ICU MANAGEMENT

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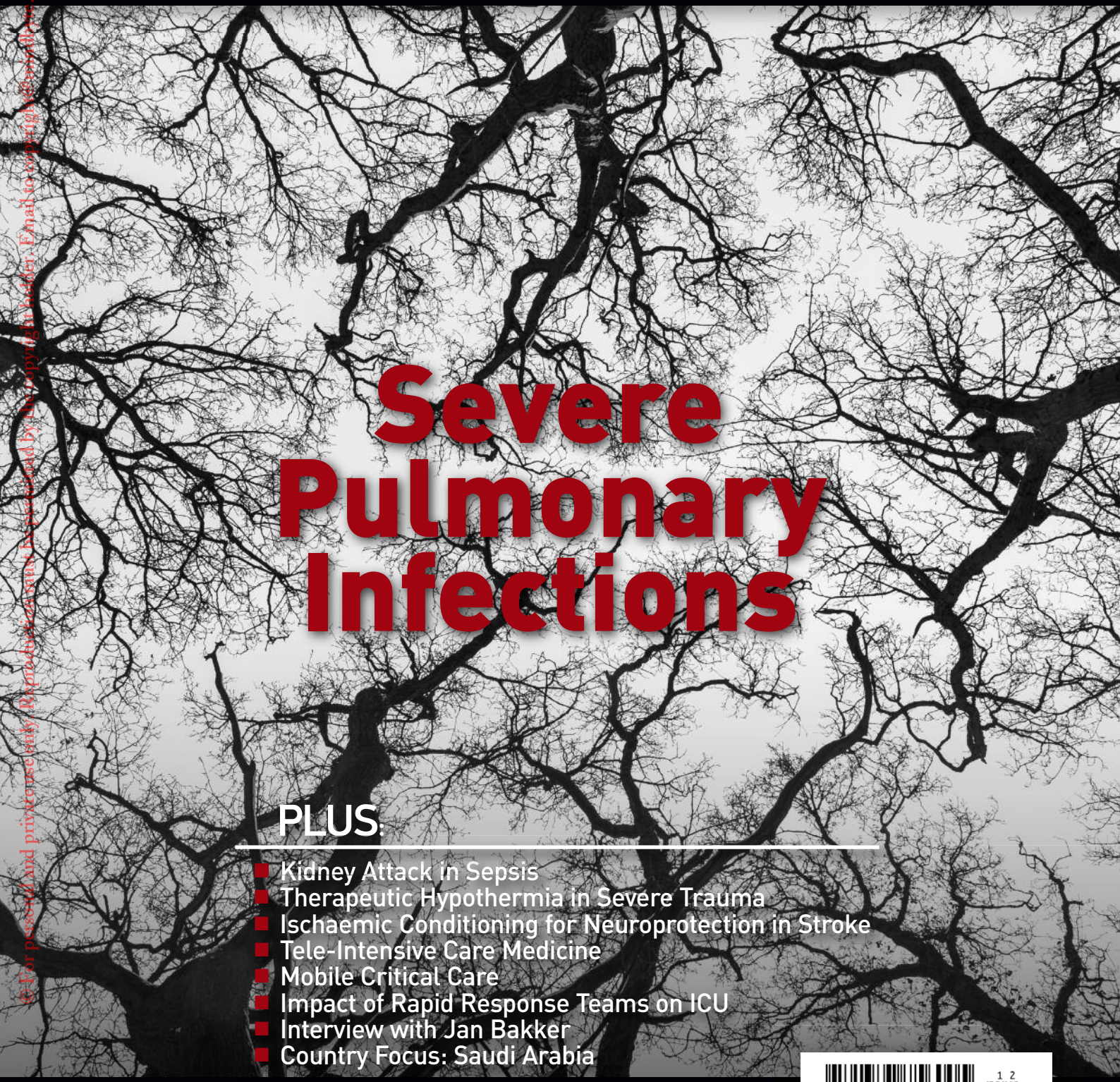

Severe Pulmonary Infections

PLUS:

- Kidney Attack in Sepsis
- Therapeutic Hypothermia in Severe Trauma
- Ischaemic Conditioning for Neuroprotection in Stroke
- Tele-Intensive Care Medicine
- Mobile Critical Care
- Impact of Rapid Response Teams on ICU
- Interview with Jan Bakker
- Country Focus: Saudi Arabia

