ICU MANAGEMENT

THE OFFICIAL MANAGEMENT AND PRACTICE JOURNAL

VOLUME 12 - ISSUE 4 - WINTER 2012/2013

The Global ICU

INCLUDING:

- West Nile Virus Encephalitis: Recognising and Diagnosing Infection
- Managing Population Immunity for Vaccine-Preventable Diseases
- Improving Obstetrical Critical Care in Developing Nations

PLUS:

- Management of Candiduria: Grey Zones Still Exist
- A Review of the Evolving Paradigm Shift in Intensive Care Unit Sedation Practices
- Therapeutic Hypothermia in the ICU: Indication, Sedation and Prognostication
- Ethics in Simulation for Intensive Care

Early. Check. Easy. Check.

Introducing the first real advance in acute kidney injury testing in more than 60 years, the NEPHROCHECK™ Test by Astute Medical. Unlike traditional renal tests that can take hours or days to provide results, these revolutionary, never-before-seen, early-rising biomarkers provide specific, accurate results in just minutes.

For details, visit CheckAKIRisk.com

ASTUTE MEDICAL™

Innovative biomarkers. Smarter healthcare.

THE GLOBAL ICU

Jean-Louis Vincent

Editor-in-Chief
ICU Management

Head Department
of Intensive Care
Erasme Hospital / Free
University of Brussels
Brussels, Belgium

jlvincen@ulb.ac.be

If we look at intensive care in the global context, a myriad of challenges, issues, and also opportunities present themselves, where involvement and commitment from developed and developing nations is increasingly recognised as necessary to reach targeted improvements. From working to enhance intensive care in developing nations and resource-poor settings to responding to endemics there are always lessons to be learned.

In this issue of ICU Management, our Cover Story, "The Global ICU", explores a number of threats to global health that are challenging intensive care units (ICUs) across the world. First, Dr. Maurizia Capuzzo and colleagues enlighten us on methods for recognising and diagnosing infection from West Nile Virus, which has spread to a worrying degree, requiring all intensivists to be prepared for its eventuality. Following this, Dr. Kimberly Thompson discusses the importance of managing population immunity for vaccine-preventable diseases, suggesting that valuing prevention is the new paradigm in global health. We then go on to look at lessons learned from a past outbreak of infection with Prof. Gilberto Felipe Vazquez de Anda and colleagues. They highlight the changes that have been made in Mexico following the influenza AH1N1 outbreak that took place in 2009, including recent additions of telepresence with robotics and tele-ultrasound.

Looking deeper into the challenges faced by the developing world, Dr. Arthur Kwizera from Mulago Hospital Complex in Kampala, Uganda, discusses intensive care in Africa, providing possible solutions to the problems faced and suggesting that African intensivists need to be more involved in global initiatives. The subsequent thematic review from Drs. Sukhminder Jit Singh Bajwa and Sukhwinder Kaur Bajwa from Gian Sagar Medical College and Hospital in Banur, India, focuses specifically on challenges and solutions for improving obstetrical critical care in developing nations.

Our nutrition series comes to a close in this final issue for 2012, culminating with an article on the new paradigm to the nutrition scene for critically ill patients: pharmaconutrition with antioxidants. Drs. William Manzanares and Gil Hardy discuss whether selenium monotherapy is the cornerstone of this strategy.

In our Matrix section, Dr. Guillem Gruartmoner and colleagues from Sabadell Hospital in Barcelona, Spain, examine fluid management tools in critically ill patients, discussing how the prognosis of patients can be improved and highlighting that use of the wrong tools and the wrong endpoints should not take place in the context of current knowledge. Next, Drs. Nidhi Singla and Jagdish Chander from Government Medical College Hospital in Chandigarh, India, highlight the grey zones that still exist in the management of candiduria. They express that lack of consensus and the availability of limited literature are the main reasons that we cannot formulate the proper guidelines. Following this, Drs. Derek Roberts and Richard Hall from Canada offer a review of a hot topic in the current critical care scene: the evolving paradigm in ICU sedation practices. Concluding our Matrix section, Prof. Eldar Soreide and his team from Stavanger University Hospital, Norway, present some new information related to indications, sedation and prognostication for out-of-hospital cardiac arrest patients undergoing therapeutic hypothermia in the ICU.

Our management section focuses on an issue which is of high importance throughout the world: ethics. Drs. Anne Lippert and Peter Dieckmann from the Danish Institute for Medical Simulation in Copenhagen, Capital Region of Denmark, look at the uses of simulation in this realm, primarily analysing the uses of simulation-based training in helping learners to improve their ethical decision-making processes and better react to and reflect upon moral dilemmas

Edgar Jimenez, President of the World Federation of Societies of Intensive and Critical Care Medicine, graces our interview pages, highlighting the federation's activities that aim to help intensivists in the developing world, and its objective to become a more active entity globally. He also briefly tells us about his recent research findings on acute respiratory distress syndrome.

We finish off with an overview of current intensive care services in Hungary, written by Dr. Ákos Csomós and colleagues. This article highlights the many difficulties Hungary's intensive care sector has been going through as well as the improvements that are being made in the country, including an objective to join forces with other countries in Eastern Europe on several forums and improve critical care practice and training across the region.

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

Jean-Louis Vincent

Join us in 2013

33rd International Symposium on Intensive Care and Emergency Medicine

BRUSSELS MEETING CENTER (SQUARE)

MARCH 19-22, 2013

Hôpital Erasme | ULB

CME Accreditation

Plenary Sessions, Mini-Symposia,
Workshop, Technical Forums, Round Tables, Tutorials, Posters

Endorsed by:

European Society of Intensive Care Medicine
Society of Critical Care Medicine
American Thoracic Society
European Society for Emergency Medicine
European Shock Society
The Institute of Critical Care Medicine
The Canadian Critical Care Society
Australian and New Zealand Intensive Care Society
International Pan Arab Critical Care Medicine Society
World Federation of Societies of Intensive and Critical Care Medicine
International Sepsis Forum

Meeting Chairman: JL Vincent
Email: jlvincen@ulb.ac.be

Manager: V De Vlaeminck
Email: veronique.de.vlaeminck@ulb.ac.be

Dept of Intensive Care,
Erasme University Hospital
Route de Lennik, 808,
B-1070 Brussels, Belgium

Phone 32.2.555.32.15/36.31,
Fax 32.2.555.45.55
Email: sympicu@ulb.ac.be

Website: http://www.intensive.org

Deadline for abstract submission: December 15, 2012

IN EVERY ISSUE

ICU Management

is the Official Management and Practice Journal of the International Symposium on Intensive Care and Emergency Medicine and was previously published as Hospital Critical Care.

RESEARCH NEWS

C. Difficile Researchers Reveal Potential Target to Fight Infections

Researchers have discovered how *Clostridium difficile*, a common germ in healthcare-associated infections, sends the body's natural defenses into overdrive, actually intensifying illness while fighting infection.

The discovery at Virginia Bioinformatics Institute at Virginia Tech in the US, which was recently published in PLOS One, may lead to new drug treatments for *C. difficile*. The bacterium has been linked to the death of 14,000 Americans annually, according to the Centers for Disease Control and Prevention.

Researchers with the Center for Modeling Immunity to Enteric Pathogens at Virginia Tech applied computational and mathematical modeling in combination with RNA-sequencing and mouse studies to understand an important regulatory pathway during *C. difficile* infection.

The human intestine must peacefully coexist with trillions of beneficial bacteria while quickly responding to pathogens such as *C. difficile*. Sometimes the immune system will go into overdrive when responding to such pathogens and in the attempt to clear infection more damage is caused. "We have found that tissue damage and disease severity in *C. difficile* infection is associated with a disruption of the peroxisome proliferator-activated receptor gamma (PPARγ) pathway," said Professor Josep Bassaganya-Riera, director of the Nutritional Immunology and Molecular Medicine Laboratory, and the principal investigator with the Center for Modeling Immunity to Enteric Pathogens.

When studying the bowels of mice, researchers found that the PPARγ pathway keeps the immune response in check, allowing the body to heal while the immune cells that fight infection do their work in a controlled manner. When PPARγ was absent or inactive, disease was more rampant and colonic lesions from *C. difficile* were much worse.

In addition, researchers found that by using an existing diabetes drug the protective mechanism could be activated and the severity of the *C. difficile* infection could be reduced. More studies will be needed before the drug can be tested against *C. difficile*.

"This research demonstrates that the integration of powerful computer simulations of host responses with immunology experimentation not only contributes to a better understanding of the immunoregulatory processes in the gut mucosa during *C. difficile* infection, but it also advances the discovery of broad-based therapeutic targets in the host for infectious diseases," said Raquel Hontecillas, assistant professor of immunology at Virginia Tech, co-director of the Nutritional Immunology and Molecular Medicine Laboratory and leader of the immunology component of the Center for Modeling Immunity to Enteric Pathogens.

This research builds on previous work from the Nutritional Immunology and Molecular Medicine Laboratory, which shows that PPARγ is critical to reducing disease caused by enteric pathogens and regulating autoimmune diseases such as inflammatory bowel disease.

C. difficile has become a widespread problem in hospitals, particularly with patients who have received heavy doses of multiple antibiotics, and the problem continues to spread in the community, increasingly being found in patients who traditionally would not be susceptible to this bacterium. Symptoms include persistent diarrhea, fever, gut inflammation, and weight loss.

Current strains of *C. difficile* have become even more virulent and antimicrobial resistant in recent years, which emphasises the importance of developing broad-based, host-targeted approaches to control the disease as opposed to just relying on anti-microbial therapies that target the bacterium and can stimulate the spread of resistance.

Source: Virginia Tech, via AlphaGalileo

Journal Reference:

Viladomiu M et al. (2012). Modeling the Role of Peroxisome Proliferator-Activated Receptor and MicroRNA-146 in Mucosal Immune Responses to Clostridium difficile. PLoS ONE 7(10): e47525. doi:10.1371/journal.pone.0047525

BOOKS IN REVIEW

Bad Pharma

Author: Ben Goldacre. Published by: Fourth Estate/HarperCollins (2012)

When making clinical decisions, physicians portray confidence and authority, and their patients are thus comforted by the thought that their health is in expert hands; however, according to "Bad Pharma", the new book from the doctor and science writer Ben Goldacre, this reality is distorted.

In this consistently compelling and shocking book, which was first published in the UK on 25 September, 2012, Dr. Goldacre describes a state of routine corruption in what is trusted to be an objective scientific process for assessing new drugs. This, he said, includes pharmaceutical companies burying clinical trials that show bad results for a drug and publishing only those which show positive results from it. In order to manipulate results, trials are often run on small numbers of unrepresentative patients, with statistical analyses shaped to portray a desired picture.

Taking revelations to new depths, beyond the industry itself, Dr. Goldacre describes the scandalous behaviour from drug regulators, who have gained access to some of the hidden results, and have often chosen to keep them buried, seemingly serving the interests of the firms whose products they are supposed to police. Every such claim is referenced and backed up by links to research and primary documents.

Of course, the unsettling result of being so plainly misled is that doctors are left ignorant about the drugs they are prescribing, and even which will improve or worsen their patients' chances of survival.

Dr. Goldacre has suggested that we need all clinical trial results from past decades, which we now know are still being withheld, on drugs that are currently in use, to be released.

Dr. Edgar Jimenez, President of the World Federation of Societies of Intensive and Critical Care Medicine, told to ICU Management his feelings on the issue: "Whether previous trials are positive or negative, the evidence should be available, so clinicians can enrich their knowledge and provide their best judgement in the management of their patients," highlighting that, "Even with the best evidence available, the results can only be generalised effectively to 20-30% of our patient populations."

Bad Pharma is a book that deserves to be widely read to inform doctors, patients, academics and people working in the industry of the corruption that is taking place and affecting everyone's lives, so that moves can be made to fix the issue.

Dr. Jimenez concluded: "Clinical trials are only one aspect of patient care for the vast majority, for now, we depend on assessment, commitment, and judgment. Medicine is still an art."

18th International Symposium on Infections in the Critically ill Patient

Sevilla
7-8 February
2013

The aim of this two days symposium is to review current concepts, technology and present advances in infections in the critically ill patients.

Sepsis, Pulmonary Infections, Basic Research, Pulmonary Infections Treatment and Prophylaxis Therapy of severe infections will be the topics of the main sessions presented by experts who will review and update the new advances on infections in the critically ill patient. At the end of each session a Clinical Controversy, Pannel Discussion or Case Report Discussion will be organized.

Organized by

Antonio Artigas, MD
Jean Carlet, MD
Michael Niederman, MD
José Garnacho, MD

ISICIP

www.infections-online.es

WEST NILE VIRUS ENCEPHALITIS:
RECOGNISING AND DIAGNOSING INFECTION

Maurizia Capuzzo, *MD*

Paolo Perna, *MD*

Delia Cadorin, *MD*

Department of Surgical, Anaesthetic and Radiological Sciences
Section of Anaesthesiology and Intensive Care
University Hospital of Ferrara
Italy

cpm@unife.it

The increasing spread of West Nile virus (WNV) infection is worrying and requires that all intensivists be ready to recognise and diagnose the disease. Most individuals infected with WNV are asymptomatic, while one-fifth experience a flu-like illness and less than 1% develop neuroinvasive disease.

Introduction

West Nile virus, the most widely distributed arbovirus, belongs to the genus *Flavivirus*, within the family of *Flaviviridae*. WNV was firstly isolated in the West Nile province of Uganda in 1937 from the blood of a woman suffering a mild flu-like illness. The first cases of WNV in its encephalitic form were reported in Algeria in 1994, and the first large outbreak with a high number of neuroinvasive cases occurred in Bucharest, Romania, in 1996. WNV was introduced to New York City in 1999, where it was responsible for a huge epidemic (Hayes 2001). Within subsequent years, the WNV appeared ubiquitous in most states east of the Rocky Mountains, as well as in some Canadian provinces. The number of yearly reported cases in the US has increased from 1,021 in 2010, and 712 in 2011 (with 57 and 43 deaths, respectively) to 5,054 cases in 2012 by November 6, including 228 deaths. Of these 5,054 cases, 2,559 (51%) were classified as neuroinvasive disease and 2,495 (49%) as non-neuroinvasive disease (Centers for Disease Control and Prevention, 2012).

The European Centre for Disease Prevention and Control monitored the WNV fever situation during the transmission season (June to November), and reported 130 probable and confirmed autochthonous cases in EU member states and 207 in neighbouring countries in 2011. As per figures on 8 November, 2012, 235 human cases of WNV fever have been reported in the EU and 587 cases in neighbouring countries so far this year (European Centre for Disease Prevention and Control, 2012). The spread of WNV has raised concerns regarding its presence in the Old World and the risks for epidemics of the neuroinvasive disease (Relter 2010). In light of this, all intensivists should know about WNV disease and be ready to recognise and diagnose it in their patients.

Virus and Transmission

WNV is a small spherical RNA virus, translated into a polyprotein, which is proteolytically processed to three structural and seven non-structural proteins. The latter hamper the host antiviral response, antagonising complement activation and inhibiting interferon-β promoter activation. It has recently been proposed that WNV can be grouped into seven lineages. Two major genetic lineages of WNV have been well described: lineage one is widespread and contains isolates from Europe, the USA, the Middle East, India, Africa and Australia (Barzon et al. 2012). Lineage two contains isolates from Southern Africa and Madagascar, and since 2004 from central and eastern Europe. In 2010 it caused outbreaks in Romania and Greece (De Filette et al. 2012). Interestingly, high and low neuroinvasive phenotypes exist in both lineages, but mutations responsible for increasing virulence in lineage two viruses have been described.

> *"As per figures on 8 November, 2012, 235 human cases of WNV fever have been reported in the EU and 587 cases in neighbouring countries"*

WNV lives in mosquitoes of genus Culex, which are considered the predominant vectors. Mosquitoes become infected with WNV after biting birds with high-level viremia, and may transmit it when taking a blood meal from a host. Indeed, birds can also be infected via the oral route and by consumption of dead or dying infected birds. In birds, the incubation period is 10 to 14 days; the infection is associated with high mortality in Northern America but not in Europe (Relter, 2010). Humans and horses are "dead-end" hosts because the viremia is insufficient to infect a feeding naive mosqui-

to. However, transmission in humans has been reported after blood transfusion, organ transplantation, or from a mother to her newborn via the intrauterine route or by breast milk (De Filette et al. 2012).

There is indirect evidence that WNV is transported to European temperate areas by migratory birds during spring migration. In addition, the transport technologies and increasing global trade of the last decades may have allowed infected mosquitoes to be transported by shipping, aeroplanes, and people travelling. Accordingly, at the county scale in eastern and western North America, human WNV incidences have increased with urbanisation and agriculture, respectively (Kilpatrick 2011).

Following inoculation from the bite of an infected mosquito, WNV replicates in the keratinocytes and then disseminates to the local lymph nodes causing a viremia. The WNV may pass into the central nervous system without disrupting the blood–brain barrier (BBB) (Rossi et al. 2010), but perivascular inflammation of lymphocytes and macrophages with glial cell upregulation has been found (Turtle et al. 2012).

Clinical Characteristics

Most of the individuals infected with WNV are asymptomatic. Approximately 20% of infected individuals develop an acute febrile flu-like illness after an incubation period of two to 14 days, with fever, malaise, myalgia, fatigue, skin rash, lymphadenopathy, vomiting and diarrhoea (Kramer et al. 2007; Rossi et al. 2010). Only approximately one in 150 infected individuals (Tyler 2010) and 5% of patients with symptomatic WNV infection (Rossi et al. 2010) develop neuroinvasive disease. The major categories of neuroinvasive disease include meningitis, encephalitis, and acute flaccid paralysis, with frequent overlap between these syndromes. Patients who develop encephalitis are typically older than those with meningitis or acute flaccid paralysis, and have a worse prognosis (Kramer et al. 2007). Additional risk factors for development of encephalitis include immunosuppression, hypertension, diabetes mellitus, and liver disease (Tyler 2010).

WNV meningitis is clinically similar to other forms of "aseptic" meningitis and is characterised by fever, headache, stiff neck, and photophobia. Cranial nerve palsies, particularly of the facial nerve, occur in about 20% of cases. The cerebrospinal fluid (CSF) shows a pleocytosis with a mean of about 200 cells/mm3, an elevated protein level, and a normal glucose level. Almost half the patients have an initial polymorphonuclear pleocytosis rather than the lymphocytic pleocytosis generally characteristic of viral meningitis (Tyler 2010).

Patients with encephalitis have clinical or laboratory evidence of brain parenchymal involvement. Signs may include fever, headache, altered consciousness, disorientation, focal neurologic signs, dysarthria, seizures, tremor, ataxia, parkinsonism, and weakness. When present, magnetic resonance imaging (MRI) abnormalities typically consist of areas of increased signal on T2 and fluid attenuated inversion recovery sequences that occur in the thalamus, basal ganglia, and upper brainstem (Tyler 2010, Kramer et al. 2007).

Acute asymmetric flaccid paralysis is a poliomyelitis-like illness that occurs in 5% to 10% of patients with neuroinvasive disease. More than half the affected patients have associated encephalitis with concomitant findings of parkinsonism, myoclonus, or tremor. Approximately 90% have associated fever and headache. The flaccid paralysis is due to a selective lesion of spinal anterior horns by WNV. There is minimal or no sensory disturbance, and cranial nerves are usually normal, but bowel and bladder functions are disturbed in some patients. Most patients have substantial muscle ache in the lower back. Deep tendon reflex can be diminished in severely paralysed limbs, and muscular atrophy develops in the late phase of the illness (Kramer et al. 2007).

MRI scans may be normal or show focal abnormal signal intensity within the anterior horns of the spinal cord (Kramer et al. 2007). Electromyography and nerve conduction velocity studies show reduced or absent compound muscle action potentials with relatively preserved sensory neural action potentials. Electromyography abnormalities due to evidence of denervation develop after several weeks (Tyler 2010).

Diagnosis

CSF examination should be performed in order to differentiate WNV infection from stroke, meningitis-encephalitis due to bacteria or other viruses, myopathy, and Guillain-Barre syndrome (Rossi et al. 2010). Nevertheless, the diagnosis of WNV disease is based on specific serologic testing, so IgM and IgG ELISA should be used for testing serum and CSF. IgM serum antibodies develop within eight days and are still present at three months post-infection in almost all patients (De Filette et al. 2012; Kramer et al. 2007). The long persistence of WNV IgM after onset of infection could confound interpretation of serology results in patients subsequently presenting with clinical syndromes that resemble WNV infection (Diamond, 2009). Specimens submitted for arboviral serology should also be tested against other arboviruses that are known to be active or present in the given area. Detection of CSF WNV IgM antibodies is diagnostic of neuroinvasive WNV disease, as the presence of large size IgM molecules, which cross the BBB poorly, in CSF is generally indicative of intrathecal synthesis. However, WNV isolation attempts should be performed in CSF or postmortem brain tis-

> "More than half the affected patients have associated encephalitis with concomitant findings of parkinsonism, myoclonus, or tremor"

sue. Confirmation of virus isolate identity can be accomplished by indirect immunofluorescence assay using virus-specific monoclonal antibodies, nucleic acid detection, or virus neutralisation. Real time-polymerase chain reaction (RT-PCR) after amplification of the genetic material requires specialised equipment, and may not detect new emerging mutated WNV strains (Tyler 2010; De Filette et al. 2012).

Treatment and Prognosis

There is no specific treatment for WNV infection. The supportive care required by patients with neuroinvasive disease includes respiratory support, nutrition, analgesia and sedation, and prevention of secondary infections (Capuzzo et al, 2011). In fact, nearly half of the patients may have respiratory impairment requiring intubation or tracheostomy (Kramer et al. 2007). A mortality rate of approximately 12 to 15% for WNV encephalitis has been reported in the US (O'Leary et al. 2004; Sejvar 2007). Long-term complications like fatigue and weakness are common. Movement disorders, cognitive complaints, and functional disability may occur after WNV neuroinvasive disease, and WNV paralysis in particular may result in limb weakness and ongoing morbidity (Sejvar 2007). Most adult patients admitted to a rehabilitation facility with WNV have required follow-up physical therapy after discharge from rehabilitation (Hoffman et al. 2012).

