et al. 2008). Future studies will help describe those risk factors that may be modifiable in the future for children during critical illness.

Outcomes

It is important to diagnose delirium in the critically ill adult patient, as the presence of delirium is associated with poorer patient outcomes, both short and long term. In the short term there is higher mortality (Ely et al. 2004), especially in patients with >2 days of delirium (Klein Klouwenberg et al. 2014), increased time of mechanical ventilation (Lat et al. 2009), increased ICU and hospital length of stays (Ely et al. 2001b) and increased cost of care. Pandharipande et al. (2013) found that longer durations of ICU delirium were associated with decreased cognitive function after one year and that the level of impairment was similar to that of a moderate traumatic brain injury in almost a third of survivors.

While the associations between delirium and outcomes have yet to be well defined in children, critical illness has been shown to have long term ramifications. Decreases in spatial and verbal memory, inattention (Fiser 1992), significantly longer school absences (Rees et al. 2004) and development of executive dysfunction months after discharge have been demonstrated among critically ill children who survive to home. Thus there may be elements of critical illness or management factors that exacerbate delirium development and predispose patients to long standing cognitive impairment after discharge.

Prevention and Treatment

Given the impact of delirium on outcomes, focus on prevention and management has become vital. Unfortunately the pathophysiology of delirium has not been fully elucidated and therefore directed therapies are not currently available. In both adults and children with delirium the prompt identification and treatment of underlying causes such as sepsis, hypoxia, poor oxygen delivery or drug withdrawal should be undertaken, leading to symptom resolution. There are other situations in which the source of delirium cannot be acutely reversed, and rather the focus becomes decreasing factors that may exacerbate or prolong acute brain dysfunction. Non-pharmacological strategies may help maintain orientation and support normal function of brain systems, thus improving outcomes (Inouye et al. 1999). Promotion of the sleep-wake cycle is crucial and can usually be achieved by non-pharmacological means. Additionally, the ongoing assessment of need for and goal of weaning psychoactive medications should be considered, including the necessary goal for level of consciousness and monitoring and treatment of pain. Non-pharmacological strategies that have been shown to be effective in reducing the incidence and duration of delirium in adults include early mobilisation (Schweickert et al. 2009) and sleep hygiene protocols (Kamdar et al. 2015). One such framework for good sedation and delirium practices is the ABCDE approach, which incorporates **A**ssessment and management of pain; **B**oth spontaneous awakening and breathing trials; **C**hoosing the right sedative; **D**elirium monitoring and management; and **E**arly exercise has been shown to be effective in reducing delirium (Balas et al. 2013).

Current pharmacological interventions are focused on treatment of the behavioural expression of delirium, both hyperactive and hypoactive, ranging from excessive agitation or combativeness to withdrawal and apathy (Balas et al. 2013; Smith et al. 2013). There are currently no U.S. Food and Drug Administration-approved medications for treatment of delirium in either adult or paediatric populations. However, both typical and atypical antipsychotics have been used successfully to modify delirium symptoms in both adults and children (Schieveld et al. 2007; Silver et al. 2010). A recent study investigated the use of haloperidol prophylaxis for adult patients with >50% predicated chance of developing delirium. Patients in the treatment group had decreased incidence of delirium and more delirium-coma free days, with the effect most pronounced in those with the highest baseline risk (van den Boogaard et al. 2013). This is consistent with other small studies that have had positive results with the use of antipsychotics for reducing delirium in adults (Skrobik et al. 2004; Devlin et al. 2010; Devlin et al. 2011). In contrast the HalOPeridol Effectiveness in ICU delirium (HOPE-ICU) trial, which randomised patients to haloperidol or placebo, showed no benefit in adult ICU patients receiving haloperidol prophylaxis (Page et al. 2013), nor did the Modifying the INcidence of Delirium (MIND) study comparing typical to atypical antipsychotics to placebo (Girard et al. 2010). The current adult SCCM guidelines thus do not recommend the routine use of any pharmacological prevention strategy for delirium including antipsychotics, but do acknowledge that atypical antipsychotics may reduce the duration of delirium (Devlin et al. 2011).

"unless routine monitoring is used, delirium will be missed"

Conclusion

Delirium is a major contributor to both in-hospital and outpatient morbidity and mortality. Delirium monitoring and management may help decrease development and duration of delirium in both adults and children. Clearly, institution of a consistent monitoring plan for sedation, pain, and delirium may benefit critically ill patients. Though risk factor and outcome data in adults are better elucidated, further understanding and future studies are required in the paediatric population. ■

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MULTIMODALITY NEUROMONITORING IN CRITICALLY ILL PATIENTS WITHOUT PRIMARY ACUTE BRAIN INJURY

This review focuses on the current experience with clinically available neuromonitoring techniques in critically ill patients at risk for neurological compromise, but without overt acute brain injury (ABI).

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The field of neuromonitoring has grown rapidly over the past 30 years, which has helped improve pathophysiological understanding, clinical care and outcomes for patients with primary ABI, including traumatic brain injury (TBI), subarachnoid haemorrhage (SAH), hypoxic-ischaemic injury and ischaemic or haemorrhagic stroke. The main goals of neuromonitoring are to better understand a patient's cerebral physiology, provide early detection of neurological worsening or cerebral dysfunction to avoid progression to irreversible neurological injury, and assist with neuroprognostication. This is accomplished through a combination of serial neurological examinations, neuroimaging studies, and continuously monitoring different neurophysiological parameters. Numerous expert opinion and evidence-based reviews on the role of multimodality neuromonitoring in ABI have been published, including a consensus statement on multimodality monitoring in neurocritical care from the Neurocritical Care Society and the European Society of Intensive Care Medicine (Stocchetti et al. 2013; Le Roux et al. 2014).

Most research and clinical practice in neuromonitoring has focused on patients with primary ABI, particularly TBI and SAH, and occurred in specialised neurocritical or neurotrauma care units (NCCUs). There is also a large population of critically ill patients without primary neurologic disease or ABI, who are at high risk for cerebral injury from their underlying disease process, systemic complications, or medical therapies, e.g. cardiac arrest, severe sepsis from extracranial sources, endocrinopathies such as diabetic ketoacidosis and hyper-/hypo-thyroidism, renal and hepatic failure, rheumatologic conditions like haemophagocytic lymphohistiocytosis, and haematological abnormalities, including leukaemias and other neoplasms. The pathophysiology of secondary ABI in these patients is complex given the heterogeneous aetiologies and the numerous physiological cascades that can contribute to cerebral injury. Like ABI patients, these high-risk patients may benefit from neurophysiological and neurodiagnostic techniques to detect the antecedents of neurologic insults, thereby identifying a therapeutic window when neuroprotective or neurorestorative interventions will have the greatest likelihood of preventing and minimising irreversible brain injury.

Clinical Components of Multimodality Neuromonitoring

The traditional cornerstone of clinical neuromonitoring is the performance of serial bedside neurological examinations. The main components of the examination in a critical care environment comprise an assessment of the patient's mental status, including consciousness and awareness, cranial nerves and gross motor abilities. The Glasgow Coma Scale (GCS) is the most widely used scale for characterising a patient's degree of consciousness (Teasdale and Jennett 1974). Although it was originally developed to assess consciousness in TBI patients, its use has since expanded, becoming the most commonly used tool to communicate global neurological status for all ICU patients. It has been tested widely and has reasonable intra-rater and inter-rater reliability, although accuracy is greater amongst more experienced providers (Rowley and Fielding 1991). Concerns exist about its accuracy and usefulness in intubated patients and those receiving sedatives, analgesics and neuromuscular blocking agents (Kornbluth and Bhardwaj 2011). A newer scale to measure the degree of consciousness is the Full Outline of UnResponsiveness (FOUR) score, which includes assessments of eye and motor responsiveness similar to the GCS, and adds tests for brainstem reflexes (pupil and corneal reflexes) and respiratory pattern (Wijdicks et al. 2005; Iyer et al. 2009). Both the GCS and FOUR score measures perform well at predicting in-hospital mortality and functional outcome (Wijdicks et al. 2011), although the utility of detecting subtle neurological changes in critically ill patients with these scales is unclear. Delirium is also a common manifestation of neurologic dysfunction in critically ill patients, and routine use of screening tools like the Confusion Assessment Method for the ICU (CAM-ICU) or the Intensive Care Delirium Screening Checklist (ICDSC) is recommended (Barr et al. 2013). Abnormalities detected while performing serial neurological examinations, whether on coma or delirium assessment scales, brainstem reflexes or detailed clinical examination could indicate the presence or evolution of ABI, and further investigation with neuroimaging or other diagnostic modalities may then be required.

Neuroimaging

Computerised tomography (CT) and magnetic resonance imaging (MRI) are the most frequently used modalities to diagnose or exclude intracranial pathology in critically ill patients. They are typically performed in response to new or changing neurologic signs or symptoms, and are not routinely used as screening tools. CT is commonly used to evaluate critically ill patients with an acute change in neurological status, and can readily detect pathology like intracranial haemorrhage, hydrocephalus, and cerebral oedema, which may require emergency medical or surgical intervention. Portable CT imaging is now readily available and provides high quality images; because no patient transport is required this reduces the risk of transport-associated brain insults and complications (Peace et al. 2010; Swanson et al. 2010). MRI has greater anatomical resolution and a variety of specialised imaging sequences that provide detailed maps demonstrating subtle areas of infarction or haemorrhage, integrity of white matter tracts and quantitative information about cerebral physiology, perfusion, and metabolism. These images, however, are acquired at single time points during evolving systemic and cerebral disease processes. While these images can provide insights into disease pathophysiology, explain clinical symptoms and provide prognostic information, they always should be related to — and combined with — continuous neuromonitoring techniques and the clinical evaluation.

Electrophysiology

Continuous electroencephalography (cEEG) monitoring provides essential information while monitoring critically ill patients at risk for ABI. Continuous EEG is the only means to detect electrical (i.e. nonconvulsive) seizures and monitor response to anticonvulsant therapy. Seizures can be a manifestation of an occult cerebral insult, and in some circumstances they can aggravate existing brain injury. Current guidelines recommend cEEG monitoring in ICU patients without primary ABI who have "unexplained impairment of mental status or unexplained neurological deficits" to evaluate for nonconvulsive seizures (Claassen et al. 2013). Seizures occur in about 10% of ICU patients without primary ABI, with severe sepsis, renal failure and hepatic failure being the most significant risk factors (Oddo et al. 2009). Nonconvulsive seizures exclusively occurred in 67% of cases (Oddo et al. 2009). ICU patients with unexplained neurological dysfunction are typically monitored with cEEG for 24-48 hours (Gavvala et al. 2014). Seizures in critically ill patients are associated with poor outcomes and increased mortality. Additionally, EEG abnormalities (e.g. abnormal background frequencies, triphasic waves, etc.) have been associated with mortality in septic patients (Young et al. 1992). Although only currently used in patients with ABI from subarachnoid haemorrhage, characteristic trends on cEEG correlate with delayed cerebral ischaemia from vasospasm have been used at the bedside to supplement clinical data (Rathakrishnan et al. 2011; Vespa et al. 1997). Modules that quantitatively process EEG waveforms and graphically display information (e.g. compressed spectral array and colour density spectral array EEG) can also be used at the bedside for seizure detection and to monitor for patterns of cerebral dysfunction from causes like ischaemia.

Unlike EEG, evoked potentials are typically recorded as isolated snapshots and generally used to help estimate prognosis in select cases, e.g. bilateral absent N20 peaks after cardiac arrest rather than guide therapy (Wijdicks et al. 2006; Carter and Butt 2001). In addition, it is difficult to maintain the stability of EPs to perform continuous monitoring (Fossi et al. 2006).

Intracranial Pressure, Cerebral Blood Flow and Cerebral Autoregulation

Although intracranial pressure (ICP) and its consequences are discussed frequently in critical care patients, it is rarely measured directly (e.g. ventriculostomy or intraparenchymal monitor) in patients without ABI. Noninvasive techniques to estimate ICP include measuring optic nerve sheath diameter with ultrasound (Ohle et al. 2015; Rajajee et al. 2011), two-depth transcranial doppler (TCD) insonation of the ophthalmic artery (Ragauskas et al. 2012), TCD-derived pulsatility index (Bouzat et al. 2010), and computationally from the relationship between the arterial blood pressure and the middle cerebral artery (MCA) flow velocity waveforms (Schmidt et al. 2003). While these methodologies have shown encouraging results, they are mostly intermittent measures aimed at screening patients with clinical suspicion for increased ICP. The TCD-based approaches have the potential for continuous monitoring, but require constant adjustment of probe placement and have technical issues relating to device compatibility. In one study using a noninvasive TCD-based technique, ICP measurements in septic patients did not increase above 20 mmHg after fluid resuscitation. Calculated CPP levels below 60, however, were associated with increased neuronal injury, as assessed by S-100ß levels (Pfister et al. 2008a).

In circumstances when the clinical history, neurological examination and neuroimaging suggest cerebral oedema and that ICP increases may lead to ABI, invasive ICP monitors can be placed to accurately assess ICP and guide medical therapy. This has been done for patients with acute liver failure (Mohsenin 2013; Blei et al. 1993), diabetic ketoacidosis (Srinivasan et al. 2012) and drug intoxications (Marklund et al. 2007). In these patients, continuous ICP monitoring is more clinically useful than intermittent measurements.