Conclusions

Intensivists should be aware of the possible risks for epidemics of the WNV neuroinvasive disease. The following factors are associated with the neuroinvasive WNV infection and may strike a chord, prompting physicians to consider WNV:

i) Seasonality, which varies according to bird migration in different geographic regions, and in temperate areas in late summer;
ii) Common flu-like symptoms before neurological impairment; and
iii) Presence of comorbidities, which are possibly responsible for immune system impairment, such as through the ensuing use of steroids. ■

References

Barzon L et al. (2012). New endemic West Nile Virus lineage 1a in northern Italy, July. Euro Surveill 2012, 17: pii=20231

Capuzzo M et al. (2011). West Nile Virus encephalitis in intensive care: a small mosquito, a tremendous danger. Minerva Anestesiol, 77: 1224-7

Centers for Disease Control and Prevention (2012). Update 6 November. Available from: http://www.cdc.gov/ncidod/dvbid/westnile/

De Filette M et al. (2012). Recent progress in West Nile virus diagnosis and vaccination. Veterinary Research, 43:16

Diamond MS (2009). Progress on the Development of Therapeutics against West Nile Virus. Antiviral Res, 83: 214–227

European Centre for Disease Prevention and Control (2012). Update 8 November. Available from http://ecdc.europa.eu/en/healthtopics/west_nile_fever/West-Nile-fever-maps/Pages/index.aspx

Hayes CG (2001). West Nile virus: Uganda, 1937, to New York City, 1999. Ann N Y Acad Sci, 951:25-37.

Hoffman JE and Paschal KA (2012). Functional Outcomes of Adult Patients With West Nile Virus Admitted to a Rehabilitation Hospital. J Geriatr Phyys Ther, Jul 10. (Epub ahead of print)

O'Leary DR et al. (2004). The epidemic of West Nile virus in the United States, 2002. Vector Borne Zoonotic Dis, 4: 61-70

Kilpatrick MM (2011). Globalization, land use and the invasion of West Nile virus. Science, 334: 323–327

Kramer LD et al. (2007). West Nile virus. Lancet Neurol, 6: 171–81

Relter P (2010). West Nile virus in Europe: understanding the present to gauge the future. Euro Surveill,15:pii=19508

Turtle L et al. (2012). Encephalitis caused by flaviviruses. Q J Med, 105: 219–223

Tyler KL (2009). Emerging Viral Infections of the Central Nervous System: Part 1. Arch Neurol, 66: 939–948

Rossi SL et al. (2010). West Nile Virus. Clin Lab Med, 30: 47-65

Sejvar JJ (2007). The long-term outcomes of human West Nile virus infection. Clin Infect Dis, 44: 1617-24

VALUING PREVENTION AS THE NEW PARADIGM IN GLOBAL HEALTH:

MANAGING POPULATION IMMUNITY FOR VACCINE-PREVENTABLE DISEASES

Kimberly M. Thompson, *ScD*

Professor of Preventive Medicine and Global Health
University of Central Florida College of Medicine
President
Kid Risk, Inc.

kimt@ucf.edu

One lesson from progress towards polio eradication suggests that using models and measurements together to manage population immunity may play a key role in supporting the paradigm shift required to value prevention and realise the full benefits of vaccines (Thompson et al. 2012b). This paper discusses individual and population immunity, prevention as a choice, valuing prevention, and some opportunities for intensive care unit (ICU) managers to further contribute to improving global health.

Introduction

Thanks to the miracle of vaccines, healthcare providers on the front lines continue to see progressively fewer cases of vaccine-preventable diseases (VPDs). Today, most medical students in developed countries graduate and expect to practice without seeing a single case of paralysis caused by polio, and their experience with many once-common VPDs remains limited to what they learnt from curriculum materials.

In these developed countries, infectious diseases once considered "horses" (referring to a likely diagnostic possibility) now fall into the category of "zebras" (referring to an unlikely diagnostic possibility) and related outbreaks no longer cause costly disruptions of health systems. However, healthcare providers still need to maintain the ability to rapidly recognise and manage a case of a no-longer-common VPD, as there remains a risk of their importation, since some susceptible individuals exist even in well-immunised populations (Sugerman et al. 2010; Thompson et al. 2012a) and global vaccine use remains uneven.

While most individuals in most developed countries enjoy significant protection from VPDs, the same is not true in all developing countries. Recognising both the inequity and opportunity presented by the current situation, the Global Vaccine Action Plan (GVAP) aspires to extend the full benefits of immunisation to all people by 2020, to create a world "in which all individuals and communities enjoy lives free from vaccine-preventable diseases" (WHO, 2012). The question remains, however, "how will we get from here to there?"

> *"As we approach the final stages of polio eradication, managing population immunity is emerging as the key to success"*

Individual and Population Immunity

Vaccines, although not entirely risk-free, provide a safe and effective way to prevent cases of disease before they occur by enabling the immune systems of individuals to avoid or better fight infections upon exposure. Immunisation protects individuals, at least until the immunity wanes or the infectious agent changes. Population immunity reflects the integration of individual immunity over all people in the community. In the case of polio, we define population immunity as the overall level of protection from poliovirus transmission within a population, which focuses on the prevention of infections and goes beyond simply focusing on the cases of disease (Thompson et al. 2012b). High levels of population immunity effectively provide a barrier that inhibits sustained viral transmission, such that transmission stops once population immunity exceeds the threshold required for any introductions of the disease to die out. Levels of population immunity above the threshold protect unvaccinated individuals (e.g. those younger than the recommended age of the first dose, those with contraindications or vaccine failures, and those who miss vaccination unintentionally or intentionally), at least so long as the population maintains sufficiently high levels. The actual thresholds vary by population and conditions. Consequently, some populations need to achieve and maintain relatively higher levels

of population immunity than others. This means that interventions that suffice in some areas fall short in others. For example, routine immunisation alone may work for some countries, while other countries may need to conduct supplemental immunisation activities.

The concept of population immunity may seem simple and obvious, but its characterisation can prove very challenging. We cannot directly observe or measure population immunity. Health systems and immunisation programmes typically monitor levels of routine immunisation coverage as a proxy for population immunity, but this metric only reveals one important part of the overall story. Similarly, while detecting cases as part of disease surveillance will indicate the lack of sufficient population immunity, the absence of cases does not provide information about potential risks or the accumulation of susceptible individuals. Serological studies provide important information about the individuals included in samples, but this only offers a snapshot view.

> *"Shifting towards prevention does not necessarily mean eradication for all VPDs, but it means not tolerating cases or bad management of these diseases"*

The ability of a population to sustain transmission depends on the integration of the entire population, and we must understand population immunity as a dynamic "stock" (i.e. a level of overall protection from infection that changes with time). The level of population immunity increases as individuals get vaccinated or recover from infection with the VPD, and the level decreases as non-immune individuals enter the population, immune individuals die, or immunity wanes. In this context, individuals who miss vaccination matter (e.g. migrants, certain age cohorts skipped due to a disruption in supply, etc.), because susceptible individuals can accumulate and participate in transmission if and when the disease occurs.

Development of a population immunity model along with the collection of measurements of current and historical vaccine coverage, demographics, and other factors makes it possible to characterise and visualise population immunity (or vulnerability). For polio, modelling population immunity facilitates consideration of the immunological implications of prior exposure to any circulating live polioviruses and/or vaccination with a live oral poliovirus vaccine (OPV) or injected inactivated poliovirus vaccine (IPV) (Duintjer Tebbens et al. 2005; Thompson et al. 2012b). Successful immunisation with either vaccine protects individuals from disease (i.e. paralytic polio), but even immune individuals can potentially become reinfected and participate asymptomatically in poliovirus transmission to some degree, with their participation likely increasing with time due to waning. The use of a model also captures the differences in how IPV and OPV work. For example, as a live virus, OPV infects vaccine recipients, which stimulates mucosal immunity and leads to the excretion of live polioviruses that can then cause secondary infections. In contrast, the relatively more expensive IPV does not cause secondary circulation or infection (i.e. it protects only the vaccine recipient). IPV also does not cause the relatively rare but real cases of vaccine-associated paralytic polio, which has made it a costly but attractive alternative to OPV for developed countries. Models can help us characterise the risks and consider the impacts of potential risk management options before we make a decision and take action. Similarly they can help to demonstrate the consequences of inaction, which is also a choice.

Choosing Prevention

Choosing to eradicate a disease represents the ultimate in prevention. Eradication presents a unique opportunity to protect current and future generations, and it requires stopping chains of transmission everywhere and maintaining this state. We can only eradicate the diseases that we can meaningfully stop from being transmitted and for which we can coordinate and cooperate globally. To date, global health systems successfully stopped the human transmission of smallpox, wild poliovirus serotype 2, and the SARS virus that circulated between November 2002 and July 2003 (Thompson and Duintjer Tebbens 2011). We also recently celebrated the global eradication of rinderpest, an animal virus similar to measles that led to devastating impacts on herd animals and food supplies. The global eradication of wild poliovirus serotypes 1 and 3, though as yet elusive, now appears within reach. The possibility of eradicating measles and rubella continues to emerge as a topic of discussion, particularly with successful elimination in the Americas and measles elimination goals in place in four of the five remaining WHO regions (WHO 2011; WHO 2012b).

The ability to use a model to characterise and manage population immunity represents a game changer for disease control and prevention. Since we can use models to make our choices and their impacts transparent, they can help us anticipate the consequences of our actions and manage expectations. As we approach the final stages of polio eradication, managing population immunity is emerging as the key to success. The case-based strategy of testing samples from patients that present with acute flaccid paralysis (AFP), which identifies symptomatic poliovirus infections after they have caused paralysis, does not provide an opportunity to identify immunity gaps before outbreaks occur. Eradication means preventing all future cases before they occur. Since polioviruses can circulate asymptomatically, eradication requires the use of a tool that supports the objective of no anticipated cases, while we also still actively use AFP surveillance to ensure that no paralytic polio cases actually occur from exposure to wild polioviruses. The models help us characterise the benefits of prevention, because they allow us to count the cases that do not occur and to give credit to prevention activities.

Valuing Prevention

Any healthcare provider who has treated a complicated case of measles, seen a child born with congenital rubella syndrome, provided respiration for a patient paralysed by polio, watched a child with pertussis whoop, or managed a serious case of any other VPD can easily appreciate the benefits of preventing these bad outcomes before they occur. Vaccines provide significant health and financial savings, and they represent some of the most cost-effective med-

ical interventions available. However, immunisation requires the investment of resources, and they pose some risks. Sustained investments in population immunity depend on the perception of need, and successful immunisation programmes have dropped the burdens of disease to such low levels that even some healthcare providers may not recognise the critical role that vaccines continue to play in achieving and sustaining community and global health. Those without direct experience of outbreaks may find it difficult to understand the dynamics of infectious diseases and the reality that they can find susceptible individuals and spread devastatingly fast.

In the western hemisphere, progress in infectious disease control and prevention in combination with national and regional commitments to the elimination of polio, measles, and rubella have created a new normal. Most individuals and populations in the Americas expect complete prevention of VPDs. Health ministers of countries in the Americas sustain their investments in immunisation and hold each other accountable for importations. When informed by front line healthcare providers about even a single case of polio, measles, or rubella, health authorities in the Americas view the case as an indication of system failure and as a signal that emergency action is required. However, the shift to prevention represents a significant change around the world. For example, recent outbreaks of measles in Europe suggest that the disease is still tolerated as a normal and acceptable sickness, even though measles has caused preventable and tragic deaths. Significant drops in vaccine coverage in Ukraine, due to vaccine scares and politicisation of immunisation, may actually present a threat to the entire European region and its commitment to eliminate measles and rubella. If we want to achieve the full potential benefits of vaccines globally, then this will require a permanent paradigm shift to one that values prevention of VPDs. Shifting towards prevention does not necessarily mean eradication for all VPDs, but it means not tolerating cases or bad management of these diseases. For example, while we cannot remove all *Clostridium tetani* from the environment, with good management we can eliminate all cases of tetanus, including neonatal tetanus.

Perhaps the largest challenge to achieving and maintaining global health relates to the lack of sustained commitments and investments for prevention. We all know that individuals often do not receive credit for their contributions to endevours that prevent bad things from happening, because it is hard to count the cases that do not occur. In addition, the limited resources allocated to prevention activities may get shifted to managing the crisis of today instead of preventing the crises of tomorrow. This unfortunately creates a vicious cycle, because prevention often represents a more cost-effective option.

> **"Significant drops in vaccine coverage in Ukraine… may actually present a threat to the entire European region and its commitment to eliminate measles and rubella"**

Opportunities for ICU Managers

All healthcare providers and health systems play important roles. At the individual level, they can monitor the immunisation status of individual patients and ensure that patients receive vaccinations on schedule or catch up on any they miss. The actions of individual providers collectively impact the health of the population, and it matters if providers pursue a goal of fully protecting 100% of their patients from VPDs.

Front line healthcare providers play a critical role in communicating the benefits of vaccines in their communities. Practicing providers should find ways to train medical students, residents and others to recognise and manage cases of VPDs. We must all appreciate the disruptive impact of VPD cases on health systems and the need for preparedness for managing outbreaks. The phrase, "preparing for the worst while managing for the best" is a powerful reminder of why prevention makes a difference. Particularly in the absence of cases, front line providers must play a critical role in advocating vaccination and helping patients and their communities to recognise the benefits of immunisation and prevention. Patients need to understand that it is not too late to get vaccinated against many VPDs and to know that if they do not get vaccinated then they remain at risk for contracting a serious disease.

Front line providers may also play an important role with respect to holding each other accountable for prevention. For example, ensuring that every individual who provides care on the front line has immunity either from vaccination or historical exposure to the VPDs that can spread through patient contact included in the national routine immunisation schedule would send an important message that the provider community values immunisation and prevention. Those who treat the cases that result when the system fails contribute powerfully to individual immunity and prevention in their immediate surroundings and all of the individual actions aggregate to global health. ■

References

Duintjer Tebbens RJ et al. (2005). A dynamic model of poliomyelitis outbreaks: Learning from the past to help inform the future. American Journal of Epidemiology, 162(4):358-372.

Nakkazi E (2012). Measles epidemic in Uganda. ScieGirl, May 24. Available at: http://estanakkazi.blogspot.com/2012/05/measles-epidemic-in-uganda.html (accessed 1 November, 2012).

Sugerman DE et al (2010). Measles outbreak in a highly vaccinated population, San Diego, 2008: Role of the intentionally undervaccinated. Pediatrics, 125(4):747-755.

Thompson KM and Duintjer Tebbens RJ (2011). Challenges related to the economic evaluation of the direct and indirect benefits and the costs of disease elimination and eradication efforts. Chapter 9 in Cochi SL and Dowdle WR (eds). Disease Eradication in the 21st Century: Implications for Global Health. Cambridge, MA: MIT Press, 115-130.

Thompson, KM et al. (2012a). Trends in the risk of U.S. polio outbreaks and poliovirus vaccine availability for response. Public Health Reports, 127(1):23-37.

Thompson KM et al. (2012b). Modeling population immunity to support efforts to end the transmission of live polioviruses. Risk Analysis. DOI: 10.1111/j.1539-6924.2012.01891.x.

World Health Organization (2012). Global Vaccines Action Plan, 2012. Available at: http://www.dovcollaboration.org/action-plan/ (accessed 1 November, 2012).

WHO (2011). Proceedings of the global technical consultation to assess the feasibility of measles eradication, 28–30 July 2010. Journal of Infectious Diseases 204(S1):S4-S13.

WHO (2012b). Global measles and rubella strategic plan. 2012-2020. Geneva, Switzerland: World Health Organization. Available at: http://www.who.int/immunization/newsroom/Measles_Rubella_StrategicPlan_2012_2020.pdf (accessed 1 November 2012).

CHALLENGES AND CHANGES IN MEXICO AFTER THE INFLUENZA AH1N1 OUTBREAK:

FROM STANDARD ICU TO TELEPRESENCE WITH ROBOTICS AND TELE-ULTRASOUND

Gilberto Felipe Vazquez de Anda, *MD, PhD*

Professor
Medical Science Research Center of the Autonomous University of the State of Mexico
Toluca, Mexico

gf_vazquez@yahoo.com.mx

Asisclo Villagomez Ortiz, *MD*

President
Mexican College of Critical Care Medicine
Mexico City, Mexico

Maria del Carmen Marin, *MD*

Intensive Care Unit
Magdalena de las Salinas Hospital of Traumatology
Mexican Social Security Institute

Suhey Resendiz García, *MD*

Intensive Care Unit
Specialties Hospital of the National Medical Center of the 21st Century
Mexican Social Security Institute

Juan Carlos Dávila Fernández, *MD*

Head of the ICU
High Speciality Regional Hospital of Oaxaca
Mexican Social Security Institute

From March to December 2009, the Influenza AH1N1 outbreak was observed in several cities of Mexico, showing deep flaws in the healthcare system and a general lack of knowledge on how to act and react in case of an epidemic. Because of that, thousands of people got infected and high mortality was observed in intensive care units (ICUs). Since then, the fragile healthcare system, particularly that of intensive care, has been recuperated through a number of programmes and initiatives, which are discussed in this article.

Health System Improvement

Mexico comprises of 32 states and has a total population of 103 million people, two thirds of whom have access to social security. Since the AH1N1 pandemic three years ago, an increase of medical coverage became available. Mexican health authorities have focused on improvement through enhancing a programme called Seguro Popular, which has been functioning since 2003, ensuring medical attention to Mexican citizens, particularly the vulnerable population. Nearly half of the country's population is now enrolled (Vence 2012)—reaching almost universal healthcare coverage—many of whom prior to this had no insurance to cover medical expenses.

The programme has increased the number of high care general hospitals and primary care clinics in remote cities and fully equipped general hospitals in small cities, preparing them for taking care of critical patients. It has increased the number of ICU beds; improved several monitoring systems; and in some places introduced diagnostics equipment like portable ultrasound for acute areas. A significant amount of mechanical ventilators have been added to ICUs and some high care hospitals, and high frequency oscillatory ventilators have been included as rescue therapy for acute respiratory distress syndrome. Regional high care hospitals have been created and improved in every state, among them high care hospitals for obstetrical patients and other vulnerable members of the population (pediatrics and neonatology).

An Enhanced ICU System

Since the revelation of flaws in the healthcare system, made evident by the AH1N1 pandemic, the Mexican health system has been preparing the population, providing them with information about how to prevent influenza as well as primary care measures for avoiding transmission of the virus and mortality. In addition, it has supplied statistics, symposiums for gaining knowledge, and improved equipment and supplies. Important campaigns for promoting sanitary measures (such as hand washing, and vaccination for influenza) have been established on every level. The Mexican Critical Care Society has been training intensivists in critical care ultrasound through World Interactive Network Focused on Critical Ultrasound (WINFOCUS) programmes.

With regard to biological threats, it is crucially important to improve efficient medical attention for critically ill patients, protect health workers from highly virulent viruses or bacteria, or both, and decrease mortality by carefully monitoring vulnerable patient populations during outbreaks. These strategies were continued after the outbreak and adapted to the newly established approach of intra hospital epidemiologic vigilance.

Since the outbreak of influenza AH1N1, healthcare professionals in Mexico have worked every day to promote the country's specialty as well as to increase the standard of safety and care to international levels. For that reason, the Ministry of Health, together with a multidisciplinary team, is working to map out directives on the minimal equipment and supplies needed for ICUs to guarantee medical attention for severely ill patients under extreme circumstances. A Mexican national norm for ICUs was written via the collaboration of Mexican authorities with the three major critical care societies: the Mexican College of Critical Care Medicine, the Mexican Association of Pediatrics in Intensive Care and the Mexican Association of Pediatrics. The main objective of

LIVES 2013

26TH ANNUAL CONGRESS
PARIS 5-9 OCTOBER

For physicians, nurses and other allied healthcare professionals.

→ ABSTRACT SUBMISSION DEADLINE : 19 APRIL 2013

For more information, contact
European Society of Intensive Care Medicine (ESICM)

www.esicm.org

Congress Department
Rue Belliard 19 - 1040 Brussels Belgium
Tel: +32 (0)2 559 03 75 - Fax: +32 (0)2 559 03 79
Paris2013@esicm.org

ESICM
EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE

The Intensive Connection

the Mexican norm for ICUs is to improve ICU system quality all over Mexico.

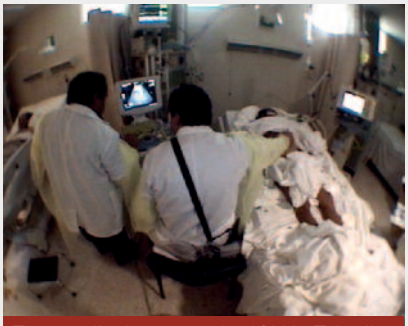
The programme has played a major role in intra hospital infection and disease control as well as increasing the level of security for patients during hospitalisation. The Mexican Academy of Surgery and other Mexican medical associations, including the Mexican College of Critical Care Medicine, released campaigns promoting sanitary measures and vaccination for influenza. Specific clinical guidelines for the 10 major diseases are distributed to ICUs in both public and private hospitals so as to standardise admission and treatment in ICUs (www.salud.gob.mx).

Robotics in the ICU

Innovative strategies for attending to patients during the pandemic were observed and adopted, including the use of telepresence with robots at suburban hospitals. This came about after the increase of hospitals, clinics and ICU beds created a lack of intensivists for full 24-hour coverage, seven days per week in several units, particularly those located in small cities away from the high care hospitals. Telepresence allows the distance and time for diagnosis to be shortened considerably, further allowing the start of specialised medical attention for a critically ill patient. It also supports the nursing team and other medical fellows. Its use has resolved one of the major problems in the ICU—the lack of intensivists. Critically ill patients in towns and cities that are geographically distant from high care hospitals can thus receive specialised medical assistance and attention, meaning that the quality and safety of care during hospitalisation in the ICU is increased.

Originally, this novel programme assisted three suburban hospitals in the State of Mexico, acute care facilities, including emergency rooms, ICUs, and isolated areas for influenza. The programme showed that it is feasible to provide assistance from highly specialised physicians to distant communities during an outbreak of influenza. In addition, it has aided in the acquisition of medical reports, nurse's reports and laboratory results, as well as supervision of ventilator settings and provision of advice regarding guidelines, all of which may result in increased quality and safety of medical care in the ICU.

The Institute of Health of the State of Mexico is leading and coordinating the telepresence experience in Mexico by using robots in acute care facilities. From August 2009 to December 2011, more than 850 interventions took place using the RP-7i® robot. Generally, optimal Internet broadband connection was available, thus providing good video images and clear audio sounds. Malfunctions were mainly due to Internet network failure at the suburban hospitals. Medical staff, patients and their relatives easily accepted the programme and were highly confident about the expertise offered. The success of the programme has led to its broad employment, with four new robots added to the programme covering all regions of the state.