"Multi-modality neuromonitoring has the capability to provide high-resolution real-time physiological data"

Cerebrovascular pressure reactivity is the mechanism through which cerebral vessels protect the brain against inappropriate cerebral blood flow (CBF) changes, irrespective of acute changes in blood pressure or cerebral perfusion pressure (CPP). This is accomplished by the brain's intrinsic ability to dynamically adjust cerebrovascular tone or resistance. Dysregulation of this system can contribute to cerebral insults by several mechanisms, including ischaemia, hyperaemia, hypoxia, increased ICP and cerebral energy dysfunction. Cerebrovascular autoreactivity can be assessed in a dynamic fashion by interrogating the relationship between arterial blood pressure (ABP) or CPP and measures of cerebral blood flow or volume. Techniques to measure CBF used in this manner are MCA flow velocity via TCD, ICP, brain tissue oxygen (PbtO2) and near-infrared spectroscopy (NIRS) (Zweifel et al. 2014).

Impaired cerebrovascular autoreactivity has been demonstrated after ABI and as a component of other systemic disease processes like severe sepsis (Taccone et al. 2010; Pfister et al. 2008b), liver failure (Macias-Rodriguez et al. 2015), and diabetic ketoacidosis (Ma et al. 2014). Some of the neurological complications in patients with these conditions may result in part from loss of cerebral autoregulation. There are currently no medical therapies to improve impaired cerebral

autoregulation, although evidence exists that autoregulation may be optimised for an individual patient within a specified range of ABPs or CPPs and carbon dioxide levels (Taccone et al. 2010; Aries et al. 2012; Steiner et al. 2002). Additionally, sedative medications may influence cerebrovascular reactivity and this effect may be modulated by patient age and underlying disease process (Kadoi et al. 2008; Hinohara et al. 2005).

Cerebral Metabolism and Brain Oxygenation

Numerous pathological cascades that involve impaired brain oxygenation and cerebral metabolism exist. These can precipitate or exacerbate neurological insult in critically ill patients. Several monitoring modalities are available to interrogate brain oxygen, including direct measurement of brain tissue oxygen tension in a specific brain region (PbtO2), global cerebral oxygen delivery via jugular bulb venous oxygen saturation (SjvO2) and noninvasive cerebral oximetry in frontal brain regions with NIRS (Barazangi and Hemphill 2008; Maloney-Wilensky and Le Roux 2010; Stocchetti et al. 2013). There is limited experience with these techniques in patients without primary ABI, although the potential information learned about cerebral oximetry and metabolic function could prove helpful to predict, manage and prevent neurologic compromise in patients at high risk for brain injury.

A few studies have used these techniques to evaluate patients with sepsis with neurological symptoms (Oddo and Taccone 2015; Taccone et al. 2013). In septic patients with altered mental status, SjvO2 and flow velocity in the MCA with TCD were measured during a dobutamine challenge. While CBF and oxygen delivery increased with dobutamine, oxygen consumption did not change (Berre et al. 1997). Another study found poor agreement between CBF estimates derived from TCD and NIRS (Toksvang et al. 2014). NIRS has potential wide applicability to examine for cerebral compromise, e.g. noninvasive evaluation of cerebral autoregulation in septic patients (Steiner et al. 2009), to assess cognition-related abnormalities in brain function in patients with mild hepatic encephalopathy (Nakanishi et al. 2014), to evaluate cerebral hyperaemia during treatment for diabetic ketoacidosis (Glaser et al. 2013), and to monitor cerebral function during volume resuscitation in dehydrated patients (Hanson et al. 2009). The best results however may be in neonates, and further study is required in adults.

Cerebral metabolism can be assessed through the sampling of the brain's extracellular fluid with surgically implanted cerebral microdialysis catheters. This technique provides an evaluation of regional cerebral bioenergetics; abnormal concentrations of certain cerebral metabolites (i.e. lactate, pyruvate, glucose, glutamate) can indicate evolving energy failure, hypoxia or ischaemia, or an imbalance between aerobic and anaerobic metabolism (Hutchinson et al. 2014; 2015). Most clinical experience with microdialysis is with ABI, and TBI and SAH in particular. However, it has been used in monitoring platforms of fulminant hepatic failure (Hutchinson et al. 2006; Tofteng et al. 2002). The ability of cerebral microdialysis to interrogate the brain's neurochemistry may increase our understanding of the pathophysiology of other systemic diseases that have neurological complications, like septic encephalopathy, diabetic ketoacidosis, toxic exposures, and assist in the critical care management of these patients by providing targets to protect against cerebral energy failure. For example, in TBI patients, tight glycaemic control (80-120 mg/dL) with aggressive insulin therapy was associated with reduced cerebral glucose concentrations and worse cerebral energy crisis (Oddo et al. 2008; Vespa et al. 2012). Both high and low cerebral glucose have been associated with poor outcome in TBI. It is unclear what the optimal range for brain glucose is, what the relationship between serum and brain glucose concentrations in a metabolically stressed brain is, and how generalisable these findings are to other types of neurological insults (Hutchinson et al. 2015). However, knowledge about brain glucose may help guide therapy. In addition, understanding metabolism has shown that alternative fuels such as lactate may be beneficial in select patients (Oddo et al. 2012; Bouzat et al. 2014).

Conclusions and Future Directions

A major challenge to prevent brain injury in critically ill patients is that the progression from neuronal dysfunction to permanent injury typically proceeds undetected through a critical period when neuroprotective or neurorestorative interventions are likely to be effective. The goal of multimodality monitoring is to integrate signals in real time from a variety of technologies to provide bedside clinicians with a metric of the relative health or dysfunction of the brain before, during and after this critical period. Physicians can then use this information to guide individualised and goal-directed therapy to help prevent and mitigate further neurological injury. The integrative capabilities of bioinformatics platforms allow for the rapid synthesis and display of this data in a format that provides clinicians reliable information that can be used to target therapies (Hemphill et al. 2011).

Selecting the appropriate components of a multimodality platform must take into account the underlying pathophysiology of the relevant disease processes and potential mechanisms of cerebral injury. For example, neurological sequelae in patients with severe sepsis occur in multiple patterns including ischaemic strokes, vasogenic oedema and white matter abnormalities (Stubbs et al. 2013). Areas of perfusional ischaemia may result from impaired cerebral autoregulation or systemic hypotension, while other areas of injury may be the result of deleterious inflammatory mediated processes like endothelial cell swelling, microvascular dysfunction, alterations in blood-brain barrier permeability, and neurotransmitter imbalance. Thus, measuring cerebral autoregulation or microdialysis may detect actionable precursors to cerebral dysfunction in this population, whereas measuring ICP may be less helpful, because rarely is there enough cerebral oedema to increase ICP.