The medical team at the ICU in Tejupilco General Hospital, Mexico (ISEM), performing a FAST protocol. Tejupilco General Hospital is 100 kilometees away from the bunker at the high care hospital located in Toluca, Mexico.

Echocardiography and Ultrasound in ICU

In recent years, the availability of portable and relatively inexpensive ultrasound units has made the technology a viable option for imaging in rural and underdeveloped clinics. Today, the use of Internet protocol transmission has proved its feasibility through the use of broadband with image compression technology. After the images are transmitted, either as asynchronous or synchronous sonograms, a remotely located expert can interpret them.

According to WHO, diagnostic imaging is a requirement for the accurate treatment of at least a quarter of all patients worldwide. Despite that, some areas, though they have access to second-level hospitals, including emergency room services, ICU radiology, CT scanning and ultrasonography, among other facilities, do not often have sufficient access to them for performing a directed, protocolised diagnosis in acute care areas. This can be achieved via the extended Focused Assessment with Sonography for Trauma (FAST) protocol and pulmonary ultrasound.

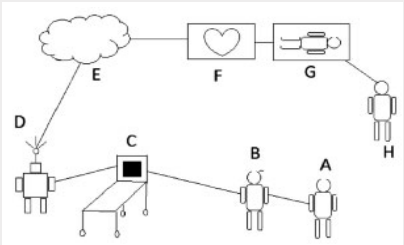


Figure 1. Tele-ultrasound at the ICU. The patient is located at a remote ICU (A), where a doctor, now highly trained in ultrasound, performs ultrasound windows according to ICU ultrasound protocols (B). The ultrasound images are projected from the ultrasound machine (C) to the robot (D, sent to a high care hospital via broadband Internet (E), and received at the computer screen (F and G) of the specialised doctor (H).

Tele-Ultrasound

New practice opportunities are emerging for intensivists: echocardiography, telepresence with robots in remote ICUs, and the combination of both strategies (Figure 1). We could say that technology and telecommunications applied in the ICU have created a new paradigm for critical care practice, extending the coverage of specialised critical care to middle-level hospitals in standard cities. The resulting new era of telemedicine and e-health services has taken advantage of technological advances and has successfully broken geographical and socioeconomic barriers. ■

References

Vence E (2012). Mexico chalks up success in health-care reforms. Near-universal coverage results from science-informed changes. Nature International Weekly Journal of Science. 17 August. http://www.nature.com/news/mexico-chalks-up-success-in-health-care-reforms-1.11222

CHALLENGES IN CRITICAL CARE IN AFRICA: PERSPECTIVES AND SOLUTIONS

Arthur Kwizera

Lecturer
Department of Anaesthesia (Intensive Care Medicine)
Makerere University College of Health Sciences
Mulago Hospital Complex
Uganda, Africa

Critical care medicine in Africa is largely an unknown entity in the medical world, though it has recently begun to emerge as a prominent concern, mostly due to increasing research that has highlighted the plight of this sub-specialty in Africa (Adhikari et al., 2010, Riviello et al., 2011). However, the fact that critical care medicine is considered an expensive sub-specialty of medicine in so many aspects does not help the cause for recognition and funding. This article aims to explore the plethora of challenges that the critical care sector in Africa is faced with, and to provide potential solutions.

Primary healthcare delivery in the developing world already faces many challenges. Infectious disease interventions with respect to HIV, tuberculosis (TB) and malaria have been prioritised, and the sectors of maternal and children's health have joined the fray in attracting funding support (Kwizera et al. 2012). This is against the backdrop of poor funding priorities by African governments.

Studies that have looked at the challenges faced in Africa with regard to critical care medicine have tried to analyse and categorise the problems related to critical illness management in low-income countries (Okafor, 2009; Dünser et al. 2006). First and foremost, the African intensive care unit (ICU) patient population tends to be younger than the ICU population in the developing world (35.5 and 61.8 years respectively) (Kwizera et al. 2012). This impacts on African countries' productivity and presents a significant hindrance to economic development. The impact is widespread since a lot of critically ill patients are breadwinners in their families. On another note, a shortage in nursing staff has led to family members taking time off income generating activities to care for the sick. The overall mortality rate is comparable across the board in Africa albeit much higher than in high income countries (30–50% and 8–20.9% respectively) (Kwizera et al. 2012; Halpern et al. 2004).

Admission diagnoses tend to be similar to those found in higher income countries but they tend to be acute; because of the younger population they should be more survivable if basic resources and practices are put in place. Head injuries are a common reason for admission, and they are associated with higher mortality rates than other conditions (Kwizera et al. 2012; Okafor 2009). This is not surprising, considering that most African ICUs are generally mixed units and do not usually have specialised neuro-critical care resources. This is coupled with the fact that many African countries do not have a functional emergency medical response system. Inadequate transportation of trauma victims to healthcare facilities and delays in definitive care are a result. Adequate emergency care at a crash scene (for example, airway management, positioning, oxygen and fluid resuscitation) is known to improve trauma outcome, but the high number of non-helmet wearing motorcycle riders in African countries, especially Uganda, contributes to the high injury severity and mortality rate of neuro-trauma (Kwizera et al. 2012).

Unsurprisingly, there is also a limited number of ICU beds in the continent. For example, Uganda as a whole has only one ICU bed for every one million Ugandans or 0.1 ICU beds/100,000 (Kwizera et al. 2012). This compares poorly with South Africa (8.9/100,000), Sri Lanka (1.6/100,000), and the United States of America (20/100,000) (Adhikari et al. 2010). This means that there is pressure on the few beds that are present, with a resultant high number of missed ICU opportunities. This limitation is further compounded by a well-documented dearth of anaesthesiologists, a critical human resource for ICUs (Hodges et al. 2006; Dubowitz et al. 2010).

> *"even though a recent paper published guidelines to help resource-poor settings manage critically ill patients with sepsis (Dünser et al. 2012), it remains to be seen whether its application will carry through if the basics are not put in place"*

Common Illnesses and High Risk Patient Groups

Sepsis is a common cause of mortality in Africa, with rates higher than those reported from industrialised countries (Jacob et al. 2009). This is due to insufficient early sepsis care characterised by delayed presentation of sepsis patients to the hospital, and subsequently to the ICU if they make it or if such facilities are available (Jacob et al. 2009). The paucity of resources for managing patients with sepsis (for example, insufficient amounts of fluids, unavailability of intravenous broad-spectrum antibiotics and unavailability/unreliability of microbiological diagnostics) is a contributing factor, and even though a recent paper published guidelines to help resource-poor settings manage critically ill patients with sepsis (Dünser et al. 2012), it remains to be seen whether its application will carry through if the basics are not put in place. Early and to a large extent preventable deaths in the ICU are a common occurrence; the most likely explanation for this is the lack of trained staff and resources for providing adequate care for critically ill patients who have a high disease severity (for example, those with brain trauma, shock or sepsis) (Riviello et al. 2011).

> *"awareness that critical illness need not lead inevitably to fatal deterioration is vital to ensuring early initiation of basic treatments"*

Looking at special groups, children account for 11–12% of all ICU admissions, of which there is a mortality rate of 40–60%, which is considerably higher than in industrialised countries (Henry et al. 2011). Paediatric medical patients have a higher mortality than paediatric surgical patients, probably because a lot of the post-operative patients are elective surgical patients who are admitted for observation. Most paediatric medical patients are children with acute respiratory failure in need of mechanical ventilation. The relatively young population in low income countries (LICs), and the fact that respiratory illness is the leading cause of deaths in under five year olds in these countries (Kwizera et al., 2012), implies that more emphasis should be placed on strengthening paediatric critical care resources in LICs.

Obstetric admissions are a common occurrence largely due to perioperative cardiac arrest occurring as a consequence of peripartum haemorrhage, eclampsia and/or sepsis (Okafor 2007). The introduction of protocolised care for peripartum emergencies and the establishment of the obstetric high dependency unit (patient monitors, more intense nursing and protocols without mechanical ventilation) will improve outcomes in this group. This would need to be significantly embedded into maternal and child health initiatives that aim at achieving the millennium development goals.

The fact that HIV is endemic in Africa explains why HIV and AIDS is one of the most common co-morbidity related reasons for admission in this population. Due to the advent of easily accessible, highly active anti-retroviral therapy, together with septrin prophylaxis, the incidence of HIV-related diseases (such as pulmonary infection with Pneumocystis jiroveci, which usually presents as acute respiratory failure) has markedly decreased (Mocroft et al. 2010). Chronic obstructive pulmonary disease is a very rare cause of acute respiratory failure in the African setting. Other rare HIV-related causes of ICU admission are viral encephalitis and liver failure.

Resource-Based Challenges and Proposed Solutions

Having discussed common illnesses found in African ICUs, we turn our focus to resource-based challenges and their solutions. We will use Uganda as an example. The per capita income in this equatorial East African nation is less than four dollars a day, and one third of the population lives below the poverty line. In light of this, the provision of critical care may not appear to be a rational or cost-effective priority in a country where the annual healthcare expenditure is just over 100 dollars per person (Central Intelligence Agency, 2008). However, looking at it more critically, poor health seeking behaviour, low doctor-patient ratios and the low numbers of primary health facilities means late illness presentations requiring life-saving acute care are rife and are the commonest causes of death in hospitals countrywide. This would make critical care medicine at regional referrals a higher priority than normal, while the government tries to solve the longer-term problems of the primary healthcare.

Assuming the governments in African countries decide to tackle this problem, development of critical care capacity must involve the education of nurses and physicians countrywide. Recognition of the initial clinical syndromes of sepsis or hypovolaemia, combined with an awareness that critical illness need not lead inevitably to fatal deterioration, is vital to ensuring early initiation of basic treatments such as antibiotics administration and fluid resuscitation. The WHO released the Integrated Management of Adolescent and Adult Illnesses guidelines that focus on acute care at the basic primary level (WHO, 2009). In Uganda this toolkit is being rolled out at the district hospital level.

Looking at infrastructure, many ICUs have old, used and donated, and poorly serviced equipment, if any. Mechanical ventilators tend to be old and they often cut out during service, thus endangering patients. Many hospitals do not have adequate or appropriate oxygen, or even medical gas to drive ventilators for that matter. Maintenance of equipment is poorly done if available and funding for capital development is limited.

Even when funding is available, the procurement system is plagued by rampant corruption that leads to tenders being fraudulently awarded. This is also characterised by the end users not being involved in the procurement process, assuming they even have the technical expertise. Simple devices like patient monitors, syringe pumps, suction machines and glucometers are a rare re-

source and yet they play a significant role in guiding and delivering therapy.

There is in addition, an increasing influx of Western world discarded or donated, but mostly useful, biomedical equipment. This equipment will work for at least six to twelve months and then breakdown due to lack of spare parts. As a result, Africa has in effect become a dumping ground. A policy toolkit needs to be put in place to guide governments on the types and categories of equipment they can purchase or receive as donations, and on recommended simple designs for the construction of ICUs.

Even without expensive resources, high impact critical care medicine can be practiced. Evidence based practices like early goal-directed therapy for sepsis, handwashing practices, early identification of childhood illnesses and early referrals for high level trauma patients are interventions that are within reach of many healthcare units on the continent. Innovative practices that try to match international guidelines have emerged, for example the lack of commercially prepared enteric feeds at our ICU led us to create a special diet for our critically ill patients. A single feed consists of a small cup of silver fish powder; a small cup of instant soya flour; two tablespoonfuls of sugar; half a teaspoonful of table salt; two crushed multivitamin tablets; and two tablespoonfuls of cooking oil, all mixed in 250mls of fresh whole milk. This feed is given through a nasogastric tube every three hours. Feeds stop at 11pm to rest the gut (and avoid overfeeding) and resume at 7am after measurement of gastric residual volumes.

To improve oxygenation in the absence of face masks and nasal prongs in children, we use mini oxygen tents made of semi-rigid discarded polyethene bags. This helps to improve the fraction of oxygen from 25% to almost 40% and has been observed with pulse oximeters.

Developments

Task shifting has to an extent been successful in other areas of medicine; a currently successful running model is using the growth of anaesthesia to grow intensive care medicine. In Uganda, a successful programme supported by the Association of Anaesthetists of Great Britain and Ireland and Global Partners in Anesthesia and Surgery (a US based physicians organisation) has transformed the training domain of physician anaesthetists from two trainees in 2007 to eight graduates and 22 trainees in 2012.

Additionally, the three- to four-year long programme adopted the European Society of Intensive Care Medicine (ESICM) diploma curriculum: Competency Based Training in Intensive Care Medicine (CoBaTrICE), and embedded it as part of a one-year intensive care medicine module. This is also topped up by a four- to six-month clinical fellowship in a Western ICU to round-off the education for those interested in pursuing intensive care medicine as a full-time career. Furthermore, the undergraduate medical curriculum now requires that trainees partake in a 17-week clinical rotation, including anaesthesia and critical care, thus equipping junior doctors with the basics of intensive care medicine. The same principle should be applied to nursing training schools as well.

While it is generally accepted that there will not be enough doctors in Africa, training a core group of anaesthesia-based intensivists would hopefully provide the leadership that is necessary to drive the growth of critical care across Africa. Many well-intended Western sourced, funded and driven initiatives fail because African physicians are not significantly involved from the outset. This failing process should stop. African critical care physicians should be networked to share experiences, carry out research and form advocacy groups to lobby for more resources to improve critical care in Africa.

It should be emphasised that critical care medicine plays a significant role in helping to lower the burden of surgical disease by providing much needed postoperative care after major surgery in high risk areas like obstetrics, trauma and paediatrics. Additionally, the realm of infectious diseases (including HIV, TB and malaria) stands to benefit from critical care, especially with respect to patients in the acute phases of the respective illnesses. One could argue that critical care medicine is the missing link to providing holistic care for patients in this category of illness. This message can be used to inform priority setting in existing well-funded programmes and to tap resources that can transform critical care medicine in low-resource countries.

Lastly, any well-intending physicians and nurses who want to help improve critical care in Africa should come open-minded, with the understanding that the culture in this continent predominates over everything. Do not be quick to judge, but politely question first why things are the way they are. You will get some really interesting answers. Please come with a mission to build capacity; choose a local champion through whom you can help to transform the community that you are visiting, and above all things, don't be in a rush. We are not.

> *"children account for 11–12% of all ICU admissions, of which there is a mortality rate of 40–60%, which is considerably higher than in industrialised countries (Henry et al. 2011)"*

Conclusion

Critical care remains a neglected area of health service delivery in Africa, with large numbers of patients with potentially treatable conditions not having access to such services. Further advocacy is necessary to highlight these challenges and to provide sustainable solutions for ensuring access to good quality, inexpensive, basic critical care. ■

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

IMPROVING OBSTETRICAL CRITICAL CARE IN DEVELOPING NATIONS:

A THEMATIC REVIEW OF CHALLENGES AND SOLUTIONS

Sukhminder Jit Singh Bajwa, *MD, MBA*

Associate Professor of Anaesthesiology and Intensive Care
Gian Sagar Medical College and Hospital,
Banur, Punjab, India

Sukhwinder Kaur Bajwa, *MD*

Associate Professor of Obstetrics and Gynaecology
Gian Sagar Medical College and Hospital,
Banur, Punjab, India

Bringing down maternal morbidity and mortality rates and thereby improving reproductive health services has been a major concern in developing nations for the past few decades. In spite of adopting on the various measures and implementing new strategies, the adversity in maternal health has not been managed entirely. This thematic review is an attempt to briefly elaborate on the various challenges encountered in improving obstetrical critical care and also to outline potential solutions to these maternal health challenges.

Introduction and Epidemiological Evidence

Maternal mortality is a major concern in developing nations in spite of various advancements in the medical field (Bajwa SK et al. 2010, 2012). WHO has laid down 2015 as the target year to bring down substantially the level of maternal mortality in developing nations, though achieving this objective so soon seems impossible, as illustrated in Tables 1 and 2.

> *"To improve obstetrical critical care health services, planning should involve representatives from both developed and developing nations"*

Apathy in obstetrical critical care in developing countries is reflected in the fact that these nations account for 99% of overall maternal mortality (Table 2). The scenario is worst in African and South Asian countries, where incidences of maternal deaths reach almost two thirds of all the maternal deaths in the world. Only 0.2–0.9% of total obstetrical patients may require intensive care unit (ICU) admission in the US, which corresponds roughly to 40,000-120,000 women in association with 4.3 million births per year (Munnur U et al. 2005; Madan I et al. 2009). Similar data from developing nations is difficult to derive but results from isolated studies have shown very high mortality of obstetric patients admitted to the ICU (Table 1).

Impact of Measures Adopted

Developing countries' governments from time to time have implemented numerous reproductive health policies and reproductive health programmes; however, the statistical figures released by WHO for 2008 in relation to emergency obstetrical critical care have portrayed a dismal picture (Table 2). Emergency medicine is still in its infancy days in South Asian and other developing countries compared with developed nations like Australia, Canada, the US and the UK (Fell DB et al. 2005; Fowler SJ 2005; Germain SJ et al. 2006; Madan I et al. 2009). Improvement of obstetrical critical care in developing nations is studded with numerous challenges and the implementation of concrete solutions is needed (Tang LC et al. 1997; Dias de Souza et al. 2002; Karnad DR et al. 2004).

Challenges in Improving Obstetrical Critical Care

Numerous guidelines have been published by various international obstetrical and critical care societies but the successful application of these guidelines has been very difficult in developing nations (Bajwa SK et al. 2010; Bajwa SK et al. 2012). Also, to date there is no universal consensus on the adoption of a particular scoring system for critically ill obstetric patients (El-Solh AA et al. 1996; Penny G et al. 2007). The partial to complete failure of these implemented measures can be attributed to various factors, such as the following:

- **Shortage of Quality Manpower**

A poor patient to doctor ratio is a common dismal scenario in many developing countries. At present, specialist intensive care services are available only in few of the urban health centers of developing nations (Bajwa SK et al. 2010). The concept of a dedicated obstetrical critical care unit has

come up recently and is yet to take momentum in these nations (Gupta S et al. 2011).

• Economic Constraints and Poverty

Countries of South Asia are experiencing a very bad gross domestic product (GDP) ratio and poverty is discouraging an early treatment seeking behaviour. It is only when a clinical condition gets out of control that people in these poverty stricken populations approach medical service providers for treatment (Bajwa SK et al. 2010). Many of these patients are so poor that earning daily bread is a huge struggle let alone the bearing of expenses incurred on critical care services.

• Illiteracy and Attitude

The lower literacy rate among populations of developing nations has further increased the obstacles for delivering effective obstetrical critical care services. The status of woman and the existence of gender bias in these societies, with families strongly desiring a male baby, chiefly reflect the mental attitude of the majority of the inhabitants of South Asia. This discriminatory ideology of gender preference is responsible for a higher incidence of septic abortions and other pregnancy related complications (Bajwa SK et al. 2010).

• Lack of Clinical Awareness

Clinical awareness about the various ailments of pregnancy is lacking in both literate and illiterate urban and rural populations. The majority of these people do not take any symptom or disease during pregnancy seriously and only when it reaches alarming proportions do they seek medical advice (Perez A et al. 2006; Faponle AF et al. 2007; Baloch R et al. 2010). This leads to delays in managing critically ill obstetric patients, thereby increasing morbidity and mortality. These complications can be further enhanced if such patients are treated by quacks which can create irreversible complications.

• Transport and Communication Snags

Many villages and remote areas of both African and South Asian countries are not properly connected with cities. As such, it becomes highly difficult to transport critically ill obstetric patients to health centres for timely intervention (Okafor UV et al. 2005; Baloch R et al. 2010). At times, low affordability of communication gadgets and networks also hampers the timely delivery of critical care health services (Guise JM 2007).

• Customs, Traditions and Socio-Behavioural Factors

Developing nations exhibit a wide variety of cultural and social practices, which somehow are largely contradictory to evidence based approaches for management of pregnant patients. Due to these socio-behavioural attitudes, urgent medical and obstetrical care may suffer.

• Health Policies

In spite of these countries implementing various reproductive health policies, not much visible improvement has been seen (Baloch R et al. 2010; Bajwa SK et al. 2010). Failure of

Table 1. Obstetrical Care Admission Pattern and Outcome in Various ICU's of Developing Nations.

Study reference	Period of study	City/ Country	Total no. of patients	Incidence of Mortality (%)	Various indications for ICU admission of critically ill obstetric patients
Gupta S et al.	2010	India	24	41.66%	Obstetrical haemorrhage and haemodynamic instability
Bhadade et al.	2009-2010	India	122	30.3%	Hepatitis E and Pre-eclampsia/eclampsia
Bajwa et al.	2006-2010	India	61	30%	Haemorrhage and eclampsia
Faponle AF et al.	2003-2007	Nigeria	14	41.2%	Eclampsia
Baloch R et al.	2000-2010	Karachi, Pakistan	152	68.4%	Haemorrhagic disorders and surgical emergencies.
Okafor UV et al.	2000-2005	Nigeria	54	27.77%	Eclampsia and obstetric haemorrhage
Perez A et al.	1998-2006	Havana, Cuba	58	50%	Post-partum haemorrhage with MOF
Mjahed et al.	1995-2002	Morocco	364	16.75%	Obstetrical and surgical emergencies
Platteau et al.	1992	South Africa	80	21.25%	Obstetrical emergencies
Dias de Souza et al.	1991-2000	Brazil	68	33.82%	Obstetrical emergencies

Table 2. Maternal mortality rate in 2008 as per WHO report

Developed/ Nearly developed countries	Maternal mortality rate	Developing nations	Maternal mortality rate
	14		290
Australia	8	Sub-Saharan Africa	640
Austria	5	Asia	190
Bahrain	19	South Asia	280
Belgium	5	Afghanistan	1400
Bosnia and Herzegovnia	9	Angola	610
Brunei Darussalam	21	Bangladesh	340
Bulgaria	13	Burundi	970
Canada	12	Cameroon	600
Chile	26	Chad	1200
Croatia	14	Congo	580
Cyprus	10	Ethiopia	470
Czech Republic	8	Ghana	350
Denmark	5	Guinea-Bissau	1000
Estonia	12	India	230
Finland	8	Indonesia	240
France	8	Kenya	530
Germany	7	Liberia	990
Greece	2	Madagascar	440
Hungary	13	Mali	830
Iceland	5	Mozambique	550
Ireland	3	Nepal	380
Italy	5	Nigeria	840
Japan	6	Pakistan	260
Netherland	9	Rwanda	540
Poland	6	Senegal	410
Singapore	9	Somalia	1200
Spain	6	South Africa	410
Sweden	5	Sudan	750
Switzerland	10	Uganda	430
UK	12	Tanzania	790
USA	24	Zimbabwe	790

these policies can be attributed to various administrative, social, attitudinal, economic and political factors, which are difficult to elaborate on in this thematic review. These health policies and programmes should be reviewed periodically in order to incorporate new plans and strategies.