Choosing the most appropriate systemic and neurophysiological monitor is particularly important for patients who are at high risk for brain insult, but have not yet sustained brain injury. Currently, strategies to manage these patients are reactive in nature, with physicians responding to changes in neurological exam or physiological variables. Multimodality neuromonitoring has the capability to provide high-resolution real-time physiological data that, when computationally integrated and synthesised, can facilitate proactive measures to detect and correct neurophysiological derangements to avoid neurological compromise (Wartenberg et al. 2007). Furthermore, this paradigm will allow for an enriched understanding of the brain's response to systemic pathological states, and help design targeted treatment strategies that are mechanistically derived rather than empiric in nature. Overall, this rapidly evolving technology will provide physicians with additional information to promote brain health and avoid neuronal insult in critically ill patients. ■

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CANADIAN RESEARCHERS AT THE END OF LIFE NETWORK (CARENET)

INTERVIEW WITH PROFESSOR DAREN HEYLAND

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The Canadian Researchers at the End of Life Network (CARENET), directed by Professor Daren Heyland, brings together health professionals from across Canada. The network aims to understand and improve palliative and end-of-life (EOL) care through improving communication and decision making between patients, their families and health professionals. They have several projects evaluating different tools or strategies to improve communication and decision-making in all sectors of the healthcare system (primary care, long-term care, cancer care, ward-based care in hospital and the ICU). Current projects in critical care include *Personalizing Death in the Intensive Care Unit* (Cook et al. 2015) and *Realities, Expectations and Attitudes to life support technologies in intensive care for Octogenarians: the Realistic 80 study* (Heyland et al. 2015a; 2015b).

CARENET's goals include fostering research on palliative/EOL care with a focus on communication and decision-making. Why this focus?
Based on our lived experience as critical care practitioners, we saw that decision-making about the use or non-use of life-sustaining treatments was done poorly in many cases. We perceived that our patients and their families were ill prepared to engage with us in important EOL decisions and that oftentimes we were perhaps over treating or intensifying the dying experience in patients. We asked ourselves if we could do a better job and how. We set out to describe the dying experience and understand the conditions around which these decisions were made and then ultimately improve them through the use of various tools and training modules.

Has medical technology been ahead of communication in critical care?
The proliferation of technology and the ageing of society has created a clash. No older person can die now without passing through an intensive care unit and having technology applied at the end of life. That's overstating the point somewhat, but the ageing society and explosion of medical technology has created a lot of challenges for those of us that work in the ICU with respect to the appropriateness of using life-sustaining technology. We wanted to drill into that and figure out how can we understand and improve communication and decision making related to use of life-sustaining treatments at the end of life.

Where do you see gaps in research into the end-of-life care in the ICU?
I think the biggest gaps are around engagement of health professionals. We know that patients say that they thought about the use of life-sustaining treatments, that they talked to their family members about their wishes (You et al. 2014a). But they had very little engagement with hospital professionals around treatment decisions at the end of life. That engagement comes too little too late and we are left with dealing with substitute decision makers or family members, who are badly prepared to step in to assist with the decision making that occurs. Patients and family members are ill prepared, and we as healthcare professionals are not active enough in asking patients about their wishes and helping them clarify their values and make decisions.

The Realistic 80 study addresses critical care for the very elderly, and you have found incongruity between family values and preferences for end-of-life care and actual care received. Was this a surprise?
The magnitude of the mismatch was surprising and the consequences of that on the prolongation on the dying experience (Heyland et al. 2015b). If a very elderly patient is admitted into the ICU and then dies, they spend an average of 12 days in an intensive care unit receiving life-sustaining treatments. This is in the context from a family's point of view that many of them didn't want this in the first place. Literature from other countries would suggest that either very elderly people are not admitted to the ICU, or if admitted at the end of life have one or two days in the ICU before life-sustaining treatments are withdrawn. So we still have real challenges related to communication and decision making that we are still struggling to fix.

Is provision of ICU beds in Canada quite generous in comparison to other countries?
Yes, our government's response over the last decade has been to increase critical care capacity rather than address the pressure on the system and question whether our resources are being appropriately utilised. Consequently, together with the ageing of society and progression of technology the attitude is that more is better, and we can reverse all of this and save lives. We end up with more and more older patients in the ICU receiving life-sustaining treatments. Please don't misunderstand, we are not opposed to admitting older patients to the ICU. We just want to make sure that it is consistent with their wishes, appropriate to the medical context and not prolonging the dying experience.

CARENET has developed resources for the public and for health professionals about starting the conversation about end-of-life care. How are these being disseminated and evaluated?
As well as describing the issues we are developing tools to improve the situation. There are a number of patient-facing tools to better prepare patients and their families and tools for health care professionals to help them engage patients and families in the conversation. We've developed several promotional campaigns to promote these tools:
ICU Workbook (**myicuguide.com**) is a novel website designed to support families of ICU

patients so they can be better advocates of best practice in respecting the wishes of their loved one.

Speak Up (**advancecareplanning.ca**) is a public health campaign aimed to promote advance care planning in Canada. We hope to get lay people to think about, reflect on and speak up with respect to their wishes for end-of-life care to family members and healthcare practitioners. We have staff working on various communication strategies, and we have partnerships with agencies across Canada – cancer foundations, palliative care and hospice associations. Every April 16 we host a national advance care planning day that is government-endorsed. We have had great success in uptake particularly around the national advance care planning days. We have conducted public opinion polls to determine the level of awareness, engagement and advance care planning (Teixeira et al. 2015). We hope our activities will better prepare patients and their families to engage with healthcare professionals when it comes time to make serious end-of-life decisions.

Just Ask (**thecarenet.ca/our-campaigns/just-ask-campaign**) is intended to encourage healthcare professionals to ask their patients about their wishes and values and ask them to state their preferences (You et al. 2014b). We have some great tools on our website — a pathway, a conversation guide and some scripts as to how healthcare professionals might engage their patients in these conversations. The evaluation of this campaign is not as straightforward as for the public campaign. We are asking patients in various settings if they had these discussions with their healthcare practitioners about what their values and preferences are and if they trust that this is accurately put in the medical record. The novelty here is that we are reaching out to patients to audit the performance of healthcare professionals and the healthcare system. We audit if these conversations happened, and look at milestones in more detail, e.g. if the health professional talked to them about their prognosis etc. There are many gaps, and there is still a lot of work to be done. We felt this is a superior way of auditing performance compared to asking health professionals if they discussed this with their patients. We have also surveyed healthcare professionals in terms of their level of engagement in conversations on advance care planning in relation to their level of comfort and in terms of their perceived barriers to further engagement (You et al. 2015).