• Lack of Coordinated Activities

One of the biggest reasons for partial to complete failure of these health policies includes gross incoordination among different health providers. The unavailability of clear-cut guidelines and protocols related to obstetrical critical care is one of the major reasons for this. As such, treatment patterns are very subjective and vary widely among different set-ups. This is highly detrimental in providing quality reproductive health services.

• Poor Antenatal Care

Various physiological and pathological fluctuations can be experienced in the antenatal period. This mandates regular check-ups to ensure a healthy mother and the delivery of a healthy baby. In the majority of instances, parturients present to the health centres only during the late stages of labour, without any previous antenatal check-up (Perez A et al. 2006; Faponle AF et al. 2007). Such patients can have high morbidity and mortality if they have comorbid diseases and obstetrical complications (Guise JM et al. 2007). In countries like India, one third of pregnant females never present themselves for any kind of antenatal check-up. Statistical figures of National Health and Family Survey, 2006, report that astonishingly a mere 7% of pregnant females come for third trimester antenatal check-ups.

• Inadequate Medical Facilities

Besides shortages of qualified manpower and poor antenatal care, inadequate medical facilities further compound the problem. In rural areas, apathy is highlighted by the fact that not many facilities and drugs for managing critically ill obstetric patients are available at the majority of health centres.

• Inadequate Infrastructure

The majority of the population in developing nations resides in rural areas, but most tertiary care centers and bigger hospitals and institutes are located in urban areas. As such, rural health infrastructure is grossly deficient in managing critically ill patients. It is difficult for the respective governments to set-up ICU's amid the circumstances that prevail in such areas.

> *"Apathy in obstetrical critical care in developing countries is reflected in the fact that these nations account for 99% of overall maternal mortality"*

• Attitudinal differences

Attitudinal differences are prevalent in all strata of society, whether among the general public, opinion makers, policy makers, doctors or paramedical staff. They arise because of previously mentioned factors such as poverty, illiteracy, economic constraints, shortage of manpower and so on, and they can be highly detrimental to delivering quality critical care services.

• Under-Reporting and Non-Reporting of Obstetrical Data

Developed nations have been able to adopt appropriate measures to improve reproductive health services on the basis of data from observational, retrospective and randomised prospective trials (Harris CM et al. 2002; Zeeman GG et al. 2003). On the other hand, scarce and sporadic data from developing nations has not been helpful in bringing any significant improvement in reproductive health services as it reveals only partial to minimal information regarding the actual state of obstetrical critical care (Table 1). It becomes extremely difficult for health administrators and policy makers to formulate and implement appropriate corrective measures to bring an improvement in overall maternal health.

• Comorbidities

The higher incidence of maternal mortality in developing nations is mainly due to severity of comorbid medical and surgical disorders which can complicate pregnancy by inflicting direct insults or leading to intensive care admissions. Various cardiac pathologies, respiratory disorders, haematological disturbances, endocrinological disorders, sepsis, altered metabolic profiles, neurological diseases, cerebro-vascular accidents, renal diseases, hepatic disorders, trauma and so on can be devastating to both mother and the foetus if not timely diagnosed and appropriately managed.

• ICU Challenges

Critically ill obstetric patients are usually young and have a good prognosis if timely therapeutic interventions are administered. This requires dedicated efforts from teams of obstetricians, anaesthesiologists, intensivists and pediatricians to plan and design the various structural and functional aspects of the obstetrical ICU.

• Political Unrest

The political situation of a country can have a direct and indirect impact on the health services of these developing nations. The ever-present political turmoil in South Asian and some African countries has gradually upset the provision of qualitative delivery of obstetrical critical care services.

Potential and Possible Solutions

To fulfill the targets set by WHO in decreasing maternal morbidity and mortality throughout the globe, concrete measures have to be taken, particularly in the developing nations with the highest maternal deaths. A multidisciplinary approach, coordinated and dedicated efforts from government officials, doctors, paramedical staff and most importantly active participation of society and the general public are required.

Shortages of manpower can possibly be overcome by:

- Recruiting new specialists by giving various incentives;
- Implementing a rotation policy so as to deploy specialist doctors for a compulsory spell of at least two to three years in rural areas;

- Giving higher pay scales and salaries to doctors posted in rural areas;
- Providing accommodation and other facilities at a minimum cost to doctors posted in rural areas;
- Regularly posting postgraduate students to these peripheral health centres on a monthly basis, under the supervision of a senior doctor; and
- Governments permitting the opening of new medical colleges only in rural areas.

In times of economic recession and crisis, governmental responsibility to improve health services is immense. Budget reallocation has to be done so as to direct maximum funds towards the management of critical care services.

A higher literacy rate in society definitely contributes towards reproductive health. Moreover, it becomes easy for doctors to make obstetrical patients clinically aware about their present condition during an antenatal visit. All patients with systemic diseases should be made aware of potential complications associated with them. Diagnostic aids, prophylactic measures and therapeutic interventions should be planned solely during these antenatal visits. Giving the contact number of doctors can be of great help in case of an emergency. Looking at customs, traditions and superstitions from a scientific angle can only be achieved by spreading literacy levels throughout society.

Means of transportation and communication can be improved with initiatives from the government. Free ambulances can be deployed at various critical focal points, facilitating attendance to critically ill patients in the shortest possible time. These ambulances should be equipped with facilities for deliveries and neonatal resuscitation. Maternal and foetal monitoring during transportation can have a significant positive impact on outcome (Elliott JP et al. 1987). In addition, helpline numbers could be displayed on the roadside, in newspapers and on television. Overall, improving logistical operations and communication networks can bring significant change.

Health policies should include launching effective programmes for all health personnel that enable learning and orientation towards obstetrical critical care. At present, developing nations mostly adopt treatment measures from the guidelines published by the American College of Critical Care Medicine. These guidelines have to be further updated as ICU admission criterion may vary significantly from one place to another. Research and data reporting should be boosted and made compulsory so as to get a real picture of obstetrical critical care.

There is an acute need to strengthen health infrastructure at grass root levels so as to ensure timely implementation of the appropriate interventions. Simple early initiatives, close monitoring and symptomatic care can help drastically in reducing maternal morbidity and mortality. To improve obstetrical critical care health services, planning should involve representatives from both developed and developing nations. They should develop new consensus with the involvement of various international communities and societies that work for the improvement of reproductive health, in which they review prevailing health scenarios, socio-political circumstances and the availability of resources. The practical and feasible application of universal guidelines could be enabled, thus aiding the provision of quality care in high risk obstetrical emergencies. ■

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

PHARMACONUTRITION WITH ANTIOXIDANTS IN THE CRITICALLY ILL:

IS SELENIUM MONOTHERAPY THE CORNERSTONE OF THIS STRATEGY?

William Manzanares, *MD, PhD*

Associate Professor
Department of Critical Care
Hospital of Clínics
Faculty of Medicine
University of the Republic
(UDELAR) Montevideo,
Uruguay

wmanzanares@adinet.com.uy

Gil Hardy, *PhD, FRSC*

Professor of Pharmaceutical Nutrition
Faculty of Medical and Health Sciences
University of Auckland
Auckland,
New Zealand

g.hardy@auckland.ac.nz

This article explores the evolving paradigm of pharmaconutrition using antioxidant micronutrients, looking at the available evidence for antioxidant supplementation in the critically ill. In particular it discusses the protective mechanisms of action of selenite in critically ill SIRS patients and how selenium supplementation as a pharmaconutrient can be best applied.

Why are Antioxidants Required in the Critically Ill?

Critical illness is characterised by a significant redox imbalance, which leads to mitochondrial dysfunction, systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndromes (MODS). Although in the last few years there have been important developments in supportive techniques for use in intensive care units (ICUs) around the world, sepsis-related organ dysfunction remains the most common cause of death in the ICU (Galley, 2012). Over the last two decades, many observational studies have evaluated oxidative stress in the critically ill. Oxidative stress is defined as a state in which the levels of toxic reactive oxygen species (ROS) and reactive nitrogen oxide species (RNOS) overcome the endogenous antioxidant defenses of the host. In fact, during critical illness antioxidant capacity is drastically decreased due to an excessive production of ROS and RNOS. ROS activate the nuclear transcription factor kappa B (NF-κB), which is one of the steps involved in amplifying SIRS (Manzanares and Hardy et al. 2012).

SIRS is associated with redistribution of micronutrients (vitamins and trace elements) from the circulating compartment to the interstitial compartment and different tissues, especially those involved in protein synthesis and immune cell proliferation. Trace elements escape to the interstitial compartment by capillary leakage, which is a distinctive characteristic of SIRS (Manzanares et al. 2009). Furthermore, low levels of trace elements may be explained by several other causes, such as losses through biological fluids and haemodilution, previous insufficient intake, low levels in enteral formulas and parenteral mixtures, and continuous renal replacement therapies (CRRTs) (Hardy et al. 2012). In this scenario, it is most likely that micronutrient status is always compromised during critical illness, despite standard micronutrient dietary intake.

What Does the Most Up-to-date Evidence Show about Antioxidant Supplementation in the Critically Ill?

In 2005, for the first time, a meta-analysis demonstrated that antioxidants were associated with a significant reduction in ICU mortality (risk ratio [RR], 0.65; 95% confidence interval [CI], 0.44–0.97; P=0.03) (Heyland et al. 2005). The authors further demonstrated that daily doses of selenium (higher than 500 μg) showed a tendency towards a decrease in mortality (RR, 0.52; 95% CI, 0.24–1.14; P=0.10). Four years later, the same Canadian group updated these results, showing that antioxidant supplementation was still associated with a significant reduction in mortality (RR, 0.76; 95% CI, 0.64, 0.91; P=0.002). Moreover, the specific effects of parenteral selenium on mortality were similar (RR, 0.84; 95 % CI, 0.67, 1.05; P=0.13).

> *"patients with more severe insults and higher mitochondrial dysfunction resulting from bioenergetic failure experienced the largest depletion of antioxidants"*

Most recently, an updated systematic review and meta-analysis, which aggregated 20 trials that had reported mortality as an outcome, concluded that combined antioxidant

European Society of Anaesthesiology

ESA

Barcelona, Spain

Euroanaesthesia 2013

The European Anaesthesiology Congress

June 1- 4

Symposia
Refresher Courses
Workshops
Industrial Symposia & Exhibition
Abstract Presentations

CME Accreditation
EACCME - UEMS

Deadline abstracts:
December 15th 2012
Online submission:
www.euroanaesthesia.org

ESA Secretariat
Phone +32 (0)2 743 32 90
Fax +32 (0)2 743 32 98
E-mail: registration@euroanaesthesia.org

supplementation was associated with a significant reduction in mortality (RR, 0.82; 95% CI, 0.72–0.93; P=0.002) (Manzanares et al. 2012). Supplementation with antioxidant micronutrients showed a significant reduction in duration of mechanical ventilation (weighed mean difference, -0.67 days; 95% CI, -1.22, -0.13; P=0.02) and a trend towards a reduction in infections (RR, 0.88; 95% CI, 0.76, 1.02; P= 0.08). However, it was not possible to demonstrate any significant overall effect on ICU or hospital length of stay (LOS). Of practical interest is the fact that antioxidant micronutrients were associated with a significant reduction in overall mortality among patients with higher risk of death (>10% mortality in control group) (RR, 0.79; 95 % CI, 0.68, 0.92; P=0.003). This finding supports the notion that patients with more severe insults and higher mitochondrial dysfunction resulting from bioenergetic failure experience the largest depletion of antioxidants (Manzanares et al. 2012). These patients may therefore exhibit a greater clinical improvement with antioxidant supplementation than less sick patients.

When aggregated, selenium supplementation was specifically associated with a trend towards a reduction in mortality (RR, 0.89; 95% CI, 0.77–1.03; P=0.12). The seven selenium trials demonstrated a trend towards a reduction in infections (RR. 0.87; 95% CI, 0.74–1.02; P=0.08), whereas three of the trials that didn't use selenium demonstrated no effect on infections (RR, 1.10; 95% CI, 0.60–2.04; P=0.75). Thus, parenteral selenium monotherapy, administered as a loading dose followed by a continuous infusion, may be strongly recommended to reduce mortality and infections in critically ill SIRS patients (Hardy et al. 2012).

What Do We Know About the Protective Mechanisms of Action of Selenite in Critically Ill SIRS Patients?

Although the optimal time to start antioxidant therapy has not yet been established, both experimental and clinical data support the concept that antioxidant micronutrients are more effective when initiated prior to injury or as early as possible after the insult. Selenium is an essential trace element with antioxidant, immunological, and anti-inflammatory properties. Selenium is essential for the activity of selenoenzymes such as selenoprotein P1, which may be protective against endothelial oxidant injury, and glutathione peroxidase, which belongs to the body's first line of antioxidant defense. Selenite is able to inhibit the activation of NF-kB by controlling selenoprotein gene expression and thus down-regulating the synthesis of proinflammatory cytokines.

An intravenous loading dose of selenite given as bolus has a biphasic action, initially as a pro-oxidant and then as an antioxidant (Vincent JL et al. 2009; Manzanares et al. 2009). Furthermore, in a sheep model of severe sepsis, the bolus of sodium selenite was able to improve haemodynamics, delaying arterial hypotension, and improving cardiac index, with delayed hyperlactataemia, and fewer sepsis-induced microvascular alterations (Wang et al. 2010). Various clinical trials have successfully implemented the bolus plus continuous infusion protocol (Angstwurm et al. 2007; Manzanares et al. 2011), showing improvement in relevant clinical outcomes, especially mortality and infectious complications. Conversely, continuous high-dose selenite infusion, without the initial bolus, has been clinically ineffective (Forceville X et al. 2007).

What is the Current Concept of Pharmaconutrition?

The concept of pharmaconutritional supplementation in supraphysiological doses is quite different from the classical nutritional concept of nutrient replacement, which is designed to replenish losses and target restoration of normal function (Berger M 2012). Pharmaconutrition considers pharmaconutrients as drugs or nutraceuticals.

During critical illness, pharmaconutrition with antioxidant trace elements and vitamins, or both, is considered an attractive therapeutic strategy for ICU patients (Manzanares and Heyland 2012). Currently, the concept of pharmaconu¬trition is quite distinct from the concept of immunonutrition, whereby immune-modulating nutrients such as arginine, glutamine, and ω-3 fatty acids are combined together with macronutrients and are provided in so-called immune-enhancing diets (IEDs) by the enteral route. According to the pharmaconutrition concept, high-dose pharmaconutrients should be provided separately from standard enteral or parenteral nutrition regimens (Manzanares and Heyland 2012) to ensure optimum delivery of the pharmaconutrients.

Selenium Supplementation as a Pharmaconutrient for the Critically Ill: When, How and How Much?

There is enough evidence in current literature to consider antioxidant cocktails and/or parenteral selenite supplementation as monotherapy in critically ill SIRS patients. The best antioxidant cocktail approach has not yet been determined. However, we know that initiating high-dose intravenous sodium selenite (1000–2000µg as a bolus over 30 minutes to two hours) immediately on admission to the ICU (within the first 24 hours), and thereafter as a continuous infusion at a daily dose between 500-1600 µg for up to 10 to 14 days, is a novel and successful strategy in the critically ill. This concept of pharmaconutrition, using selenium as monotherapy, is quite distinct from the routine incorporation of selenium (and other micronutrients) in standard parenteral or enteral nutrition. High-dose sodium selenite should be supplemented in the most seriously ill ICU patients, including those with severe sepsis and septic shock. High-risk cardiac surgery patients may also benefit in the near future, but more evidence from on-going clinical trials is awaited before recommendations can be made for this patient population.

What is the Future for Antioxidant Micronutrient Supplementation for Intensive Care?

The largest randomised controlled trial on antioxidants in combination with high-dose glutamine supplementation has been the REducing Deaths due to OXidative Stress (REDOXS) Study, which is unpublished; but it seems to have failed to demonstrate any improvement on clinical outcomes in MODS patients. In this multicentre trial, more than 1,200 patients were enrolled to receive intravenous glutamine in combination with enteral or parenteral antioxidant cocktails, including vitamins C (1500

Continues on page 44

FLUID MANAGEMENT IN CRITICALLY ILL PATIENTS: A GUIDED APPROACH

Critically ill patients are at risk of developing acute cardiovascular insufficiency or shock from any cause, defined as the imbalance between oxygen delivery and tissue oxygen consumption. This state is characterised by cellular dysoxia that, maintained over time, might progress to multi-organ failure and death. In order to prevent these consequences, haemodynamic resuscitation has to be started early and aimed at correcting tissue hypoperfusion. Since most common causes of shock have some degree of insufficient intravascular volume, volume expansion with fluids is recognised as the first step of resuscitation, and is one of the issues in critical care practice that shows a high level of controversy and debate in most of its aspects. In this review, we will analyse two fundamental questions: "which tools should we use to guide fluid management?" and "what strategies for fluid administration can improve the prognosis of our patients?"

Guillem Gruartmoner, MD

Jaume Mesquida, MD

Xaime García, MD

Antonio Artigas, MD PhD

Critical Care Centre
Sabadell Hospital
Taulí Park Health Corporation
University
Autonomous University
of Barcelona
Spain

Applied Physiology at the Bedside: Current Approach to Fluid Administration

According to the Frank-Starling law of the heart, there is a positive relationship between preload (defined as end-diastolic volume) and stroke volume, and this relation follows a curvilinear shape (Figure 1). Consistently, a uniform increase in preload produces a significantly greater increase in stroke volume on the steep ascending portion of the curve, defining a preload-dependence area, where volume expansion significantly increases cardiac output. On the opposite, flatter part of the curve, we can define a preload-independence area, where volume expansion produces no significant changes in stroke volume. This increase in stroke volume as a result of volume expansion depends not only on the increase in end-diastolic volume, but also on ventricular function, since a decrease in ventricular contractility decreases the slope of the relationship between end-diastolic volume and stroke volume (Pinsky 2005).

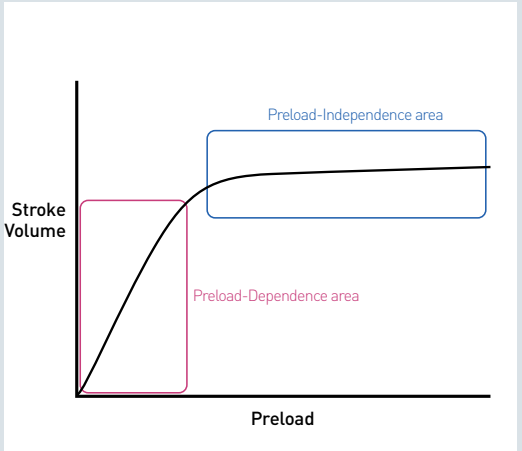


Figure 1. Representation of the Frank-Starling Curve

> *"aggravating fluid balance by using the wrong tools and the wrong endpoints should not take place in the context of current knowledge"*

Fluid Responsiveness

Fluid responsiveness is arbitrarily defined as a ≥15% increase in cardiac output (CO) in response to a fluid challenge (normally 500 ml) (Michard et al. 2000). In the assessment of preload-dependence, the simplest method is to give a bolus of intravenous fluid and evaluate the haemodynamic response. This practical approach is also still considered to be the "gold standard" of fluid responsiveness. Volume expansion in normal individuals almost always produces an increase in stroke volume, but in shock states, the rate of response markedly falls to approximately 50%. Furthermore, fluid overload due to aggressive volume expansion may lead to deleterious effects, such as an increase in extravascular lung water or acute cor pulmonale, or both (Michard et al. 2002). Therefore, it seems of critical importance to detect if a

shocked patient is on the preload-dependence part of the curve before starting fluid administration. For use in such instances, practical tools have been accessed to predict fluid responsiveness at the bedside

• Static Parameters for Assessing Fluid Responsiveness

Static parameters are based on the evaluation of cardiovascular pressures and volumes, and they try to estimate the absolute value of ventricular preload. However, predicting response to fluid challenge based on ventricular preload evaluation may be problematic.

1. Cardiovascular filling pressures

Commonly used measurements of preload include central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP). However, a significant relationship with reference to values of CVP and PAOP has not been found between fluid responsive and non-responsive patients (Michard et al. 2002). This can be explained by an inability of these static filling pressures to precisely estimate preload in different clinical scenarios, especially in those situations where intravascular pressure may overestimate transmural pressure (Pinsky 2003). However, it is accepted that extremely low values of filling pressures (<5 mmHg in CVP, and <7 mmHg in PAOP) can be considered as predictors of a positive response to fluid expansion (Teboul et al. 2004).

2. Cardiovascular volumes and areas

Although ventricular volumes are more accurately used for estimating ventricular preload than filling pressures, they are still far from being good predictors of fluid responsiveness. Fluid expansion is expected to increase right ventricular end-diastolic volume (RVEDV) as well as left ventricular end-diastolic volume (LVEDV). However, the relationship between ventricular volumes and telediastolic pressures depends also on ventricular compliance; so for a given telediastolic volume, the intravascular pressure will depend on ventricular compliance and not on the real value of preload.

The key concept that explains the inability of these static parameters to assess fluid responsiveness is again found in the Frank-Starling curve. For a given preload value, whatever the precision of the method used to assess it, cardiac output response might not be predicted unless it is known in which part of the curve the patient is operating (Sabatier et al. 2012). Despite their failure to do so, static volumes and filling pressures continue to be massively used in daily practice as tools for assessing fluid-responsiveness.

• Dynamic Parameters for Assessing Fluid Responsiveness

Recently, the use of a more dynamic approach to the prediction of fluid responsiveness has been proposed: a real-time evaluation of the cardiovascular response to temporary and reversible changes in preload, such as intrathoracic pressure secondary to mechanical ventilation or certain postural manouvres.

1. Changes in left ventricular output induced by positive pressure ventilation: The pulse pressure variation and the stroke volume variation

During the inspiratory phase of positive pressure ventilation, rising intrathoracic pressure leads to increases in right atrial pressure and decreases in venous return, with a consequent fall in right ventricular output. Simultaneously, blood volume contained in the pulmonary circulation is squeezed, thus increasing left ventricular preload and left ventricular output. After two or three beats, the previous fall in right ventricular output will produce a decrease in left ventricular output in the expiratory phase. Thus, in preload dependent patients, cyclic changes in left ventricular stroke volume and its coupled arterial pulse pressure are seen, and the magnitude of these changes are proportional to the grade of volume-responsiveness (Magder 2004; Michard et al. 2000).