We believe we can have the greatest improvement on EOL care by improving communication and decision-making. ■

Further Information

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a CANADIAN CRITICAL CARE KNOWLEDGE TRANSLATION NETWORK (aC³KTion Net)

A QUALITY IMPROVEMENT INITIATIVE

The Canadian Institutes of Health Research (CIHR) defines knowledge translation (KT) as:"a dynamic and iterative process that includes the synthesis, dissemination, exchange and ethically-sound application of knowledge to improve the health of Canadians, provide more effective health services and products and strengthen the healthcare system" (CIHR 2015)

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Approximately 360,000 Canadians require critical care services annually (Statistics Canada 2011), at an estimated cost of over six billion Canadian dollars (Leeb 2006). As the population ages, and the ability to treat previously fatal illnesses improves, it is expected that demand for critical care services will continue to grow (Hill 2009). Optimal care of critically ill patients is evolving rapidly, and the application of best practices or high-quality relevant research evidence incorporated into clinical care can reduce morbidity (Damiani 2015), mortality (Collingsworth 2014) and healthcare costs (Shorr 2007). It is only through strategies to increase the uptake of best practices that we can ensure optimal care and outcomes at the lowest cost. In spite of the large number of critical care consumers and the costs of care, there has not been a systematic, coordinated strategy in Canada to ensure that the critically ill receive best practices, nor have there been any mechanisms to audit care or outcomes.

As a quality improvement initiative, the aim of the Canadian Critical Care Knowledge Translation Network (aC³KTion Net) is to increase the adoption of best practices in intensive care units (ICUs) across the country by developing a national knowledge translation network whose efforts would survey current practices to identify knowledge gaps, develop concise, user-friendly knowledge products, and measure their uptake and impact.

Methods

Developing the Network

At the inception of the network, both Steering and Scientific committees were established to oversee the Network. The 26-member Steering Committee provides general oversight and direction of the network and is comprised predominately of critical care physicians, but also includes representation from the Canadian Patient Safety Institute (CPSI 2015), Critical Care Services Ontario (CCSO 2015), the Canadian Association of Critical Care Nurses (CACCN 2015) and the Canadian Society of Respiratory Therapists (CSRT 2015). The 11-member Scientific Committee is made up of senior researchers within the Canadian Critical Care community, whose main role is to provide clinical input into the network so that any initiatives undertaken are scientifically relevant. (See **acktionnet.ca** for list of committee members). To initialise the network, activities included recruitment of participating hospitals, a survey of baseline practices, development of a repository of practices and knowledge translation activities.

Recruitment of Participating Centres

The goal of aC³KTion Net was to recruit as many academic and community hospitals in Canada as possible into the network. Academic centres were recruited by identifying hospitals and ICUs affiliated with the Canadian Critical Care Trials Group (CCCTG 2015). A public list of hospitals, which included community hospitals, was used to identify other hospitals not affiliated with the CCCTG. Those with ICUs were identified by investigating hospital websites, and were then contacted by telephone for confirmation (CBC 2013). Identified ICUs were encouraged to register with aC³KTion Net via email, personal contacts and telephone solicitation. All units with self-identified ICUs were eligible for inclusion into aC³KTion Net and were encouraged to participate. A web-based registration platform (**acktionnet.ca**) was set up to enable registration.

Core Data Set

To enable the function of the network and collect information on baseline practice, a modular data set was developed. It was designed to be used in all activities of the network and consisted of a Core Data Set (CDS) on to which modules could be added reflecting the data requirements of new initiatives as they were identified and implemented. The CDS was designed to be able to be used for any future research, knowledge translation or quality improvement initiatives depending on the add-on modules collected with the CDS. The CDS is comprised of admission, daily and outcome report forms. The Scientific and Steering Committees together defined the core data variables required for the CDS. The individual data elements in the CDS were explicitly defined to improve uniformity of the data collected. The definitions associated with each variable in the CDS were vetted through the Cana-

dian Critical Care Trials Research Coordinator group (CCCRCG 2015).

To assess the clarity of the definitions and time burden associated with data abstraction of the CDS, a Research Ethics Board-approved feasibility study was conducted in which data abstractors at five sites were asked to collect data on five patients each. Strict records of the time required to collect this data were kept. Source charts were then obtained and the data abstracted was compared with the source charts as a way to verify the utility of definitions and to determine variability in their interpretation.

Baseline Survey of Practices

In order to assess the penetration of research evidence into practice a baseline practice survey was conducted. A stepwise approach was used to determine which practices to survey. First the Steering committee identified nine potential ICU practices using the key requirement that current evidence-based practice guidelines existed. This was used as an indicator of the maturity of evidence and potential for knowledge translation (KT) activities. Moreover the presence of existing guidelines would allow for the determination of concordance to best evidence. The practices chosen included: Ventilator-Associated Pneumonia (VAP), Hypothermia after Cardiac Arrest, Nutrition for Critically Ill, Noninvasive Ventilation, Pain, Agitation and Delirium, Neurological prognostication after cardiac arrest, Thromboprophylaxis, Central Line infections and Sepsis. In addition the committees were asked to contemplate critical care practices for longer-term initiatives including surveys of practice and guideline development. Thirty-four initiatives were put forward as options for future initiatives. These included, but were not limited to: End-of-Life Care, Early Mobility, Mechanical Ventilation, Antimicrobial Stewardship, Staffing practices and Acute Kidney Injury. A modified Delphi process (RAND 1994) was then conducted using SurveyMonkey (SurveyMonkey 1999) involving all the members of the Steering and Scientific Committees. The respondents ranked each initiative using a Likert scale as "not very important" (1) to "very important" (9). The results for each initiative were then summed and ranked in order from highest to lowest score. The bottom four of both the current and future initiatives were removed after the first iteration. By the third round, stability had been reached; Ventilator-Associated Pneumonia (VAP) (Muscedere 2008a; 2008b), Sepsis (Dellinger 2008) and Nutrition (Dhaliwal 2014) were the three identified as being of highest priority. Among the practices where no guidelines are available, End-of-Life Care was identified as being the highest priority. Once the initiatives were identified, data modules were developed and added to the CDS. An electronic database REDCap (Vanderbilt University 2015) was used to collect data.

Table 1

Province	Acute care Hospitals	Hospitals with ICU's	Registered ICU's	Sites participating in baseline survey
Northwest Territories-Nunavut-Yukon	6	2	1	0
British Columbia	73	31	12	2
Alberta	93	23	13	11
Saskatchewan	59	9	4	0
Manitoba	61	10	7	6
Ontario	154	102	40	10
New Brunswick	19	9	2	0
Nova Scotia	31	9	4	2
Newfoundland and Labrador	30	6	2	1
Prince Edward Island	7	2	0	0
Quebec	102	*	13	1
	635	203	98	33

*due to logistical challenges it was difficult to confirm the number of acute care hospitals with ICUs in Quebec.

"Dedicating resources to quality improvement in the busy environment of the ICU remains challenging"

Registered sites who had agreed to participate in the baseline survey of practice collected patient-level data for the CDS and practice modules as applicable. The number of participants requested from each site was predicated on the number of ICU beds at the site: ≥20 beds = 30 participants, ≤19 beds ≥ 10 beds =20 participants and ≤ 9 beds = 10 participants. As a quality improvement initiative, patient-level data was anonymised, and would only be presented in aggregate; Central Research Ethics Board approval, including a waiver of consent was sought and granted from Queen's University.

Repository

Housed on the website, a restricted-to-member repository of Canadian critical care documents was established. The repository was primarily populated with documents shared on the *Critical Care Google Group*, an online discussion group affiliated with the Canadian Critical Care Society (CCCS). Each document conserved in the repository was protected by a caveat emptor disclaimer drafted to mitigate liability, and was only shared in the repository after permission was granted by the original Google Group poster.

Undertaking Knowledge Translation

Due to the widespread nature of the network, KT primarily consisted of passive KT, dissemination of material via the distribution lists, or by posting on the website. Webinars were hosted, including those on VAP guidelines and Sepsis. aC^{3}KTion Net also hosted a six-month long *Accelerated Collaborative* in conjunction with the Canadian ICU Collaborative (Northway 2008) targeting sepsis, VAP and nutritional support in the ICU.

Results

The number of acute care hospitals, those with an ICU, the number of sites registered with aC^{3}KTion Net and the number of sites that participated in the baseline survey of practice is outlined in Table 1. A total of 98 ICUs across Canada enrolled in aC^{3}KTion Net with 33 of them agreeing to collect data on baseline practices.

Data Collection Metrics

Based on the feasibility study, the time to abstract the CDS for a patient with an average length of stay (LOS) of eight days was a mean of 50.9 minutes (± 24.9 minutes) with a range of 26.0 minutes to 1.3 hrs. For the same average LOS, abstracting 30 patients would take a mean 25.5 hours (±12.5 hours).

Survey of Practice and Repository

Approximately 900 participants have been entered into the REDCap database. Analysis is pending the

receipt of additional data from some of the sites. The repository of critical care documents was organised according to Organ Systems, Trauma, Pharmacology in the ICU, End-of-Life Care and Advanced Care Planning, Diagnostic Modalities, Rehabilitation, Nursing Management, ICU design and Laboratory medicine. This repository houses over 500 documents from across Canada and the database is searchable by keyword. In spite of aggressive recruitment efforts, only four sites registered for the collaborative with a total of seven projects. Passive KT efforts continue.

Discussion

We have developed a national network of ICUs which is inclusive of both academic and community centres. The creation of a standardised CDS, element data dictionary and scalable modular data system, which can be utilised for quality improvement or research will enable any future initiatives in this regard. We have amassed a repository of practice documents from across the country in a searchable, retrievable manner, which is and will continue to be a resource into the future for any clinician wishing to adapt them to their practice environment. This repository will continue to grow over time. We will continue to build the relationships within the network and with external organisations as we go forward, including the *Choosing Wisely* campaign (Choosing Wisely Campaign Canada 2015). In spite of these successes, aC^{3}KTion Net encountered many challenges and was not able to carry out many of the activities envisioned at its initiation.

The nature of healthcare in Canada is that it is rendered regionally. Without federal oversight each province or territory is responsible for overseeing its own healthcare, resulting in thirteen systematically different healthcare systems, presenting a challenge when creating a national network. Further compounding this is the lack of public availability of a catalogue of acute care resources on either a federal or provincial basis, which made it difficult to identify all the acute care hospitals in Canada. In addition, determining which hospitals had critical care units was even more challenging. This necessitated a long labour-intensive process to identify ICUs, contact them and recruit them into the network. Although some provinces maintain up-to-date registries of critical care units, a registry of ICUs at the national level would facilitate initiatives such as ours, critical care resource management, human resource management and would be of importance during crises such as pandemics. This initiative has reinforced the need for the development of such a resource.

Despite broad support and enthusiasm for the baseline survey of practice, by June 2015 only one-third of registered ICUs had contributed data to the survey or approximately 900 participants nationwide. The lack of financial incentives from aC^{3}KTion Net and lack of local resources at the site level were anecdotally identified as being responsible for not being able to contribute data at all or in a timely manner. Although the average time to abstract the CDS was significant, it was less than one hour per patient and we estimate that data collection per patient was less than two hours when the modules were included with the CDS. Although most ICUs maintain that quality improvement is a priority, in reality, dedicating resources to its conduct in the busy environment of the ICU remains challenging. This was a common refrain from our participating sites. Other factors which may have led to the poor response of baseline practice included the launch of multiple initiatives at once and perceived lack of return for the time spent on data collection. Financial incentives were not available for the collection of the data, and it is possible that the offer of standardised comparative reports of performance, ability to participate in our KT activities and access to the repository of practices was perceived to be insufficient. This will require further investigation.

The purpose of the baseline survey of practice was to ascertain penetration of research evidence into current practice and thereby target our knowledge translation efforts to the largest gaps. Since the baseline survey is incomplete, we have not been able to do this on a large scale. To this end, we offered the collaborative opportunity to ICUs which would or had completed the baseline survey. In spite of aggressive recruitment for the collaborative and expressed interest, participation was very limited with the expressed barriers being lack of availability of staff and the time commitment required. For the hospitals that participated in the collaborative, it was well received, and garnered positive feedback. Again, the ability to commit resources to external quality improvement initiatives appears to be limited. We are unable to comment on internal quality improvement.

Conclusion

We have developed a platform for KT activities that is nationally inclusive of both academic and community centres. Once complete, the analysis of the baseline practice data will provide insights and directionality forward. Many resource challenges and barriers to the conduct of KT and quality improvement in Canadian critical care units are present and provided challenges for the operation of the network as it was originally envisioned. More efforts are required to overcome these challenges and these are ongoing. ■

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FUNDAMENTALS OF CRITICAL CARE

INTERVIEW WITH PROFESSOR MICHAEL PINSKY

Michael Pinsky is Professor of Critical Care Medicine at the University of Pittsburgh, with secondary appointments in Cardiovascular Diseases, Clinical & Translational Science, Anesthesiology and Bioengineering. He is presently a Visiting Professor, Department of Anesthesiology, University of California, San Diego, USA.

Why is it important to take an applied physiologic approach to understanding bedside pathophysiologic processes?

When trying to comprehend the problems that your patient is feeling in terms of their potential cardiovascular respiratory insufficiency, the only way to understand is to apply pathophysiologic principles at the bedside to identify that your patient has as their disease. If done using functional haemodynamic monitoring approaches, you can identify cardiovascular reserve or its lack and then treat the patient accordingly. If they are volume responsive and in shock, and if they need fluids, you know that they will get an increase in cardiac output in response to that fluid challenge. The whole concept of applied physiology at the bedside is what critical care medicine is. All we have simply done is codify it.

What are the most promising applications of functional haemodynamic monitoring?