The stroke volume variation (SVV) measurement requires the use of Doppler echocardiography or analogue estimation of left ventricular stroke volume with pulse-contour analysis haemodynamic monitoring tools. Multiple studies have shown that SVV >10% predicts fluid responsiveness with high sensitivity and specificity (Marik et al. 2009). Since pulse pressure is primarily determined by left ventricular stroke volume in a given respiratory cycle, the pulse pressure variation (PPV) in this space of time will be dependent only on stroke volume variation. PPV is easily obtained at the bedside, automatically calculated from the signal of the arterial line in most haemodynamic monitors. Again, multiple studies have proven that PPV >13% predicts fluid responsiveness with high sensitivity and specificity (Marik et al. 2009).

Changes in the diameter of inferior vena cava (ΔDIVC) secondary to positive pressure ventilation, assessed non-invasively by transthoracic echocardiography, have also been explored. As occurs with SVV and PPV, the magnitude of inferior vena cava diameter change within a respiratory cycle is proportional to the grade of fluid responsiveness. Indeed, recent studies showed that ΔDIVC ≥12% predicted fluid responsiveness with high sensitivity and specificity (Feissel et al. 2004).

Some limitations of these parameters deserve mention. First, the patient has to have a stable and regular cardiac rhythm, as any kind of arrhythmia or frequent extra-systoles will interfere in the calculation of the parameters. Second, the patient has to be fully adapted to mechanical ventilation in a controlled mode, as spontaneous respiratory swings might lead to overestimation of those parameters. Third, patients with right ventricular dysfunction may generate false positives. Finally, the predictive power of these parameters is decreased through using tidal volumes set to <8 ml/Kg of ideal weight, since minimum modifications in intrathoracic pressure are required to observe the described haemodynamic effect (De Backer et al. 2005).

2. Passive leg raising

The passive leg raising (PLR) manouvre is a simple and reliable method to evaluate fluid responsiveness. It consists of a passive elevation of the legs to 45° while keeping the head at 0°, for three minutes (Monnet and Teboul 2008). The manouvre causes an autotransfusion of blood contained in the lower limbs to the central compartment, with a consequent increase in venous return and in cardiac pre-

load. If the ventricles are operating in the preload-dependence area of the Frank-Starling curve, it also triggers a transient increase in cardiac output. It is considered a reversible fluid challenge equivalent to approximately 300cc. To evaluate the transitory cardiac response to PLR, it is important to use a haemodynamic monitoring device to assess rapid changes in cardiac output. PLR-induced increases ≥10% in cardiac output during the first 60-90 seconds predict fluid responsiveness with high sensitivity and specificity (Cavallaro et al. 2010). This manouvre can be performed in ventilated or spontaneously breathing patients, and also in absence of sinus rhythm. Its primary limitations are: potential risk of increasing intracraneal pressure, risk of aspiration, and decreases in test efficacy in patients with intrabdominal hypertension, extreme hypovolemia or cardiogenic shock (Monnet and Teboul 2008).

A huge amount of evidence endorses the superiority of these dynamic parameters over the static ones in assessing fluid responsiveness. However, these dynamic parameters have not been fully incorporated in current resuscitation guidelines (Dellinger et al. 2008), probably because of their limited applicability to certain patient populations.

Fluid Administration: Resuscitation Strategies

An accurate knowledge of fluid-responsiveness parameters is helpful in the haemodynamic resuscitation decision-making process, but it should be noted that the patient being preload-responsive does not imply that he/she needs volume. The clinician must bear in mind that recognising the need for further resuscitation (and when to stop) is just as important as being familiar with the tools used during the process, if not more so.

• Endpoints of Resuscitation

The goal of fluid therapy in critically ill patients is to restore tissue oxygenation, thus preventing or minimising tissue damage. From Shoemaker's group studies to Rivers' landmark early goal-directed therapy (EGDT) protocol, many groups have demonstrated that optimising oxygen delivery to tissues by means of standardised haemodynamic resuscitation protocols results in substantial improvements in morbidity and mortality of critically ill patients (Shoemaker et al. 1982; Rivers et al. 2001; Levy et al. 2010). Standardised care requires defined and validated endpoints, ranging from global DO2 to surrogates of global end-organ perfusion (such as lactate, and either central or mixed venous oxygenation) (Mesquida et al. 2011). Achieving these predetermined physiological endpoints would denote the culmination of the resuscitation process; therefore, volume administration or other interventions that aim to increase DO2 would no longer be indicated. However, during the last decade, overwhelming evidence has emerged indicating that, despite normalisation of global surrogates of tissue perfusion, local tissue hypoperfusion might persist, and these microcirculatory alterations are associated with worse outcome (De Backer et al. 2002). Regardless of the chosen endpoint, fluid administration is crucial for any of the proposed algorithms, and fluids are given while fluid responsiveness is suspected and global tissue perfusion surrogates have not normalised. Still, the response of the microvascular system, the ultimate target of the resuscitation process, might be independent to the behaviour of the macro-haemodynamic parameters. Then, macro-haemodynamic fluid responsiveness might not be equal to microcirculatory fluid responsiveness. The increasing proof of the uncoupling between macro- and microvascular compartments has taken us to the next query in resuscitation: should we monitor microcirculation to titrate the administration of fluids? Using video microscopic imaging techniques, several authors have reported persistent microcirculatory alterations, despite improvements in cardiac output after volume expansion, with dissociated response of the micro- and macrovascular compartments (Sakr et al. 2004; Trzeciak et al. 2007; Ospina-Tascon et al. 2010). In the near future, guiding fluid administration by using technologies that evaluate the microcirculatory perfusion seems unavoidable. Microcirculatory monitoring probably needs to be complementary to the macrovascular approach, and further clinical investigations should explore whether this combined approach results in better patient outcomes.

> "Despite the fact that current sepsis management guidelines offer well-established tissue perfusion endpoints, intravenous fluid administration remains highly empirical during the resuscitation process"

• Misleading Endpoints

Despite the fact that current sepsis management guidelines offer well-established tissue perfusion endpoints, intravenous fluid administration remains highly empirical during the resuscitation process. The Surviving Sepsis Campaign guidelines for management of sepsis recommend an initial administration of repeated fluid challenges of >1000 ml of crystalloids or 300-500 ml of colloids (Dellinger et al. 2008). According to these guidelines, the infusion of fluids should be maintained until certain predetermined values of central venous pressure (CVP) are achieved. Importantly, CVP is presented as an endpoint per se, not only as a tool for assessing volume-responsiveness. On a physiological basis, volume expansion should only be performed when an increase in stroke volume is expected and, as we already exposed, CVP has repeatedly failed in predicting preload-dependen-

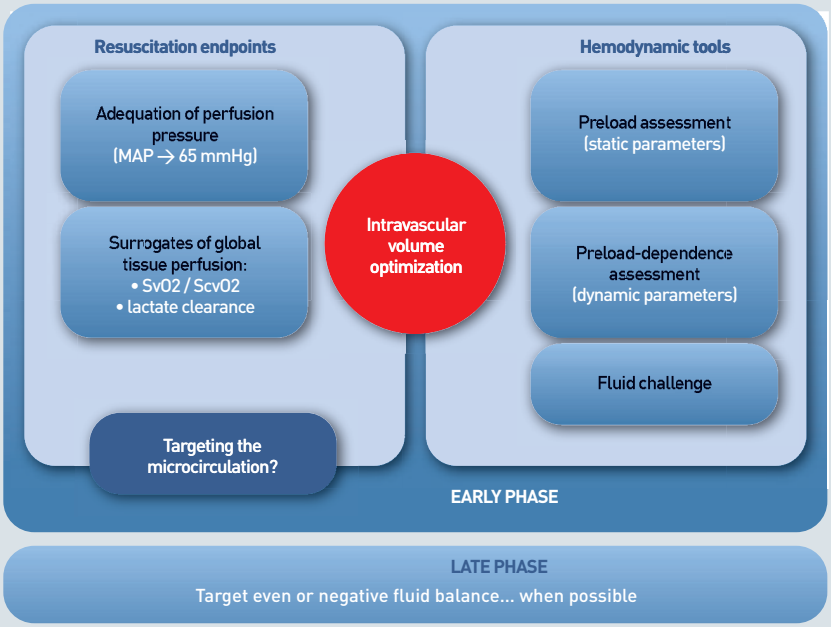


Figure 2. Summary of Approach to Fluid Management in Critically Ill Patients

cy (Michard and Teboul 2002). Therefore, CVP seems to be an unreliable surrogate of the adequacy of intravascular volume status, and using CVP not only as a tool, but also as an endpoint in the resuscitation process, might be deleterious for patients. In the study by Rivers and colleagues (Rivers et al. 2001), patients in the EGDT treatment group, where CVP was used to guide fluid administration, received up to 1.5 litres more volume than patients in standard care within the first six-hour period; although, in the final 72-hour fluid balance, no difference between the EGDT and standard groups was recorded. Importantly, a more positive fluid balance has been associated with increased mortality (Vincent et al. 2006; Boyd et al. 2011), either within the first 12 hours or after four days of ICU stay (Boyd et al. 2011). Whether fluid balance independently affects outcome or it is just a confounder and a marker of severity of illness remains unclear, but aggravating fluid balance by using the wrong tools and the wrong endpoints should not take place in the context of current knowledge. In Figure 2, we summarise the global current approach to fluid management in critically ill patients.

> *"Whether incorporating additional targets, such as microcirculatory variables, will impact on outcome deserves further investigation"*

• Early Versus Late

Finally, when analysing some failed goal-directed studies, it was noted that resuscitation interventions did not result in outcome improvements when initiated too late in the time course of the disease (Gattinoni et al. 1995; Kern and Shoemaker 2002), once tissue damage was presumably present. The EGDT study carried out by Rivers and his team (Rivers et al. 2001) also highlighted the importance of time: a six-hour initial resuscitation bundle, including aggressive fluid administration was associated to better prognosis. This fluid loading strategy has been adopted in sepsis management guidelines, with apparently favorable results (Levy et al. 2010). However, compliance with current volume loading recommendations (within the initial resuscitation bundle) has not been independently associated to increased survival rates (Ferrer et al. 2009). Evidence appears more consistent when evaluating the effect of fluids administered late in the time course of the disease. On this behalf, several authors have reported the negative effect on outcome derived from positive fluid balance within three to seven days of ICU admittance (Rivers et al. 2001; Boyd et al. 2011; Murphy et al. 2009). Supporting these epidemiological findings, the significance of the time factor has been endorsed by some observations at the microcirculatory level, where the response to fluid administration has proven to differ according to the elapsed time since the onset of the disease. Using sublingual video microscopy, Ospina-Tascon and colleagues (Ospina-Tascon et al. 2010) detected improvements in perfusion of small vessels in response to volume expansion only when fluids were administered early (within 24 hours) after diagnosis of septic shock, but not when administered late in the course of the disease. Importantly, this effect was again independent from those at the global haemodynamic level.

Conclusions

In conclusion, there are still many grey zones regarding fluid management, but current knowledge permits to fill some pieces of the puzzle. Understanding our patients' physiology, estimating their position in the Frank-Starling curve to better direct fluid administration, and targeting well-defined global tissue oxygenation endpoints in order to guide and/or finish the resuscitation process are key factors in providing a high standard of care and improving our critically ill patients' prognoses. Whether incorporating additional targets such as microcirculatory variables will impact on outcome deserves further investigation. ■

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

MANAGEMENT OF CANDIDURIA: GREY ZONES STILL EXIST

Candida species cause a wide spectrum of diseases, of which the prevalence of candiduria varies considerably between nosocomial settings, being most prevalent among patients admitted to the intensive care unit (ICU). However, lacking management and treatment guidelines and the existence of dilemmas have inhibited efforts to curtail cases of candiduria for this vulnerable population.

Nidhi Singla

Assistant Professor
Department of Microbiology
Government Medical College Hospital
Chandigarh, India

Jagdish Chander

Professor and Head
Department of Microbiology
Government Medical College Hospital
Chandigarh, India

jchander@hotmail.com

Critically ill patients are a susceptible group for opportunistic *Candida* infections. The major risk factors identified with candiduria are extremes of age, female sex, diabetes mellitus, use of immunosuppressive agents, interruption of the flow of urine, radiation therapy, and so on. However, in nosocomial settings, the major risk factors are the use of urinary catheters and the prior use of broad-spectrum antimicrobial agents (Passos et al. 2005).

Presently, the incidence of candiduria in the ICU population ranges from 19% to 44% of urine specimens, depending upon the patient cohort and the definition of candiduria (Toya et al. 2007). The causative species of candiduria vary in different studies. *Candida albicans* is responsible for at least 50% of all cases of fungiuria, followed by *Candida glabrata* (15.6%), *Candida tropicalis* (7.9%), *Candida parapsilosis* (4.1%), and *Candida krusei* (1%) (Kauffman et al. 2000). *C. glabrata* most often is isolated from individuals who have been treated with fluconazole, while *C. parapsilosis* is seen most frequently in neonates. It is noteworthy that for approximately 10% of patients with candiduria, at least two types of *Candida* species are isolated from the same urine culture. Candiduria frequently coexists with or follows bacteriuria.

Treatment Dilemmas

The major problem with candiduria is in determining its practical importance. The condition can arise as a result of contamination, colonisation or a true urinary tract infection. Due to lack of a reliable method for differentiating colonisation from infection, the condition is a dilemma for the clinician from the treatment point of view. Frequently it has been reported to be the first sign of disseminated disease or candidaemia. After adjusting the various covariates, the overall ICU mortality rate among patients with candiduria has been found to reach 20-50% (Hollenbach 2008). Therefore, if neglected, it can evidently be detrimental for the patient. As a result, even if the decision is not to treat the patient, the clinician has to be vigilant. In the case of isolation of *C. albicans*, the possibility of colonisation should be kept higher than true infection as it is a part of normal flora, especially in female patients. However, if non-*albicans Candida* are isolated, it is advisable to determine whether it is really colonisation. There is also need to perform surveillance cultures at various body sites of the same patient to determine the colonisation index.

> *"Lack of consensus and the availability of limited literature are the main reasons that we cannot formulate the proper guidelines"*

As far as the question of when to start the treatment cutoff is concerned, there are no clear-cut guidelines. The decision lies upon the clinical acumen of the attending physician. Asymptomatic candiduria is usually expected to resolve within weeks to months without therapeutic intervention in the vast majority of individuals. Treatment is warranted only in certain patient populations, such as those at risk for developing a disseminated fungal infection. These include neutropenic or oncology patients, patients with sepsis, infants with low birth weight, neonates, those with a known urologic obstruction and those likely to undergo urologic manipulations (Lundstrom et al. 2008). In cases of asymptomatic candiduria in outpatients or other predisposed inpatients, the best method is to get rid of predisposing conditions.

However, in ICU patients, it may not be possible to remove the catheter permanently, stop the ongoing antibiotic therapy or make the patient undergo surgery for predisposing urologic abnormality immediately. In such conditions, careful monitoring is required. The patient's urine cultures should repeatedly be tested for *Candida* so that if presence is detected the possibility of contamination can be ruled out. The Microbiology laboratories cannot help much in differentiating colonisation from infection on their own. The cutoff value for candiduria that indicates presence of infection varies from 103 to 105 colony-forming units (CFUs) The problem of multiple species in the same sample, and cutoff criteria for cases of non-*albicans Candida* species isolation, are still to be addressed. There have been some attempts to distinguish infection from colonisation of the bladder by looking for the presence of pseudohyphae or antibody-coated yeasts in the urine. However, species such as *C. glabrata* do not produce pseudohyphae, and *C. albicans* can be induced to form pseudohyphae by varying the pH and nutrients in the urine. Detection of antibody-coated yeast has also been shown to be non-specific (Hollenbach, 2008).

For the symptomatic conditions like pyelonephritis and fungus ball, clear-cut treatment guidelines have already been defined (Pappas et al. 2009). Even in cystitis, the patient is usually symptomatic and fluconazole is given as a first line of treatment. In cases of fluconazole resistant species, the treatment is amphotericin B (deoxycholate, as liposomal amphotericin B achieves low concentration in renal tissue) or flucytosine. However, fluconazole use is limited in the context of advanced renal failure and infections with non-*albicans* species, most notably *C. glabrata*. Echinocandins are usually recommended in invasive or disseminated candidiasis, but in renal involvement their efficacy is not proven, due to their poor urinary bioavailability. Some authors have found that candiduria was eradicated in their patients after parenteral caspofungin therapy was given (Sobel et al. 2007). Parenteral caspofungin achieved high renal tissue concentrations independent of glomerular filtration. Currently, IDSA guidelines do not recommend echinocandins for treatment of candiduria because of very limited clinical data. The feasibility of caspofungin administration via a nephrostomy tube also needs to be determined. It is still to be seen whether the potent activity of caspofungin against *C. glabrata* (a frequent uropathogen) and other non-*albicans Candida* can be exploited or not (Sobel et al. 2007).

Last but not the least, the presence of yeast cells in urine is labelled as candiduria traditionally; but now many new fungi like *Trichosporon* species are emerging as frequent isolates in urine samples of hospitalized patients (Singla et al. 2012). The existing data also reveals a profile of high resistance of the genus *Trichosporon* to amphotericin B and itraconazole with moderate resistance to 5-flucytosine (Sun et al. 2012).

Management and Guidance

Due to increasing *Candida* infections, an increase in non-*albicans Candida* and other yeast, increasingly compromised immune systems increasing predisposition to *Candida* and *Candida* establishing itself at position four in the isolation list from bloodstream infections, we can no longer neglect *Candida*'s isolation from body sites, even from a urine sample. There is a need to establish a *Candida* surveillance programme for all ICU patients and to follow-up patients with candiduria even after their discharge from an intensive care facility, to generate authentic data regarding its pathogenicity. Guidelines available do not dwell much on cutoff definitions and culture techniques to be employed. Various studies have kept their own criteria for analysis of candiduria. Some studies even show gender bias (Achkar et al. 2010). This variability and unreliability in laboratory procedures skews the analysis of the incidence and outcome of candiduria. Most of the studies have concentrated on epidemiology and risk factor evaluation, but it is also important to have data on recurrences and relapses, with uniform definitions for these terms, after treatment has been given. *Candida*, being a master in opportunism, exhibits strain microevolution and genetic variability. This fact has been supported in cases of candidaemia (Toya et al. 2007). Similar reasons could be there for persistence and relapse in cases of candiduria too. Lack of consensus and the availability of limited literature are the main reasons that we cannot formulate the proper guidelines. For the time being, the approach to candiduria remains individualised and proper assessment of the patient's risk factors is the key to treatment. ■

> **"There is a need to establish a Candida surveillance programme for all ICU patients"**

References

Achkar JM and Fries BC (2010). Candida infections of the genitourinary tract. Clin Microbiol Rev; 23: 253-73.

Hollenbach E (2008). To treat or not to treat – critically ill patients with candiduria. Mycoses; 51: 12-24.

Kauffman CA et al. (2000). Prospective multicenter surveillance study of fungiuria in hospitalized patients. Clin Infect Dis; 30: 14-8.

Lundstron T and Sobel J (2008). Nosocomial candiduria: a review. Clin Infect Dis 2001; 32: 1602-7.

Pappas PG et al. (2009). Infectious Diseases Society of America. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis; 48:503-35.

Passos XS et al. (2005). Candida colonization in intensive care unit patients' urine. Mem Inst Oswaldo Cruz; 100: 925-8.

Singla N et al. (2012) Candida colonization in urine samples of ICU patients: determination of etiology, antifungal susceptibility testing and evaluation of associated risk factors. Mycopathologia; 174: 149-55.

Sobel JD et al. (2007) Caspofungin in the treatment of symptomatic candiduria. Clin Infect Dis; 44: e46-9.

Sun W et al. (2012). Nosocomial urinary tract infections of intensive care units patients due to Trichosporon asahii: genotypes, virulence factors and antifungal susceptibility testing. J Med Microbiol. Sep 6. [Epub ahead of print]

Toya SP et al. (2007). Candiduria in intensive care units: association with heavy colonization and candidaemia. J Hosp Infect; 66: 201-6.

A REVIEW OF THE EVOLVING PARADIGM
SHIFT IN INTENSIVE CARE UNIT SEDATION PRACTICES

Most mechanically ventilated, critically ill adults will require some degree of sedation during their intensive care unit (ICU) stay, an area which has been experiencing significant change in recent years. The goal of this article is to afford a concise, state-of-the-art review of the evolving paradigm shift in ICU sedation practices; current indications for prolonged, uninterrupted, and/or deep ICU sedation; clinical pharmacology of commonly used sedatives, including the novel sedative agent dexmedetomidine; comparative efficacy and safety of sedative agents as reported by systematic reviews and meta-analyses; and cost considerations regarding sedative agents used in the ICU.

Derek J. Roberts, *MD*

Departments of Surgery and Community Health Sciences
University of Calgary
Calgary, Alberta,
Canada

Derek.Roberts01@gmail.com

Richard I. Hall, *MD*

Division of Critical Care Medicine
Departments of Anaesthesia, Medicine, Pharmacology, and Surgery
Dalhousie University
Halifax, Nova Scotia,
Canada.

Although prolonged, deep, and/or uninterrupted sedation has long been believed to be indicated for many ICU patients, this belief is now changing. As the technology of mechanical ventilation has evolved with time, is has become increasingly possible for critically ill adults to be awake and interactive while receiving assisted ventilation (Roberts et al. 2012). This shift in the paradigm of ICU sedation has been supported by several randomised controlled trials (RCTs), which have reported that sedation interruption or limitation may be associated with improved outcomes (Roberts et al. 2012).

An Evolving Paradigm Shift in ICU Sedation Practices

Evolution in assisted ventilation over time has made it increasingly feasible for intensivists to avoid neuromuscular blockade and limit the degree of sedation afforded to mechanically ventilated, critically ill adults (Roberts et al., 2012). Sedation interruption may reduce accumulation of sedative drugs and their active metabolites and prevent prolonged sedative drug effects or over-sedation (Augustes & Ho, 2011). Moreover, some RCTs have reported that sedation limitation or interruption may reduce requirements for neurological investigations such as head computed tomography scans, and decrease the length of mechanical ventilation or ICU stay (de Wit et al. 2008; Girard et al. 2008; Kress et al. 2000; Mehta et al. 2008; Schweickert et al. 2009; Strom et al. 2010; Strom et al. 2011). Despite these potential benefits, concerns regarding the practice of sedation interruption remain. These include the possibility of patient discomfort or anxiety, inadvertent removal of the endotracheal tube or central venous catheter, and increased nursing workload (Augustes and Ho 2011; Mehta et al. 2012; Roberts et al. 2012).