Functional haemodynamic monitoring simply tells you the cardiovascular reserve of your patient, for example if the blood flow is adequate to meet metabolic demands, or if the cardiac performance is such that if you give volume cardiac output will go up, etc. It gives you a very intuitive way of understanding cardiovascular state, and can also in certain circumstances identify disease ideologies. It is a way of saying "If the patient has a certain disease can I predict how the patient will respond to treatments." It should never be examined outside the context of the patient and their disease. For example, you are volume responsive now, but hopefully you are not in shock. So if I have assessed functionally that you are volume responsive but otherwise stable it would be inappropriate to resuscitate you with fluid. If I used functional haemodynamic monitoring to treat all healthy people, I would be giving them a large quantity of volume and I should not do that. But if I have a person who is sick I can use functional haemodynamic monitoring to identify which treatments will work and have a very good predictive value.

How has your research on heart–lung interactions translated into clinical practice?

I have been studying cardiopulmonary physiology since 1978, and our very first paper was published in the *New England Journal of Medicine* in 1979 (Buda et al. 1979). The study of heart-lung interactions is the study of cardiopulmonary physiology, and it is the fundamental basis of why patients who have pulmonary embolism and hyperinflation go into heart failure. It includes the effects of spontaneous versus positive pressure breathing and ventricular-arterial coupling. It is the fundamental basis for functional haemodynamic monitoring. Without those studies on cardiopulmonary physiology, there would be no functional haemodynamic monitoring parameters today.

Research in that field now has gone from the left ventricle to looking at the right ventricle and ventricular-arterial coupling in the setting of pulmonary hypertension, thromboembolism, thrombectomy and right ventricular volume response.

You've written about the right ventricle: "The genie's out of the bottle" (Pinsky 2014). Can you elaborate?

For many years, the cardiology literature has celebrated the left ventricle as the primary determinant of cardiovascular function, centred around the two primary issues of coronary disease and arrythmias, both of which can limit survival. What was known for many years, but not appreciated, is that the primary determinant of cardiac output is the right ventricle not the left. The right ventricle is profoundly limited by outflow pressure, and thus when we are trying to determine cardiovascular state, we now appreciate that understanding right ventricular function is by far and away more important to assess.

The most common form of heart failure today in the world is referred to as heart failure with preserved left ventricular injection fraction. Many of these cases represent right heart failure. Now we know that, and we can assess it with echocardiography and other monitoring approaches. Looking at right ventricular function as a primary way of accessing cardiovascular state is now a standard approach. The more people look at the right ventricle, the more they realise that it is the major determinant of cardiovascular response and survival. That's what I meant when I said "the genie is out of the bottle".

You noted in an editorial that there is a presumed bias against studies published more than 10 years ago (Pinsky and Lumb 2013). What is the solution?

The problem is that students (in the sense that we are all students) have a very superficial understanding of the fundamental scientific underpinnings of the fields they are studying. We teach more about phenomenology and representing a pattern in treating disease rather than understanding the disease process. Thus when students search the literature, they tend to go for the more recent papers, because they give them answers. They perceive that the latest paper is the latest science. Regrettably that's almost never the case.

Initially the way the Google Scholar search engine worked was that the number of hits a site gets would determine its priority for being listed. If you put in heart-lung interaction, for example, or mitochondrial function and sepsis,

you would get as the very first article, the article that has the most hits, which would usually be a recent paper from the last two years. We complained to Google that in fact most of these papers were simply modifying or reviewing the initial studies. Now in Google Scholar, you'll see that the results you are viewing now show the older papers first; below that listing are the ones that cite those older papers.

You developed a professionalism and leadership curriculum for intensive care fellows at Pittsburgh. Is such a curriculum unusual? Is enough done to develop these skills?

We developed the first leadership and professionalism course that is routinely taught to all fellows. It includes topics such as negotiating a salary, dealing with hospital infrastructure, conducting quality improvement initiatives, the nature of how you would fit into an academic or clinical job, dealing with families, etc. It covers the professional aspect of being a doctor in an acute care setting that is the epicentre of the hospital. The course director Jason Moore and I just published a position paper in the *Journal of Critical Care* (Moore and Pinsky 2015). We describe how we developed this course, how it is evolving and the feedback from the fellows, who are now in private practice, on how important they have found it in terms of practical applications.

I think that such courses should be given nationally and internationally. The strength of the University of Pittsburgh is that we have 60 faculty and we cover all aspects of professionalism. I got immediate buy in from our faculty. Most training programmes don't have that luxury. The way forward is providing web-based materials as CME, or running courses in the critical care society meetings.

A Pittsburgh team reported research this year on a machine learning approach that is able to distinguish between real and artifact alarm alerts (Hravnak et al. 2015). Is this going to be commercialised?

When you are taking care of critically ill people, you are trying to assess if they are stable or unstable. We look at the haemodynamic monitoring of our patient and if the values that they get exceed what we consider to be normal, alarms go off. Regrettably over 50% of alarms that go off are not due to true physiologic alerts, but are due to pure artifacts — the probe comes off the finger, the ECG electrode falls off or the patient has Parkinson's disease and their hand is shaking. If you have ever seen a movie in which they have an ICU, you always hear alarms going off in the background. It is part of the acoustic wallpaper of the ICU, and accordingly alarm fatigue is thought to be one of the primary safety hazards in the hospital setting, specifically in the ICU (ECRI Institute 2015).

We reasoned that the structural pattern of the alarm itself in real time as a biological signal would be significantly different from the actual shape of that alarm if it was due to artifact. Using machine learning approaches over the last three years we have been able to accurately identify those alarms that are artifacts. At the European Society of Intensive Care Medicine 2015 meeting we presented an abstract showing that in a prospective analysis of one year's worth of data, we were able to accurately eliminate in real time 90% of the artifact (Hravnak et al. 2015). If this was made available in a commercial device as machine algorithms, it would mean that if an alarm goes off now it is real. That would solve a fundamental safety issue. We started this initially because we were looking at patterns of disease and trying to identify instability, and we discovered very early on that we had to first filter out the artifacts. The algorithms have been published and the University of Pittsburgh and Carnegie Mellon University are talking to industry about using these. I am sure it will become commercially available.

What would you like to learn about long-term outcomes from critical illness?

Why am I treating my patients? I am treating them to make them go back and have a productive life and be happy. To the extent that I can save a person from acute illness does not mean that they have gone back to be happy. Dr. Lakshmipathi Chelluri was the principal investigator of a study that we did at the University of Pittsburgh in which we looked at long-term outcome from prolonged mechanical ventilation (> 2 days) as a surrogate of acute illness (Chelluri et al. 2004). What we found was that there was profound morbidity in the patients up to a year afterwards. Furthermore the families' harm, which we call collateral damage, in terms of economic loss, depression and for example leaving college to stay home and help their loved one, was amazing. That was a landmark study. There is a profound economic impact of critical illness that goes far beyond the walls of the ICU. It is not the cost of ICU care, when that patient leaves the unit; they are taking with them for up to a year the morbidity and the mortality associated with that. Its impact on the family even if they have socialised medicine is overwhelming. Since one-fifth of all the patients that are in the hospital are in the ICU, the economic impact that this has on society as a whole is absolutely profound. I am studying it, because it is the right thing to do. It is the reason why I am a doctor.