In an attempt to better characterise the comparative efficacy and safety of daily sedative interruption among critically ill adults, Augustes and Ho conducted a systematic review and meta-analysis of RCTs in 2011 (Table 1). They identified five RCTs of daily sedative interruption (Anifantaki et al. 2009; de Wit et al. 2008; Girard et al. 2008; Kress et al. 2000; Mehta et al. 2008), which enrolled a total of 669 critically ill adults, and used opioids in combination with midazolam or a mixture of benzodiazepines and propofol for analgo-sedation. Although this meta-analysis reported that daily sedative interruption was safe and may reduce the risk of tracheostomy among critically ill medical and surgical patients, it suffered from several limitations. These include the small number of included patients and the possibility of a type II error in their findings, inconsistency or imprecision in their reported effect estimates, significant heterogeneity in their pooled effect estimates, and the lack of long-term data on mortality or other patient-important outcomes (Augustes and Ho 2011). Finally, although a small observational study suggested that daily sedative interruption may be safe among critically ill adults at risk for coronary artery disease (Kress et al. 2007), the meta-analysis by Augustes and Ho was unable to specifically analyse the outcomes of these patients given that they were uncommonly included in the reviewed RCTs (Augustes and Ho 2011).

Table 1. Efficacy and Safety of Daily Sedative Interruption for Critically Ill Adults as Reported by a Meta-analysis of Randomised Controlled Trials (Augustes and Ho 2011)

Outcome	No.		Effect Estimate (95% CI)	Heterogeneity Statistics*	
	Studies	Patients		I^2	p-value
Efficacy					
Hospital or 28-day mortality	5	699	OR, 0.84 (0.58 to 1.21)	19%	0.29
Duration of ICU stay (days)	NR	NR	WMD, 0.16 (-3.30 to 3.62)	84%	NR
Duration of hospital stay (days)	NR	NR	WMD, -0.67 (-3.00 to 1.66)	81%	NR
Duration of MV (days)	4	364	WMD, 0.72 (-2.49 to 3.92)	71%	0.01
Re-intubation within 48 to 72 hours	4	602	OR, 0.98 (0.55 to 1.78)	28%	0.25
Requirement for tracheostomy	4	602	OR, 0.57 (0.35 to 0.92)	3%	0.38
Safety					
Removal of the endotracheal tube	3	528	OR, 1.30 (0.41 to 4.10)	49%	0.14
Removal of the central venous catheter	NR	NR	OR, 0.95 (0.10 to 9.34)	0%	NR

CI: confidence interval, NR: not reported in the meta-analysis, OR: odds ratio, WMD: weighted mean difference.
*The I^2 inconsistency statistic can be interpreted as the percentage of the observed variability across studies due to factors other than chance. The p-value from Cocran's Q test similarly tests the null hypothesis that the observed variability across studies is due solely to chance (Higgins et al. 2003).

Although avoiding prolonged, deep sedation may improve outcomes, several RCTs have questioned whether sedative interruption is the optimal means of achieving sedation limitation. A recent multi-centre RCT found no difference in median time to successful extubation, duration of ICU and hospital stay, or delirium among 430 medical and surgical critically ill adults allocated to either protocolised light sedation or protocolised light sedation plus sedation interruption (Mehta et al. 2012). Moreover, the sedation interruption group received more opioids and benzodiazepines, and nurses self-assessed their workload as being higher (Mehta et al. 2012). In a second RCT that compared a protocol of no sedation to daily sedative interruption, the no sedation group was reported to have had a shorter duration of mechanical ventilation and hospital and ICU stay (Strom et al., 2010). However, the no sedation group was observed to have had a significantly higher risk of agitated delirium (Strom et al. 2010).

Thus, while it remains unclear which method of sedation limitation (i.e. sedative interruption or limitation via a sedation protocol or other means) is most optimal, it is becoming increasingly obvious that over-sedation is harmful for critically ill adults, and should generally be avoided (Roberts et al. 2012).

Indications for Prolonged, Uninterrupted, and/or Deep ICU Sedation

In certain situations prolonged, uninterrupted, and/or deep ICU sedation may still be appropriate (Roberts et al. 2012). Indications for this approach include:

1. Requirement for alternate ventilation strategies, neuromuscular blockade, or extracorporeal membrane oxygenation for management of significant hypoxemia or hypercarbia;

2. Management of agitation, intracranial hypertension, and airway secretions among those with severe traumatic brain injury (TBI) or other causes of reduced intracranial compliance;

3. Cardiogenic shock as a result of myocardial ischemia or infarction, in order to reduce myocardial oxygen demand; and

4. Certain agitated intoxications associated with an increased risk of harm to self or others (Brodie and Bacchetta 2011; Levine et al. 2011; Pipeling and Fan 2010; Roberts et al. 2011; Roberts et al. 2012; Sanborn and Feldman 2004).

Clinical Sedative Agent Pharmacology

Most available sedative drugs produce their effects by activation of either the gamma-amino-butyric-acid type A (GABAA) receptor (benzodiazepines, volatile anesthetic agents, and propofol) or the alpha-2 adrenergic receptor (dexmedetomidine) (Roberts et al. 2012). GABAA receptor stimulation produces dose-dependent anxiolysis, amnesia, muscle relaxation, sedation, hypnosis, seizure threshold elevation, decreased level of consciousness, and respiratory depression (Devlin and Roberts 2011; Roberts et al. 2012). Activation of the alpha-2 adrenergic receptor produces sedation and may lead to bradycardia and hypotension (Gerlach and Dasta 2007; Hoy and Keating 2011; Roberts et al. 2012).

An understanding of sedative pharmacokinetics is required to achieve an adequate level of sedation for several reasons. Critically ill adults often develop dysfunction of one or more organs involved in drug elimination. Moreover, sedative agents are prone to numerous drug-drug and drug-disease interactions, and their half-lives are often context sensitive. Therefore, critically ill adults exhibit inter-individual variability in sedative drug response, and their dosage regime must therefore be frequently adjusted. This is best accomplished using a tool for sedation assessment, such as the Richmond Agitation Sedation Scale (RASS), and adjusting sedation levels accordingly. Although this topic has clinical relevance, its discussion is complex; therefore, interested readers should refer to more comprehensive reviews.

Although several sedative agents have been used among critically ill adults, below is a discussion of the clinical pharmacology and pharmacotherapeutics of only those that are commonly used or newly available.

Benzodiazepines

Benzodiazepines (diazepam, lorazepam, and midazolam) are frequently used sedatives and differ mostly in terms of their pharmacokinetics (Mehta et al. 2006; Roberts et al. 2012). Midazolam has a significantly more rapid onset and offset of action than lorazepam. Moreover, midazolam and diazepam are more prone to drug interactions than lorazepam as these agents are

ORION PHARMA

INTRODUCING A NEW ERA IN ICU SEDATION:

Effective sedation. Effective response.

Depend on *dexdor*®:

- *Maintain light-to-moderate sedation**
- *Improve patient manageability**
- *Facilitate better patient communication**
- *Decrease time to extubation**

* Jakob S et al. JAMA 2012;307(11):1151-1160, Riker RR et al. JAMA 2009; 301(5):489-99

dexdor®
[dexmedetomidine hcl] injection

Cooperative comfortable sedation

Indication: Sedation of adult ICU patients requiring sedation level not deeper than arousal in response to verbal stimulation (RASS 0 to -3). Dosage and administration: Hospital use only, by healthcare professionals skilled in management of patients requiring intensive care. Administer only as diluted intravenous infusion using controlled infusion device. Dexmedetomidine is very potent and the infusion rate is given per hour. Switch patients already intubated and sedated to dexmedetomidine with initial infusion rate of 0.7 micrograms/kg/h and adjust stepwise within range 0.2 to 1.4 micrograms/kg/h to achieve desired sedation level. Consider lower starting infusion rate for frail patients. After dose adjustment, new steady state sedation level may not be reached for up to one hour. Do not exceed maximum dose of 1.4 micrograms/kg/h. Switch patients failing to achieve an adequate level of sedation with maximum dose to an alternative sedative agent. Loading dose not recommended. Administer propofol or midazolam if needed until clinical effects of ***dexdor***® established. No experience in use of ***dexdor***® for more than 14 days. Use for longer than this period should be regularly reassessed. *Elderly:* No dosage adjustment required. *Renal impairment:* No dosage adjustment required. *Hepatic impairment:* Caution advised; consider reduced dose. *Children aged 0-18 years:* Safety and efficacy not established. Contraindications: Hypersensitivity to dexmedetomidine or the excipients. Advanced heart block (grade 2 or 3) unless paced. Uncontrolled hypotension. Acute cerebrovascular conditions. Warnings and precautions: Intended for use in intensive care setting, use in other environments not recommended. Continuous cardiac monitoring required. Monitor respiration in non-intubated patients. Do not use as induction agent for intubation or to provide sedation during muscle relaxant use. ***dexdor***® reduces heart rate and blood pressure but at higher concentrations causes peripheral vasoconstriction and hypertension. Not suitable in patients who will not tolerate lack of deep sedation and easy rousability. Users should be ready to use alternative sedative for acute control of agitation or during procedures, especially during the first few hours of treatment. Caution with: pre-existing bradycardia; high physical fitness and slow resting heart rate; pre-existing hypotension, hypovolaemia, chronic hypotension or reduced functional reserve; severe ventricular dysfunction; the elderly; impaired peripheral autonomic activity (e.g. due to spinal cord injury); ischaemic heart disease or severe cerebrovascular disease; severe hepatic impairment; severe neurological disorders such as head injury and after neurosurgery. Reduce dose or discontinue if signs of myocardial or cerebral ischaemia. Additive effects may occur with other substances with sedative or cardiovascular actions. Some patients receiving ***dexdor***® have been observed to be arousable and alert when stimulated; this alone should not be considered as evidence of lack of efficacy. Do not use as sole treatment in status epilepticus. Consider possibility of withdrawal reaction if patient develops agitation and hypertension shortly after stopping dexmedetomidine. Not recommended in malignant hyperthermia-sensitive individuals. Discontinue treatment in event of sustained unexplained fever. Undesirable effects: Very common (>1/10): Bradycardia, hypotension, hypertension. Common (1>100 to <1/10): Hyperglycaemia, hypoglycaemia, agitation, myocardial ischaemia or infarction, tachycardia, nausea, vomiting, dry mouth, withdrawal syndrome, hyperthermia. Uncommon (1>1,000 to <1/100): Metabolic acidosis, hypoalbuminaemia, hallucination, atrioventricular block first degree, cardiac output decreased, dyspnoea, abdominal distension, drug ineffective, thirst. See SPC for further details. Pack sizes: 5 x 2 ml ampoules; 25 x 2 ml ampoules;4 x 4 ml vials; 4 x 10 ml vials Marketing authorisation holder: Orion Corporation, Orionintie 1, FI-02200 Espoo, Finland. ***dexdor***® is a registered trademark. Date of Prescribing Information: Sep 2011.

www.dexdor.eu

metabolised by the cytochrome P450 (CYP450) enzymes CYP3A4/CYP2C19 and CYP3A4, respectively. Diazepam and midazolam also have active metabolites that may accumulate in renal failure or during prolonged, uninterrupted intravenous infusions.

Benzodiazepines have several associated adverse drug reactions. These include delirium, hypotension, respiratory depression, and a withdrawal syndrome associated with acute discontinuation. Lorazepam has been associated with paradoxical agitation, and may precipitate in intravenous line tubing if not diluted to a concentration <1mg/ml before administration. Finally, as vials of lorazepam contain propylene glycol, this drug may produce propylene glycol toxicity, which often manifests as an elevated osmolar gap metabolic acidaemia associated with acute tubular necrosis.

Propofol

Propofol is a commonly used sedative and ultra-short acting intravenous anaesthetic agent that has sedative, anxiolytic, and amnestic effects (Roberts et al. 2012). The drug has a very rapid onset of action. Although time to recovery from sedation with this drug is shorter than that for benzodiazepines, its exact duration of action is context-sensitive and dose-dependent, with clearance of the drug occurring through hepatic and extrahepatic glucuronidation and sulphation.

Propofol-related adverse drug reactions include injection-site pain during peripheral intravenous administration, bacterial infection or bacteraemia, respiratory depression leading to apnea, hypotension, and hyperlipidaemia, which may induce acute pancreatitis (Devlin et al. 2005; Devlin et al. 2010; Roberts et al. 2012). Propofol infusion syndrome, characterised by metabolic acidaemia, refractory bradycardia, hyperkalaemia, rhabdomyolysis, hyperlipidaemia, and fatty hepatomegaly is a rare but potentially lethal complication of propofol sedation (Roberts et al. 2012). Management of propofol infusion syndrome includes discontinuation of the drug and supportive management, including use of temporary cardiac pacing when necessary (Roberts et al. 2012).

Dexmedetomidine

Dexmedetomidine is a novel, highly selective, alpha-2 receptor agonist that has sedative, analgaesic, and anxiolytic properties (Roberts et al. 2012). The drug has been approved for sedation of adult ICU patients in North America and Europe. Advantages of dexmedetomidine over other sedative agents include its seemingly lower risk of drug-associated delirium (Gerlach and Dasta, 2007; Pandharipande et al. 2007; Roberts et al. 2012). The drug has also been associated with a reduction in the required dosage of other sedatives and decreased time to extubation when compared with other intravenous sedatives (Riker et al. 2009; Roberts et al. 2012; Venn et al. 1999). As dexmedetomidine is metabolised in the liver by CYP2A6 and N-glucuronidases, dosage reduction should be considered in patients with hepatic impairment (Roberts et al. 2012). Common adverse effects of dexmedetomidine include bradycardia and hypotension (Roberts et al. 2012). As such, the drug is rarely given as a bolus dose, and is instead slowly titrated up to 0.2-0.7 mcg/kg/hour, and then increased in 30-minute intervals until desired sedative effects are achieved (Roberts et al. 2012).

Efficacy and Safety of Sedative Agents as Reported by Systematic Reviews and Meta-analyses

No large RCTs yet exist comparing light sedation with one sedative agent versus another; thus, when choosing between

Table 1. Efficacy and Safety of Daily Sedative Interruption for Critically Ill Adults as Reported by a Meta-analysis of Randomised Controlled Trials (Augustes and Ho 2011)

Study	Focus of Systematic Review	No.		Main Findings
		RCTs	Patients	
Roberts et al. 2011	Compare the effect of different sedative agents on neurologic outcome, mortality, ICP, MAP, CPP, and ADRs among adult ICU patients with severe TBI.	13	380	No agent was more effective at improving neurologic outcome or mortality. Propofol and midazolam had similar effects on ICP, MAP, and CPP. Bolus doses of opioids resulted in transient increases in ICP and decreases in MAP and CPP.
Ho and Ng, 2008	Assess the effect of medium- (24 h to 7 d) and long-term (→7 d) sedation with propofol versus alternative sedative drugs on mortality and length of MV and ICU stay among MV critically ill adults.	16	1386	Mortality similar between propofol and alternative sedative agents. Propofol reduced length of ICU stay versus all other sedative agents combined. However, although propofol decreased length of mechanical ventilation when compared against midazolam alone, it did not reduce length of ICU stay.
Walder et al. 2001	Compare the effect of propofol to that of midazolam on efficacy of sedation, weaning time from MV, ADRs, length of ICU stay, mortality, and costs among MV critically ill adults.	27	1624	Duration of adequate sedation longer with propofol. Average weaning time from MV shorter with propofol. No meaningful conclusions regarding length of ICU stay. Hypotension and hypertriglyceridaemia more common with propofol.
Magarey 2001	Compare the effect of propofol to that of midazolam on quality of sedation; duration of ICU admission, MV weaning, and sedation recovery; and incidence of haemodynamic complications among MV ICU patients.	36	NR	Shorter time to extubation and recovery from sedation with propofol among cardiac surgery and general ICU patients. Propofol associated with a greater risk of hypotension and bradycardia.
Ostermann et al. 2000	Determine which sedatives are associated with the best level of sedation and the shortest time to extubation and ICU discharge among MV critically ill adults.	32	NR	Propofol as effective as midazolam in affording quality sedation. Propofol associated with faster time to extubation, but produces more hypotension than midazolam.

ADR: adverse drug reaction, CPP: cerebral perfusion pressure, ICP: intracranial pressure, ICU: intensive care unit, MAP: mean arterial pressure, MV: mechanical ventilation/mechanically ventilated, NR: not specifically reported in the systematic review, RCT: randomized controlled trial, TBI: traumatic brain injury, h: hours, d: days.

agents, physicians must rely largely on the outcome data previously reported in RCTs of continuous or deeper sedation. Therefore, in an attempt to compare the efficacy and safety of individual drugs, we examined the evidence presented in systematic reviews and meta-analyses that compared two or more sedative drugs or a sedative drug versus placebo (Table 2) (Ho and Ng, 2008; Magarey 2001; Ostermann et al. 2000; Roberts et al. 2011; Walder et al. 2001).

The findings of these studies, in combination with those of a recent structured and comprehensive review of all of the available evidence on sedation for critically ill or injured adults (Roberts et al. 2012), allow for several general conclusions to be made. First, no sedative agent appears to be associated with an improved mortality among critically ill adults or those with severe TBI (Roberts et al. 2012). Moreover, although most sedative agents (except opioid analgaesics) appear to improve intracranial pressure and cerebral perfusion pressure among mixed populations of patients with severe TBI, no drug appears to improve neurologic outcome (Roberts et al. 2011). While propofol and midazolam appear to produce a largely similar quality of sedation among critically ill adults, propofol may be associated with an accelerated weaning time after discontinuation of sedation and possibly a shortened duration of mechanical ventilation (Roberts et al. 2012). However, in contrast to midazolam, propofol increases the risk of hypotension, hyperlipidaemia, and possibly bradycardia. Finally, while dexmedetomidine appears to be associated with a lower risk of drug-associated delirium, this drug increases the risk of hypotension and bradycardia, and has not yet been evaluated among mechanically ventilated adults with TBI (Roberts et al. 2011; Roberts et al. 2012).

> *"while it remains unclear which method of sedation limitation (i.e. sedative interruption or limitation via a sedation protocol or other means) is most optimal, it is becoming increasingly obvious that over-sedation is harmful for critically ill adults, and should generally be avoided (Roberts et al. 2012)"*

Cost Considerations

Although several studies have examined the cost-effectiveness of alternate sedative agents and reported variable results, several factors must be considered when examining these studies (Roberts et al. 2012). These include the drugs' acquisition costs, the efficacy and safety of the sedative, and the setting of the cost-effectiveness analysis (including the healthcare system in which it was conducted) (Roberts et al. 2012). Interested readers may refer to a recent structured review by our group that presented the results of individual cost-effectiveness analyses and an approach to their interpretation (Roberts et al. 2012).

Conclusions

An evolving paradigm shift from deep, prolonged, and\or uninterrupted ICU sedation towards a sedation strategy that limits the degree of sedation is occurring in critical care medicine (Roberts et al. 2012). Although it remains unclear which method of sedation limitation (i.e. sedative interruption, limitation via a sedation protocol, or other means) is most optimal for critically ill adults, over-sedation appears to be harmful and should be avoided (Roberts et al. 2012). However, in certain situations, prolonged, uninterrupted, and/or deep ICU sedation may still be appropriate, such as for management of intracranial hypertension after severe TBI (Roberts et al. 2012). Future research should aim to clarify the indications for limited versus prolonged, uninterrupted, and/or deep sedation, and to define the most appropriate method and agent(s) to be used for sedation limitation among critically ill adults. ■

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

Note to reader

Dexmedetomidine is marketed under the trade name Dexdor® in Europe, where it is indicated for sedation of adult ICU patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to RASS 0 to –3). There are no limits as to the duration of treatment and the dosage recommendations allow the use of a wider dose range from 0.2 mcg/kg/hour up to 1.4 mcg/kg/hour. In addition, the use of a loading dose is not recommended as it may be associated with an increased risk of adverse reactions.

THERAPEUTIC HYPOTHERMIA IN THE ICU: INDICATION, SEDATION AND PROGNOSTICATION

Eldar Søreide, *MD PhD*

eldar.soreide@sus.no

Kristian Strand, *MD PhD*

Michael Busch, *MD PhD DESA EDIC*

Department of Anesthesiology and Intensive Care
Stavanger University Hospital
Stavanger,
Norway

Mild therapeutic hypothermia (TH) applied for 24 hours in the intensive care unit (ICU) is now recommended in comatose survivors of an out-of-hospital cardiac arrest (OHCA), though some uncertainty around indication, clinical management and prognostication still remains. We will probably see this exciting field of intensive care further evolve in the coming years. The aim of this overview is to present some new information related to indications, sedation and prognostication in OHCA patients undergoing TH in the ICU.

Indications

The landmark studies of TH only included OHCA patients with a witnessed ventricular fibrillation (VF), and there has since been an ongoing discussion about whether the initial heart rhythm matters to the injured brain and how to secure widespread implementation of this simple and very effective therapy (Søreide and Sunde, 2008). In other words: Should TH be used indiscriminately and independently of initial heart rhythm and cause of cardiac arrest? From a pathophysiological point of view this makes sense, but due to the overall much worse prognosis in patients with non-shockable rhythms, many centres have been reluctant to cool such patients. Observational studies have provided conflicting results, but a recent systematic review (Kim et al. 2012) found that TH was associated with reduced in-hospital mortality for adult patients resuscitated from non-shockable OHCA. Still, the authors cautioned that only a randomised controlled trial (RCT) could confirm the benefit of TH in patients with a non-shockable rhythm. The soon to be finished targeted temperature management RCT includes patients with non-shockable rhythms as a pre-specified subgroup (Nielsen N et al. 2012) and may therefore provide some answer to this question. Still, we foresee a discussion around indications for cooling in the ICU taking place for many years to come (Sunde K and Søreide E, 2011). Some issues to explore include: Should we cool older patients (Busch and Søreide 2011) than those included in the initial studies? What about patients with a non-cardiac cause (like trauma, drowning, or hanging); should they also be cooled? In the ideal world, RCTs should be performed to answer these questions. However, in the real world, this may not be possible or even needed. If one accepts the notion that TH ameliorates reperfusion injuries in the brain with a very low risk of harm, no further proof of concept studies are needed. Instead, the focus should be on standardising and improving care provided from the scene of the cardiac arrest through to the hospital and further on through the rehabilitation phase. The impact of post-resuscitation care depends on the quality of care in the rest of the chain of survival. Hence, authors have suggested more use of a quality improvement study design (Sanders A 2011) and observational studies (Rea T and Dumas F 2012) in resuscitation science. More use of local quality improvement strategies (Kwok H and Rea T 2011) could improve community-based OHCA survival worldwide.

Sedation

TH requires sedation and analgaesia in order to provide patient comfort and blunt protective reflexes like shivering to increase endogenous heat production (Polderman K 2009). Animal studies have even suggested that sedation is a prerequisite for the neuroprotective effects of TH. Conversely, sedation may cause haemodynamic instability through vasodilatation and myocardial depression. Although required during the induction and maintenance phase of TH, sedation is frequently unwarranted after rewarming, during the phase of prognostication and weaning from mechanical ventilation. Hence, the sedative drugs used should have short duration of action, predictable metabolism during hypothermia, and acceptable haemodynamic side-effects.

In the original landmark trials, the patients were sedated with midazolam and fentanyl. These drugs con-

Targeted Temperature Management

Elements of Success

PRECISION

- One of the most advanced algorithms in use today
- Hospital protocols can be applied

NON-INVASIVE

- Minimal surface area coverage
- Hydrogel coated pad provides direct contact with the skin to maximise energy transfer

EXPERTISE

- Advanced education for hospital therapy leaders
- Built-in education tutorial

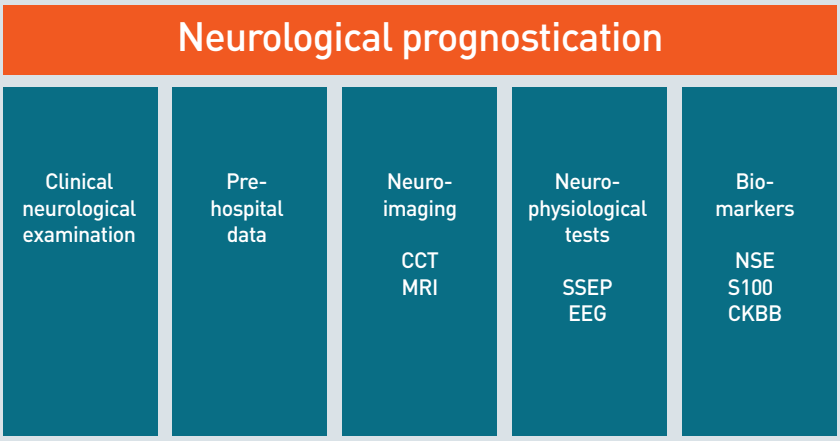
ARCTIC SUN® 5000

TEMPERATURE MANAGEMENT SYSTEM

Please consult product labels and inserts for any indications, contraindications, hazards, warnings, precautions, and instructions for use.

To Learn more, visit www.bardmedical.com/PatientTemperatureManagementSystems

BARD | MEDICAL



Based on Busch M and Søreide E (2008)

Figure 1. Prognostication Information Used in Comatose Out-of-Hospital Cardiac Arrest Survivors in Descending Order from Left to Right.

tinue to be the most widely used agents of sedation and analgesia, with and without neuromuscular blocking agents (Polderman K 2009). A recent study (Bjelland TW et al. 2012) found a reduction in total clearance of propofol, fentanyl and morphine during TH, but surprisingly the same was not found for midazolam. In a RCT, the same authors compared midazolam and fentanyl to a propofol/remifentanil-protocol (Bjelland T 2012b). They found a marked shortening of time from cessation of drug infusions to extubation in the group that could be extubated according to protocol. However, only 35 of the 60 patients included were considered eligible for termination of sedation within 72 hours after start of sedation. Further, the use of propofol and remifentanil resulted in increased haemodynamic instability.

Monitoring of sedation depth by spectral analysis may offer a method of reducing side-effects and detecting seizure activity masked by the administration of paralytic drugs. A protocol applying the BIS-monitor for this purpose has been published (Chamorro C et al. 2010), but no clinical studies have evaluated this approach.

Ten years into the era of TH there is still a profound lack of data on the efficacy and safety of alternative sedation regimes. Worldwide, clinicians apply alternative protocols based on local experience and tradition. Most likely the ideal protocol does not exist. Sedation should be tailored to the individual patient, taking into account the degree of haemodynamic instability, severity of illness and predicted length of mechanical ventilation. An alternative approach would be to convert from longer acting sedatives to short acting sedatives at specific time points during TH, thereby promoting haemodynamic stability in the immediate post-arrest phase, while still reaping the benefits of shorter acting agents.

Prognostication

Before TH, prognostication in comatose post-cardiac arrest was pretty straightforward (Wijdicks EF et al, 2006). TH has definitely changed this, as it alters the natural course of the recovery of hypoxic-ischemic encephalopathy and, as such, affects the prognosis. The sedative drugs used to facilitate cooling and mechanical ventilation also affect prognostication. Previously well-accepted clinical predictors of a dismal outcome are no longer valid (Rossetti AO et al. 2010; Oddo M and Rossetti AO, 2011; Bouwes A et al. 2012). Delayed awakening is observed more often. It has been shown that despite the widespread implementation of TH (Busch M and Søreide E 2008), clinical neurological examination and prehospital information still constitute the main part of prognostication data in such patients (Figure 1). Early prognostication without acknowledging the uncertainty of the used predictors may lead to withdrawal of life support and self-fulfilling prophecies (Perman SM et al. 2012; Bouwes A et al. 2012).

Somatosensory evoked potential (SSEP) has been considered the most reliable prognostic method in TH treated patients, with a false positive rate (FPR) of 0% for poor prognosis (not waking up) (Rossetti AO et al. 2010; Bouwes A et al. 2012). However, a recent study (Leithner et al. 2010) questioned the absolute negative predictive value of an absent bilateral SSEP N20 response. Electroencephalography (EEG) has also been comprehensively evaluated as a prognostic predictor after cardiac arrest (Oddo M and Rossetti AO. 2011). Some investigators have found a FPR of zero for unreactive EEG background activity in TH treated OHCA patients (Rossetti AO et al. 2010). Although the reported FPR=0 with specific SSEP and EEG findings is impressive, the remaining problem is the limited number of patients studied and resulting wide 95% confidence intervals (up to 10%). The predictive value of cranial computer tomography (CCT) and magnetic resonance imaging (MRI) in anoxic-ischemic remain undetermined due to the small number of studied patients, the wide variety of tested parameters and the timing of examinations (Morrison LJ et al. 2010). Considering this, a multimodal, multi-specialty systematic approach to prognostication, which is employed no earlier than 72 hours after rewarming to normothermia and stop of sedation, has been suggested (Morrison LJ et al. 2010; Oddo M and Rossetti AO. 2011; Nolan JP et al. 2012). We think a team approach to prognostication will help us avoid overt misjudgments in the early acute phase. The roles and input of intensivists, cardiologists and neurologists in this respect need to be clarified. The multi-disciplinary approach, making use of advanced neurophysiological testing and imaging in the prognostication, is also an argument for more centralised care of post-cardiac arrest patients. Several authors have pointed towards this and other potential benefits of regionalised post-cardiac arrest care (Morrison LJ et al. 2010; Nolan JP et al. 2012). ■

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

ETHICS IN SIMULATION
FOR INTENSIVE CARE

Anne Lippert, *MD, CHPE*

Deputy Director
Danish Institute for Medical Simulation (DIMS)
Copenhagen, Capital Region of Denmark

Peter Dieckmann, *PhD*

Director of Research
Danish Institute for Medical Simulation (DIMS)
Copenhagen, Capital Region of Denmark

In this paper we investigate the relationship between simulation and ethical care in the intensive care unit (ICU), primarily analysing the uses of simulation-based training in helping learners to improve their ethical decision-making processes and better react to and reflect upon moral dilemmas.

Ethics and simulation-based training can be connected from different perspectives:

1. The whole idea of using simulation is to enhance patient safety. Using simulation to train both technical skills and non-technical skills like communication and decision making is an ethically sound method, as the patient is not endangered in the process of training. While it will not be possible to eliminate the contact between students and patients, this contact can be reduced in the most challenging periods—for example, during first tries—by using simulation (Ziv A et al. 2006).

2. When using simulation-based training, ethical principles must be kept in mind. The patient—even though during these scenarios the patient is a manikin—must be treated with decency and informed about procedures and the like, as if it were a human being. As an example, discussions about the patient case should not be carried out above and around the head of the patient, but a little aside from the patient/manikin. In an ICU setting in particular, where many patients are sedated or otherwise not able to follow the conversation, it can be tempting to forget this.

3. Simulation can and should be used in an ethically responsible way. The instructors have a very powerful position and should use it responsibly, making sure not to negatively expose the participants or to trick them. The participants in simulation- based training must feel safe and well treated even though they put themselves and their abilities on display; the instructors and facilitators must never forget this, but respect the integrity of participants. A clear agreement on the confidentiality of the aspects discussed and the behaviour of the participants seen during simulation training should be expected, and this agreement should be strictly stuck to.

4. Simulation can be used to help learners reflect upon and improve on making ethical decisions during diagnosing and treating patients (Gigerenzer and Gray 2011; Kahneman 2011; Groopman J 2007). Moral dilemmas and ethics in the decision-making processes in simulation-based courses are often incorporated in full-scale simulation. It is this last perspective that we discuss in more detail in this paper. In ICUs, moral dilemmas and difficult decisions are frequent. Training on the decision-making process and how to explain and inform about often sensitive information to relatives is difficult during every day clinical life, except by direct observation or trial and error. Using simulation-based training is getting more and more widespread. This article will go deeper into the thoughts behind this and give several examples.

Bioethical Principles

When considering the use of simulation for training of ethical issues, we need to discuss the standpoints. Four principles have gained some acceptance in healthcare (Lawrence DJ 2012):

1. The principle of respect for autonomy. Through simulation, participants can be sensitised to these issues and, by working through challenging situations in this regard, they can be better prepared and reflect upon their actions. An example is a trauma situation where the victim is a Jehova's Witness and will not give consent to a necessary blood transfusion.

2. The principle of non-maleficence. This can be addressed in situations where the necessary treatment would have negative unwanted effects and where participants might need to balance different treatment options with their known or expected positive and negative effects, or even consider palliative care and allowing the patient to die as he or she wishes instead of maximising the medical possibilities to prolong life.

3. The principle of beneficence. This can be discussed in those situations where the patient presents a certain problem, which might actually be an indicator for larger underlying problems. Consider for example a child patient who shows injury patterns that indicate non-accidental injuries.

4. The principle of justice. This can be worked with in simulation in those situations where the amount of resources is not sufficient for the patients to be treated. A lack of ICU beds is an example of this, which may impose a decision of whether or not to treat patients with very low chances of recovery.

Examples of Scenarios from the ICU

- **Breaking Bad News**

These situations are often trained by role-playing, but can also be incorporated successfully into simulation scenarios in various ways:

AUTHOR GUIDELINES

ICU MANAGEMENT

Content

Articles may focus on any management or practice issue in intensive care related to economics, quality of care or patient outcome. We only accept scientific papers with a clear connection to management and practise issues. We also invite opinions for publication in our Viewpoints section, which can be personal opinions of the author and/or reactions to articles published in prior issues. These are published at the discretion of the editors. Submissions may not have been published previously or be currently submitted for publication elsewhere. Articles must be written by independent authorities and any sponsors for research must be named. If manufacturers are named in an article, the text must present an unbiased view, not in support of any particular company.

Submission Guidelines

Authors are responsible for all statements made in their work, including changes made by the editor and authorised by the submitting author. The text should be provided as a word document via email to editorial@icu-management.org. Please provide a contact email address for correspondence. Following review, a revised version, which includes the editors' comments and recommendations, is returned to the author (at the contact email address) for authorisation.

Length

- Articles: maximum 1400 words (less if figures or tables are included)
- Viewpoints: maximum 700 words
- News/research/product updates: maximum 200 words

Please note that contributions longer than the specified number of words may not be accepted.

Structure

Article texts must contain:

- Title
- Names of authors with abbreviations for the highest academic degree
- Affiliation: Department and institution, city and country
- Main authors are requested to supply a portrait photo (see specifications below)
- Summary of one or two sentences (no more than 30 words) describing the content
- Contact name for correspondence and an email address which may be published with the article
- Website, if appropriate
- Acknowledgements of any connections with a company or financial sponsor
- Introduction, main text and summary/conclusion, with subheadings as appropriate
- Authors are encouraged to include checklists and/or guidelines, which summarise findings or recommendations
- References or sources, if appropriate, as specified below

Writing Style

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

Images

Main authors are asked to supply a portrait photo for publication with their article. This and any other relevant images for publication with an article should be sent by email as separate files (only high resolution images with 300dpi) and their order of placement in the article must be clearly indicated. Only the electronic formats ".tif" or ".jpg" can be used for images, i.e. not Microsoft Word or PowerPoint. Images must be no smaller than 9cm x 9cm at 100% scale. Only images meeting these specifications can be published. If an image has been published before, permission to reproduce the material must be obtained by the author from the copyright holder and the original source acknowledged in the text, e.g. © 2012 Marianna Keen.

Format for References

Any references that are deemed important to understanding of the article should be cited in concise form within the article. Please use the Harvard reference system. Citations within the text for a single author reference should include the author surname and year of publication; for a citation with two authors include both author surnames and year of publication; for more than two authors, include the first author surname followed by "et al." and the year of publication. Multiple citations should be separated by a semicolon, and listed in alphabetical order.

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

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

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

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

Acceptance

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

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

• Acute situations.
A relative (portrayed by one of the simulation crew) phones during the simulation scenario to ask about their loved one. This is done at a critical instant where the patient just deteriorated severely or just had a cardiac arrest. The participant of the course—often a critical care nurse—will have to conduct the conversation with tact and decide how much to tell the relative over the phone, i.e. whether to ask him/her to come to the ICU or whether to tell him/her straight away about the death or imminent threat to the patient.

• More slowly evolving situations.
In a one day course the same patient is followed in multiple scenarios in succession. The patient deteriorates during the day (time lapses between the scenarios are simulated to cover a patient case during a week or more, i.e. the "simulation time" of a day covers a "simulated time" of a week) and news about the deterioration has to be brought to the relatives as part of the scenario. The final scenario is about withholding or withdrawing further treatment and initiating palliative care. These scenarios work particularly well when multi-professional trainings are carried out. The nurses and physicians can collaboratively plan and execute the talks with the relatives, as they would in a real Danish ICU.

• Changing the Objective of the Treatment
The setting for the first part of the simulation is the emergency room, where the participants encounter a seriously traumatised victim of a car accident. The patient is unconscious and a severe head injury must be suspected. The patient also has a liver laceration and is bleeding into the abdomen. In the scenario the participants quickly realise they have to secure the airway by intubation and begin rapid fluid resuscitation. During the scenario, the patient's pupils change from equal and reacting to light to unequal and unresponsive to light; if a urinary catheter is inserted, profuse urinary output is seen; the pulse is decreasing and the blood pressure increasing – all signs of brain incarceration. The participants must detect this and change their mindset from rapid resuscitation of a trauma victim to regarding the patient as a potential organ donor and change the treatment accordingly. Also, a plan for sharing the information and discussing with the relatives must be created. The subsequent debriefing of the scenario facilitates the learner's realisation and reflection regarding this transition.

During a simulation, the participant is called to see another patient who needs intensive care. The participant has been told who the patients in the ICU are and is asked to prioritise: who should be transferred to a ward or a step-down unit (if any patient can be and beds are available) or transferred to another ICU, who should stay, and whether the "new" patient should be admitted or even transferred to another ICU in another hospital.

Role of Simulation

Simulation has lots of potential in the situations described above and others. Learning can be tailored to the situations and to the levels of expertise of the participants and the challenges can be varied systematically. Pregraduate students could be presented with rather straightforward challenges, while consultants might encounter much more difficult and complex cases.

The key learning messages are usually distilled during the post-simulation debriefing, where the facilitator helps participants to reflect upon advantages and disadvantages of different approaches. During such debriefings, it is possible to investigate the situation from the perspective of different ethical principles, including emotional aspects, different norms, values and beliefs. In the scenarios that follow, participants can then try the approaches discussed and again investigate their characteristics and impact.

The facilitators need to be trained for creating the open and constructive atmosphere necessary for such discussions. Scenarios that deal with both medical technical issues and ethical issues are quite demanding for the instructors and facilitators. Not only do they need to be experts in intensive care treatment but a substantial experience and knowledge of ethical decision-making is also required. To be able to write and conduct scenarios and debriefings of this character requires reflection and self-awareness on their behalf.

Inter-Professional Dealing with Ethics

By bringing people from different backgrounds together we can reflect on similarities and differences in their norms, values and beliefs. This could include people of different professions as well as different nationalities. This method fosters discussions and respect for each other's viewpoints and challenges and helps create a better working climate and more ethically sound decisions in practice.

"During such debriefings, it is possible to investigate the situation from the perspective of different ethical principles, including emotional aspects, different norms, values and beliefs."

Conclusion

Simulation offers to create, recognise and use learning opportunities regarding ethical decisions in intensive health care. It poses substantial requirements to make use of these opportunities, but offers powerful learning possibilities in return. ■

References

Gigerenzer G and Gray JA (2011). Better doctors, better patients, better decisions : envisioning health care 2020. Cambridge, MA: MIT Press.
Groopman J (2007). How Doctors Think. Boston: Houghton Mifflin.
Kahneman D (2011). Thinking, fast and slow. 1st ed. New York: Farrar, Straus and Giroux.
Lawrence DJ (2012). Four Principles of Biomedical Ethics (Online: http://archive.journalchirohumanities.com/Vol%2014/JChiroprHumanit2007v14_34-40.pdf, Access Oct. 15). Journal of Chiropratic Humanities. 2007:35-40.
Ziv A et al. (2006). Simulation-based medical education: an ethical imperative. Simulation in healthcare : journal of the Society for Simulation in Healthcare. Jan 1;1(4):252-6.

COLLECTIVE GLOBAL ACTION IN CRITICAL CARE

AN INTERVIEW WITH DR. EDGAR JIMENEZ

As President of the World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM), as well as Head of the Corporate Division of Critical Care Medicine at Orlando Health Physicians Group, Dr. Edgar Jimenez is an expert in intensive care on many levels. In this interview, Dr. Jimenez tells us about the most significant developments he has led in the global intensive care field, and what is still to be done to help in improving quality of care worldwide.

You recently completed an exciting research project on lung injury and acute respiratory distress syndrome (ARDS). Please could you tell us about your most significant findings? What does this signify for the future of critical care for ARDS patients?

The proper adjustment of mechanical ventilation, particularly the positive end-expiratory pressure (PEEP), has been a quest for many research groups. In our translational research lab, we have found that adjusting PEEP using transpulmonary pressures not only improves oxygenation and compliance, as described by Danny Talmor and colleagues (Talmor et al. 2008), but also decreases the extravascular lung water, the inflammatory response (by cytokines), and improves the histological analysis (at 24 hours) when compared to traditional low-volume lung ventilation.

Of course, new advancements, innovative technology and changing processes translate to costs for intensive care units, which can often be too high for hospitals in developing countries to implement. Can you tell me which advancements for ARDS could be most easily and cheaply adopted by developing nations and their hospitals?

The ARDS Network has done a fantastic job in providing us with evidence that the settings of the ventilator can significantly alter the patient's outcome. The low volume ventilation strategy (tidal volume of 6 ml/kg of predicted body weight) is aimed at avoiding inspiratory plateau pressures greater than 30 cm H2O, and is an easy and accessible approach that can be implemented with even the most rudimentary of ventilators, and should be applied across the board to decrease further lung injury. As clinicians increase their resources, which enable them to measure other parameters (compliance, transpulmonary pressures, volumetric capnography, axial tomography, and so on), ventilator strategies could be individualised.

> *"The low volume ventilation strategy… is an easy and accessible approach that can be implemented with even the most rudimentary of ventilators"*

We hope that simple methodologies, like the measurement of transpulmonary pressures using a small oesophageal balloon, can help us in individualising adjustments of the ventilator, thus better adapting to the patient's physiology and decreasing ventilator-induced lung injury.

What research projects do you currently have underway?

In the translational lab we are working on several projects; one of the more interesting protocols involves the utilisation of greater than zero end-expiratory transpulmonary pressures as a prophylactic intervention for ARDS. The pilot results have been outstanding.

What critical care management issues do you think warrant the most consideration and research on a global scale?

Of all the initiatives that WFSICCM is involved in, the most relevant one is that which focuses on the awareness, early recognition and treatment of sepsis. We had the privilege of working with the Merinoff Foundation and the Sepsis Alliance, as well as other major groups —World Federation of Pediatric Intensive and Critical Care Societies, World Federation of Critical Care Nurses and the International Sepsis Forum —in founding the Global Sepsis Alliance. This group has been networking with organisations like WHO, and celebrated its first world-wide Global Sepsis Awareness Day on 13 September, 2012, with an aim of increasing awareness and recognition of sepsis as a major matter, responsible for the vast majority of admissions and mortalities in ICUs around the world. If we could teach people how to prevent sepsis, how to recognise it early and treat it in an expedited (emergency) fashion, many lives would be saved around the world. It has been estimated that one person around the world dies from this condition every two seconds.

What are the most pressing clinical concerns in the developing world?

Specifically addressing critical care delivery, two things are striking: the lack of basic knowledge and the lack of resources. We (at WFSICCM) are supportive of the delivery and availability of courses such as the Fundamental Critical Care Support (FCCS) course from the Society of Critical Care Medicine in the US, as well as the Basic Assessment and Support in Intensive Care (BASIC) course, which was developed in Southeast Asia and is endorsed by the European Society of Intensive Care Medicine (ESICM).

The fundamental theme of the next world congress in August 2013, in South Africa, is "Critical Care for All". We are planning a meeting with Health Ministers from many countries that have

Optimize your ventilation strategy

The AVEA® ventilator with advanced monitoring parameters such as Transpulmonary Pressure, provide information to optimize positive end-expiratory pressure (PEEP) and help improve your overall ventilation strategy.

For more information and access to a free webinar replay on A Physician's Approach to Transpulmonary Pressure Monitoring, visit carefusion.com/TPPWebinarOus.

carefusion.com/TPPWebinarOus

CareFusion

limited resources, to establish priorities regarding the availability of basic resources for the management of critically ill patients; we expect to have a declaration document signed at this meeting.

Can you tell me how WFSICCM is helping to develop and support critical care in the areas of the world that need it most?

We are committed to supporting intensivists within these countries in organising and forming societies that will allow them to develop administrative structures and raise professional recognition and legislative support for their respective country or region, thus helping it to exist and thrive.