This interview will be in our Emergency Medicine (EM) & Trauma issue. How can EM physicians and intensivists work better together?

In the old days, emergency medicine was considered to be an outpatient field. When a patient was critically ill they needed to be admitted to the ICU or hospital. The emergency medicine doctor would simply call the ICU doctor and walk away from the patient. We know from the early goal-directed therapy studies onwards that this is associated with a very bad outcome. The Australasian Resuscitation in Sepsis Evaluation (ARISE) (ARISE Investigators et al. 2014), Protocolized Care for Early Septic Shock (ProCESS) (ProCESS Investigators et al. 2014) and Protocolized Management in Sepsis (ProMISe) trials (Mouncey et al. 2015) all documented the exact same thing. That is why we now have a tighter link between the emergency room and the ICU in terms of the continuity and aggressiveness of resuscitative care. Manny Rivers' original study (Rivers et al. 2001), though the specific treatment protocol was proven not to be needed, has been a godsend in terms of changing the practice and attitude in the emergency departments and linking more closely ICU to emergency medicine.

At the University of Pittsburgh six of our attending physicians in critical care medicine have emergency medicine as their primary training. We consider the management of the patient, though they are still in the emergency department, the domain of the ICU. This change has significant implications in terms of continuity of care.

Trauma has always done this. When a patient comes in with trauma, they call the trauma team; they go to the trauma room in the emergency department and from there on the trauma team is managing them whether they are in the emergency room, operating room or the ICU. So now we are doing the same with sepsis and acute respiratory failure. ■

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

CRITICAL CARE IN EGYPT

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The healthcare system in Egypt has come a long way, but still faces many challenges when it comes to improving the health and wellbeing of its people. Egypt has a high rate of population growth, and it is estimated that the population will reach 92 million by 2020.

With respect to critical care, Egypt is dealing with the problem of overcrowded hospitals, staff shortages and lack of adequate healthcare equipment. State hospital ICUs function on very low budgets, and there is an acute shortage of nurses. ICU patients often have to be transferred to other hospitals because of lack of space and/or resources. Many die during this process while others end up facing serious health complications.

In order to improve the standards of critical care and to ensure physicians have a greater understanding and knowledge of critical care medicine, several organisations exist to promote programmes and services that could help achieve these goals. These include:

Egyptian College of Critical Care Physicians (ECCCP)

The Egyptian College of Critical Care Physicians (ECCP) comprises critical care physicians, who are committed to advancing the goals of academic critical care medicine.

The College organises annual meetings and other educational events, and publishes a scientific journal, the Egyptian Journal of Critical care Medicine. The ultimate goal of ECCCP is to ensure that the highest standards of critical care are implemented. In addition, ECCCP is an active player in generating support from the government, the healthcare industry and individuals involved in the field of critical care.

Egyptian Society of Intensive Care and Trauma (ESICT)

The Egyptian Society of Intensive Care and Trauma (ESICT) is an interdisciplinary organsation dedicated to improving patient care by improving and advancing the science and practice of intensive care medicine. The primary objective of ESICT is to promote excellence in intensive care through education, research and practice. ESICT aims to create a healthcare environment where every patient will be able to receive the safest, most efficacious and the highest quality care.

ESICT aims to achieve its goals by guiding the healthcare community on adopting and implementing best clinical practices, to promote safe, effective and compassionate patient care, to educate healthcare providers about new ideas and innovation and to conduct quality research and implement evidence-based practices. ESICT actively collaborates with both national and international organisations to ensure excellence in intensive care medicine. ICEM Egypt is an annual conference organised by ESICT and is one of the leading events for Intensive Care & Emergency Medicine in Egypt.

Egyptian Cardiac Arrest Project (ECAP)

The Egyptian Cardiac Arrest Project (ECAP) is a four-year project that aims to survey the magnitude of the problem of out-of-hospital cardiac arrest. It is estimated that only about one-third of patients who suffer from an out-of-hospital cardiac arrest receive CPR and only 2 percent of such patients receive automatic external defibrillation. The goal of ECAP is to increase awareness amongst the community on ways to better handle this condition and to train lay people and healthcare providers on appropriate resuscitation strategies that could help save many lives. In addition, ECAP aims to investigate and identify those who are at risk of occurrence and to take measures that could improve the primary and secondary prevention of cardiac arrest. Associations involved in this project include the Egyptian College of Critical Care Physicians and the American Heart Association. The project is partially funded by the National Bank of Egypt and Misr Al-Kheir. ■

Statistics

Total population	82,056,000
Gross national income per capita (PPP international $)	10
Life expectancy at birth m/f	69/74
Probability of dying between 15 and 60 years m/f (per 1,000 population)	193/117
Total expenditure on health per capita (Intl $)	539
Total expenditure on health as % of GDP	5.1

Source: World Health Organization who.int/countries/egy/en/ Statistics are for 2013.

I-I-I Interview

See the 1 Minute, 1 Question, 1 Answer Interview I-I-I with Associate Professor Ayman Ibrahim Tharwat on the challenges of ICU care in Egypt at **https://iii.hm/1cx**

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registration@esahq.org

European Society of Anaesthesiology

ESA

AGENDA

December

2-4 German Interdisciplinary Meeting on Intensive Care and Emergency Medicine (DVI)
Leipzig, Germany
divi2015.de/startseite

7-9 Intensive Care Society: State of the Art Meeting 2015
London, UK
ics.ac.uk

January 2016

10-15 6th Annual Winter Symposium in Intensive Care, Anaesthesia & Emergency Medicine
Vail, Colorado, United States
colloquium.com.au

28 Resuscitation Symposium
London, UK
infomedltd.co.uk

28-30 33rd Annual Meeting of the German Society for NeuroIntensiv- and Emergency Medicine and the German Stroke Society (ANIM)
Berlin, Germany
anim.de

31-5 February 6th International Winter Symposium of Intensive Care Medicine
Pontresina, Switzerland
kongress.imk.ch

February

5-7 Indian Society of Critical Care Medicine 22nd Annual Congress (CRITICARE)
Agra, India
criticare2016.com

12-13 21st International Symposium on Infections in the Critically Ill Patient
Barcelona, Spain
infections-online.com

16-19 21st International Conference on Advances in Critical Care Nephrology - AKI & CRRT
San Diego, USA
crrtonline.com

20-24 Society of Critical Care Medicine 45th Critical Care Congress
Orlando, USA
sccm.org

March

11-12 International Symposium on Neuromonitoring in the OR and ICU
Abu Dhabi, UAE
neuroanesthesiasymposium.org

15-18 International Symposium on Intensive Care and Emergency Medicine
Brussels, Belgium
intensive.org

April

7-9 12th Emirates Critical Care Conference
Dubai, UAE
eccc-dubai.com

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