During the past three years, we have been able to develop over twenty societies in the Middle East, Central America and the Caribbean, Mongolia, Bangladesh, Pakistan and Eastern Europe, among others.

WFSICCM was instrumental to the formation of the Global Sepsis Alliance and International Forum for Acute Care Trialists (INFACT). INFACT is coordinating with WHO and other organisations to become a network for syndromic surveillance for early detection of potential pandemic outbreaks around the globe (like that of AH1N1 in 2009). Additionally, this group is structured to coordinate Fluid Accumulation Status Trials (FAST trials) to determine best treatment strategies and make recommendations to the public health authorities within a very short period of time from detection.

What significant developments and agreements were made in the federation's recent meeting in Peru?

We concentrated our efforts on finalising the draft, so that we can bring a proposal to our General Assembly in South Africa that will allow us to modernise WFSICCM. As the federation was founded in 1978, some of the statutes are outdated and need revision. We have a vision for the federation to become a more active entity globally; thus, we are considering cutting the four-year cycle between worldwide congresses to two years, and aim to assure proportionate regional composition of the WFSICCM Council, with continued utilisation of web-based meeting tools, so that council sessions can be held more frequently. This would allow a better response to the needs of our member societies.

A conservative culture among physicians has been partly blamed for resistance to change, reluctance to adopt new management methods, and lacking multidisciplinary cooperation. Do you think this is true and, if so, how could the culture slowly be altered?

Physicians, as scientists, may be more reluctant than most to accept change, unless they have compelling evidence that the change will positively impact their patients' outcomes. WFSICCM is committed to providing a forum (web-based) that will allow members to share their educational, therapeutic and innovative experiences on a global scale. We expect this availability of exchanges of information to evolve toward best practices as resources become regionally available. Groups with large resources can mentor initiating ones as they mature in their environment. ■

For more information on the Global Sepsis Alliance, visit: www.globalsepsisalliance.org

References

Talmor D et al. (2008) Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med, 359(20): 2095-104

Continues from page 24

mg), E (500 mg), b-carotene (10 mg), zinc (20 mg), and selenium (300 μg). Although this strategy was safe, it was unfortunately unable to demonstrate efficacy by improving relevant clinical outcomes, including ICU and 90 day survival, in critically ill SIRS patients.

How can we explain the unexpected REDOXS results regarding antioxidants supplementation? Perhaps the absence of an intravenous bolus of selenite as a loading dose inhibited stimulation of the protective effects of selenium as an anti-inflammatory strategy for ICU patients with organ failure. This could be considered as a methodological weakness. Furthermore, some patients received an insufficient daily dose of intravenous selenium. In fact, according to the recent meta-analysis on antioxidant micronutrients (Manzanares et al. 2012), a daily parenteral dose greater than 500 μg is necessary for better clinical outcomes. Although some patients in the REDOXS protocol received 800 μg of selenium, this was administered by either the enteral or the parenteral route, and we do not know enough about the pharmacokinetic profile of enterally administered selenium in SIRS patients. We suspect that enteral absorption in septic shock patients is unpredictable and these doses may have been insufficient.

Among the antioxidant micronutrient strategies, parenteral selenite should be the cornerstone of a pharmaconutrition approach for the critically ill. We believe, there is sufficient evidence to consider initiating high-dose intravenous selenium therapy routinely in SIRS patients, immediately on admission to the ICU. Nonetheless, more research is needed to define the true role of pharmaconutrients in the prevention or treatment of cellular and tissue dysfunctions. A research strategy that combines basic investigations into the pharmacokinetic and pharmacodynamic profiles of pharmaconutrients, with well-powered prospective clinical trials for safety and efficacy, will clarify the future of pharmaconutrition in critical care medicine and clinical nutrition. This type of study would be able to further elucidate the best antioxidant micronutrient approach, including safety, tolerability, and feasibility of high-dose antioxidants in ICU patients. ■

Key References

Angstwurm MW et al. (2007). Selenium in Intensive Care (SIC) study. Results of a prospective, randomized, placebo-controlled, multiple-center study in patients with severe systemic inflammatory response syndrome, sepsis, and septic shock. Crit Care Med, 35: 118-126.

Berger M (2012). Micronutrients: myths and realities. Rev Med Suisse, 7:230.

Forceville X et al. (2007) Effects of high doses of selenium, as sodium selenite, in septic shock: a placebo controlled, randomized, double-blind, phase II study. Crit Care 11:R73.

Galley HF (2011). Oxidative stress and mitochondrial dysfunction in sepsis. Br J Anaesth (BJA), 107: 57–64.

Hardy G, Hardy I and Manzanares W (2012). Selenium supplementation in the critically ill. Nutr Clin Pract, 27:21–33.

Heyland DK et al., Canadian Clinical Trials Group (2006). REducing Deaths due to OXidative Stress (The REDOXS Study): rationale and study design for a randomized trial of glutamine and antioxidant supplementation in critically-ill patients. Proc Nutr Soc, 65:250–63.

Heyland DK et al. (2005). Antioxidants nutrients: a systematic review of trace elements and vitamins in the critically ill patient. Intensive Care Med, 31:327–37.

Manzanares W et al. (2011). High dose selenium reduces ventilator-associated pneumonia and illness severity in critically ill patients with systemic inflammation. Intensive Care Med, 37:1120-1127.

Manzanares W et al. (2012). Antioxidant micronutrients in the critically ill: a systematic review and meta-analysis. Crit Care, 16:R66.

Wang Z et al. (2009). A large-bolus injection but not continuous infusion of sodium selenite improves outcome in peritonitis. Shock, 32:140–6.

OVERVIEW OF CURRENT INTENSIVE CARE SERVICES IN HUNGARY

Ákos Csomós, *MD, DEAA, PhD*
Department of Anaesthesia and Intensive Care
Semmelweis University
Budapest, Hungary

Béla Fülesdi, *MD, PhD, DSc*
Department of Anaesthesia and Intensive Care
University of Debrecen
Debrecen, Hungary

Zoltán Molnár Marin, *MD, DEAA, PhD*
Department of Anaesthesia and Intensive Care
University of Szeged
Szeged, Hungary

Lajos Bogar, *MD, PhD, DSc*
Department of Anaesthesia and Intensive Care
University of Pécs
Pécs, Hungary

János Gál, *MD, PhD*
Department of Anaesthesia and Intensive Care
Semmelweis University
Budapest, Hungary

Introduction

The Hungarian Society of Anaesthesiology and Intensive Therapy (MAITT) was founded as a section within the Hungarian Surgical Society in 1958. Since then, anaesthesia became an independent specialty, and in 1978 it was linked with intensive care. There are four medical universities in Hungary, and during the late 1970s all of them established an Anaesthesia and Intensive Care Department, with the Semmelweis University, Budapest, being the most recent to do so in 1991 (52 years later than in Oxford, England).

There are now 89 intensive care units (ICUs) in Hungary. Traditionally these units were divided into so-called city hospitals, county hospitals and university hospitals, which represented the level of care, with city hospitals providing only short-term ventilation, whereas university hospitals were able to look after patients with multi-organ failure. Nowadays, ICUs are categorised as level 1, level 2 and level 3, based on the facilities of the ICU rather than the size of the city itself. During the years spent in the Eastern Block, healthcare bed provision in Hungary was not a major issue: each city had its hospital, and the services provided were more dependent on political relationships than on the actual need for them. This has changed now: each hospital has its territory precisely set and the level of care is determined by the central, but not by the local, government.

Funding of Intensive Care in Hungary

Funding of intensive care services is done by a diagnosis-related group (DRG), which was introduced in 1993. The main aim of implementing this system— as with almost anywhere in the world— was to reduce healthcare costs. This had led to severe underfunding of intensive care in Hungary. The difference between the actual costs incurred and the reimbursement provided can often be up to three times; but in one extreme example of a case report, in which a patient suffered from tetanus and spent 102 days on the ICU, the actual cost was 4.4 times more than the reimbursement given (Ocsai et al. 2008). Individual funding does not exist; therefore, hospitals refrain from overspending.

The Major Problems with intensive care funding in Hungary are:

1. DRG is a hospital funding system, in which intensive care receives only part of the full DRG reimbursement. Those, who have prolonged length of stay are not taken into account.
2. The complexity of care at level 3 is not reimbursed; level 3 ICUs receive the same amount as Level 1 ICUs; and
3. Equipment costs, maintenance and depreciation are not covered by DRG funding. Hospitals do not have a budget for equipment.

The significant inherited economic difficulties make it very unlikely that funding itself can be increased. Although the total expenditure on health as a percentage of Gross Domestic Product (GDP) is similar to other European countries, the GDP per capita is less than half (Csomos et al. 2005). Furthermore, although there is an increase in per capita spending each year, this can only match the continuous rise in healthcare expenditure.

Organisation of Intensive Care

Apart from intensive care funding, there are nationwide organisational problems as well. This has been shown in the analysis of Hungarian national intensive care data collected between 2000 and 2010, which was presented at the ISICEM Congress 2012 (Csomos et al. 2012). Results showed that during the last 10 years, the total number of active hospital beds decreased dramatically by 33.4% (from 65,532 to 44,300); however, the number of intensive care beds increased by 9.8% (from 1,189 to 1,306). As a result, the percentage of ICU beds to hospital beds increased from 1.89% in 2000 to 2.95% in 2010. The intensive care bed occupancy

Table 1. National Distribution of Intensive Care Services in Hungary .

National data, Year 2010	Total No of intensive care units	Total No of intensive beds	Case Mix Index (mean ±SD)	p value
Level 3 (=University Hospitals)	10	412	7,67 (±4,06)	0.204
Level 2 (=County Hospitals)	30	584	8,08 (±2,89)	0.376
Level 1 (=City Hospitals)	39	280	6,05 (±1,97)	0.093

Table from Csomos et al. 2012

rate ranged between 58.43% and 63.78%; it showed no correlation with the case mix index (CMI) (r^2=0.2799). The number of days spent on ventilator increased from 28.9% to 66.1%, showing good correlation with CMI (r^2=0.9125). Looking at the distribution of services for 2010, there was significantly lower mortality in level 3 units (30%±18%) compared to Level 2 (51%±20%) and level 1 care (56%±19%) (P=0.001 and 0.003), without significant differences in CMI (Table 1). In 2010, the mean ICU bed occupancy rate was 59.5% (SD ±12%), and length of stay was 12.3 days (SD ±3.0). Geographic distribution of intensive care beds per 100,000 population ranged between 7.3 and 27.4 (nationwide average: 12.9 per 100,000). This showed no correlation with regional GDP values (r^2=0.4593). This implies that there is still an unequal distribution of ICU services across the country. The nationwide number of ICU beds per 100,000 population is higher than in the UK, despite Hungary having a much lower GDP. The increase in the number of intensive care beds during 2000 and 2010 does not seem to be justified in Hungary; what is needed before this rises any higher is for more attention to be paid on improving bed occupancy rate.

> *"we are trying to join forces on several forums and improve critical care practice and training in this region of Europe as best we can"*

Table 2. Monitoring of Mechanically Ventilated Patients: Nationwide Survey

	Invasive blood pressure monitoring	Measurement of hourly urine output	At least 2 $ScvO_2$ measurements/day in ventilated patients	Invasive haemodynamics in septic shock
Level 1 care	46,9	51,4	43,7	29,6
Level 2 care	66,0	71,9	54,6	32,3
Level 3 care	92,5	82,5	45,0	46,5
TOTAL	**56,9%**	**58,9%**	**48,2%**	**31,9%**

Table from Bogar et al. 2012

Quality of Care

The quality of care in intensive care varies widely across the nation. This is caused by the virtually non-existent quality-control mechanism. There is a National Board of Anaesthesia and Intensive Care, which works hard in implementing international guidelines and/or creating protocols, including national guidelines on sepsis, acute respiratory distress syndrome, and interhospital transfer, among other areas; however, the adherence to these guidelines is not monitored. This was clearly shown in a recent national survey, which focused on some educational issues of junior doctors as well as quality indicators of intensive care (Bogar et al. 2012). Invasive blood pressure monitoring is only performed in 66% of patients at level 2; further to this, invasive haemodynamic monitoring is only performed in 46% of patients in level 3 care (Table 2). This is an unacceptably low number, and one of the reasons is inadequate funding. As an example, quite a few level 3 ICUs cannot afford to buy disposables for invasive haemodynamic monitoring. Furthermore, there is a very low nurse-ICU bed ratio. In the study by Bogar and colleagues, the correlation analysis of the number of nurses and the monitoring frequency showed a significant relationship: r=0,300, P<0,01 (Bogar et al. 2012).

Number of Nurses

The number of nurses per bed is lower in Hungary than in Western countries, varying between 1.7 and 2.9 (Bogar et al. 2012). There is plenty of evidence in international literature about the positive effect of the number of nurses on ICU outcome. This was also confirmed by a Hungarian study, which conducted a five-year retrospective survey analysing the effect of an adequate number of nurses (Mikor et al. 2008). The study included 449 patients who were treated with multi-organ failure over the ob-

served period. Multivariate regression analysis revealed that the best independent predictors of mortality were the simplified acute physiology score II (P<0,001), the number of nurses (p<0,001) and age (P=0,021).

Education

Anaesthesia together with intensive care is a well recognised basic specialty in Hungary. There is a five-year training programme, including a set time spent in each subspecialty, and two years out of five is to be spent in accredited ICU. The curriculum of training has traditionally been set by the four university departments, and the Competency-Based Training in Intensive Care (CoBaTrICE) syllabus is now translated and awaiting implementation. The national specialist exam consists of an multiple-choice question (MCQ) part and a viva. There was an agreement signed in 2006 between the Ministry of Health in Hungary and the European Society of Anaesthesiology about using part 1 of their exam as the Hungarian national examination. The MCQs are translated into Hungarian. This year, 79 candidates from Hungary took the exam, and the overall pass rate was only 41.77%. Since 2008, it has also been possible to take an independent intensive care specialist exam on top of a few basic specialties: internal medicine, paediatrics and cardiology.

> *"the CoBaTrICE syllabus is now translated and awaiting implementation"*

Table 3. Number of Doctors Specialised and Practicing in Hungary in the Last Five Years

Year	Specialised in anaesthesia and intensive care	Still in medical practice in Hungary
2007	55	36
2008	86	48
2009	54	24
2010	68	48
2011	78	26
Total	341	182

Table from www.eekg.hu

Number of Doctors

The number of doctors working in Hungarian ICUs is way below the international recommendations. For example, it is common practice, especially in small hospitals, for a doctor to provide anaesthesia and ICU cover at the same time, during the daily routine and during on call hours alike. Needless to say, it is due to an inadequate number of doctors in the nation's system. Furthermore, physicians' workload has increased by 13.2% in line with the rise in the total number of anaesthetic procedures performed per physician per year in last five years (Nagy et al. 2010). According to Ministry of Health data, only 53% of doctors (182/341) who became specialists in the last five years still work in Hungary (Table 3). This is a striking number and should warrant the attention of any healthcare provider. However, instead of making moves to improve the conditions, the Ministry of Health introduced a new law last year, which stipulated that doctors who complete their specialist training in Hungary have to sign an agreement that they will work in the country for the same length of time as the duration of their training.

Despite all of the above difficulties, we have a very active and enthusiastic intensive care community, which is willing to change the system. The quality and attendance rate of our national and regional conferences has been extremely high. Research activity is also on the rise. Our international relationships are getting stronger, and now we know that countries of the former "Eastern Block" are facing similar difficulties to us. Therefore, we are trying to join forces on several forums and improve critical care practice and training in this region of Europe as best we can.

For more information about the Hungarian Society of Anaesthesiology and Intensive Therapy, visit: www.anesztinfo.hu

References

Bogar L et al. (2012). National survey of quality in intensive care services in Hungary. Aneszteziológia és Intenzív Terápia, 42(2):69.

Csomos et al. (2012). Intensive care services in Hungary 2000-2010: an analysis of bed numbers, occupancy rates, case mix and economics. Crit Care, 16(Suppl1):P509.

Csomos A et al. (2005). Comparative costing analysis of intensive care services between Hungary and United Kingdom. Intensive Care Medicine.

Mikor A et al. (2008). Influence of the number of nurses on survival in multiple system organ failure. Crit Care, 12: S166.

Nagy G et al. (2010). Hungarian web-based nationwide anaesthesia and intensive care data collection and reporting system: its development and experience from the first 5 yr. British Journal of Anaesthesia, 104(6):711.

Ocsai A (2008). Tetanus: life threatening condition vs. cost-effectiveness. Aneszteziológia és Intenzív Terápia, 38(4):201.

Statistics:

Total Population
9,984,000

Gross national income per capita (PPP international $)
19,550

Life expectancy at birth m/f (years)
70/78

Probability of dying aged under five (per 1,000 live births)
6

Total expenditure on health per capita (International $, 2010)
1,469

Total expenditure on health as a percentage of GDP (GDP)
7.3

Figures are for 2009 unless indicated otherwise.
Source: Global Health Observatory

AGENDA

FEBRUARY

7-8 18th International Symposium on Infections in the Critically Ill Patients
Sevilla, Spain
www.infections-online.es

20-22 10th Annual Canadian Critical Care Conference
Whistler, BC, Canada
www.canadiancriticalcare.ca

MARCH

14-15 IT @ Networking Awards 2013
Brussels, Belgium
www.itandnetworking.org

19-22 33rd International Symposium on Intensive Care and Emergency Medicine (ISICEM)
Brussels, Belgium
www.intensive.org

APRIL

4-6 The 9th Emirates Critical Care Conference (ECCC Dubai 2013)
Dubai, UAE
www.eics.ae

8-10 The 10th Anniversary World Health Care Congress
Washington, DC, US
worldcongress.com/events/HR13000/index.cfm?confCode=HR13000

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

MAY

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

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

JUNE

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

In our Next Issue

COVER STORY
Organ Interaction

COUNTRY FOCUS
Italy

MATRIX
Glycaemic Control
Nutritional Loss

MANAGEMENT
McLaren F1 System to Monitor Health

Letters to the Editor & Requests for References Cited in ICU Management: editorial@icu-management.org

ICU Management is the Official Management and Practice Journal of the International Symposium on Intensive Care and Emergency Medicine.

EDITOR-IN CHIEF
Jean-Louis Vincent, Head, Department of Intensive Care, Erasme Hospital, Free University of Brussels, Belgium — jlvincen@ulb.ac.be

EDITORIAL BOARD
Prof. Antonio Artigas (Spain) — aartigas@cspt.es
Dr. Richard Beale (United Kingdom) — richard.beale@gstt.sthames.nhs.uk
Prof. Julian Bion (United Kingdom) — j.f.bion@bham.ac.uk
Dr. Todd Dorman (United States) — tdorman@jhmi.edu
Prof. Hans Kristian Flaatten (Norway) — hans.flaatten@helse-bergen.no
Prof. Luciano Gattinoni (Italy) — gattinon@policlinico.mi.it
Prof. Armand Girbes (Netherlands) — arj.girbes@vumc.nl
Prof. Jeff Lipman (Australia) — j.lipman@uq.edu.au
Prof. Konrad Reinhart (Germany) — konrad.reinhart@med.uni-jena.de
Prof. Paolo Pelosi (Italy) — ppelosi@hotmail.com
Prof. Peter Pronovost (United States) — ppronovo@jhmi.edu
Prof. Jukka Takala (Switzerland) — jukka.takala@insel.ch

NATIONAL CORRESPONDENTS
Dr. Maurizia Capuzzo (Italy) — cpm@unife.it
Nathalie Danjoux (Canada) — nathalie.danjoux@uhn.on.ca
Prof. David Edbrooke (United Kingdom) — davidedbrooke117@btinternet.com
Prof. Dr. Dominique Vandijck (Belgium) — dominique.vandijck@ugent.be

MANAGING EDITOR
Marianna Keen — editorial@icu-management.org

SCIENTIFIC EDITOR
Dr. Sonya Miller — science@icu-management.org

EDITOR
Lee Campbell

EUROPEAN AFFAIRS EDITOR
Sonja Planitzer

GUEST AUTHORS
Mariam Alansari, Albertus Beishuizen, Lorenzo Berra, Arlene S. Bierman, Paulo Alexandre Boto, Luís Coelho, Andrea Coppadoro, Fernando Leal da Costa, Armand R.J. Girbes, João Gouveia, Jennifer Innis, Maxim Kartachov, Marc Leone, Khalid Maghrabi, Christophe Mariette, Claude Martin, Irit Nachtigall, Riccardo Pinciroli, Benoit Ragonnet, Andrew Rhodes, Claudia Spies, Sandra N. Stapel, Sascha Tafelski, Jean-Louis Vincent, Peter J.M. Weijs

ICU MANAGEMENT IS PUBLISHED BY
MindBYTE Communications Ltd
9, Vassili Michailidi CY-3026 Limassol, Cyprus
E-mail: office@icu-management.org
Website: www.icu-management.org

PUBLISHER
MindByte Communications Ltd — office@icu-management.org

MEDIA CONTACT, MARKETING, ADVERTISING
Katya Mitreva — k.m@icu-management.org

SUBSCRIPTION RATES

One year	Europe	53 Euros
	Overseas	68 Euros
Two years	Europe	89 Euros
	Overseas	105 Euros

Note: Participants of the International Symposium on Intensive Care and Emergency Medicine receive a one year subscription as part of their symposium fee.

ART DIRECTOR
Tassos Kostis — art1@mindbyte.eu

PRODUCTION AND PRINTING
Total circulation print and online: 12,640
ISSN = 1377-7564

REFERENCES
References cited in this journal are provided to ICU Management by the authors and are available on request at editorial@icu-management.org.

VERIFIED CIRCULATION
according to the standards of International Business Press Audits.

ICU Management is independently audited on behalf of ISICEM by AKC

11th Congress of the World Federation of Societies of Intensive & Critical Care Medicine

CRITICAL CARE SOCIETY OF SOUTHERN AFRICA

VISIT SOUTH AFRICA - A WORLD IN ONE COUNTRY

WFSICCM CONGRESS
DURBAN 2013

28 August to
1 September 2013
Durban, South Africa

www.criticalcare2013.com

CRITICAL CARE FOR ALL

PROVIDING MORE FOR LESS

REWARDING EXCELLENCE & INNOVATION

GLOBAL HEALTHCARE IT AND MEDICAL TECHNOLOGY COMPETITION

WINNING PROJECT
GETS PRIZES
WORTH € 20,000

14 - 15
MARCH 2013
Clinique St-Jean
BRUSSELS

FOR MORE INFORMATION:
www.itandnetworking.org

ITa NETWORKING AWARDS 2013