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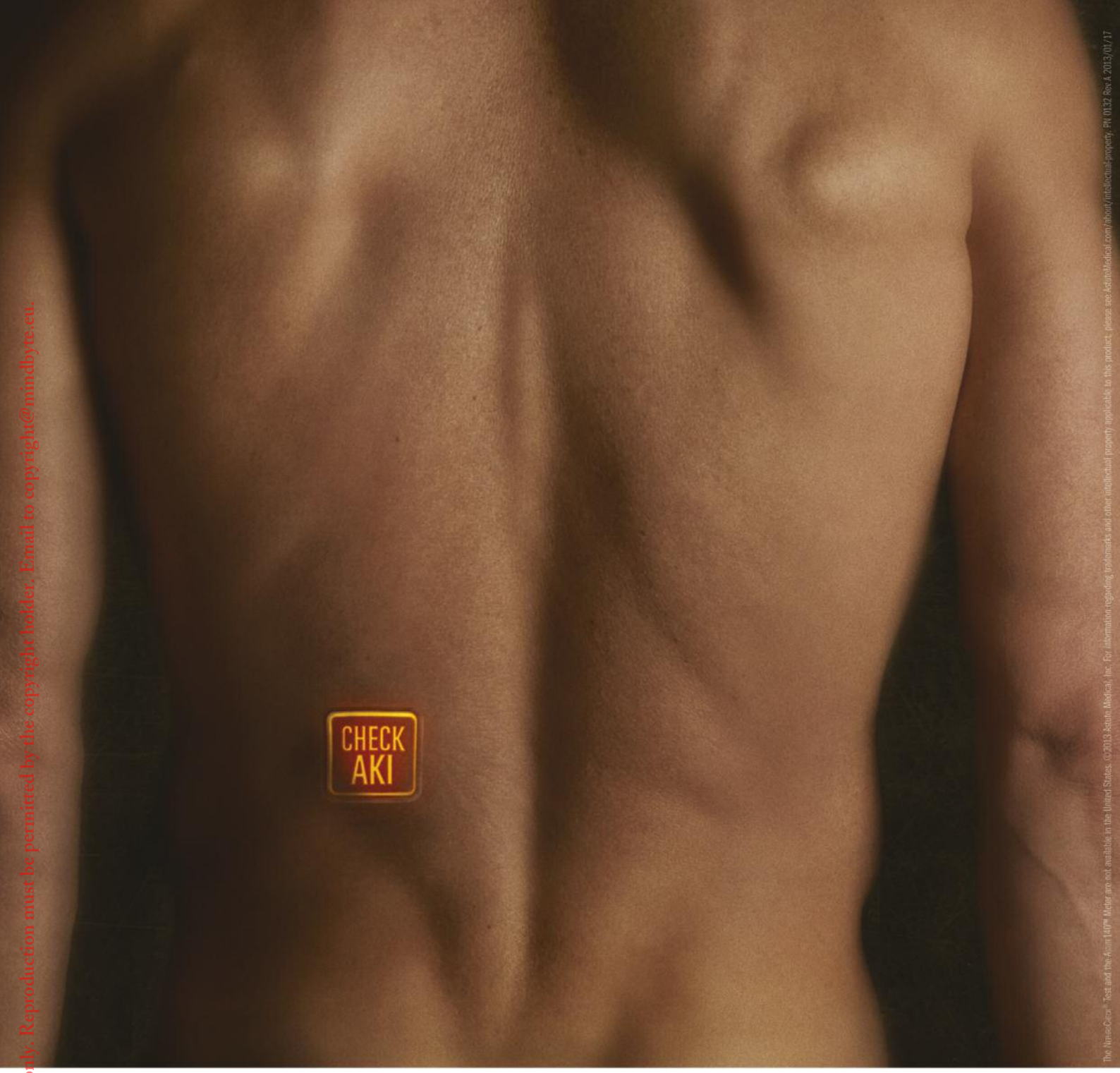

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SEVERE PULMONARY INFECTIONS

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Prevention and treatment of severe pulmonary infections is the subject of this issue's cover story. Lung infections are common in the ICU and have a number of challenges in prevention, diagnosis and treatment.

First, Dr. Matthieu Boisson and Prof. Olivier Mimoz outline measures for the prevention of ventilator-assisted pneumonia (VAP), which they think must be a priority in the management of critically ill patients. The incidence of VAP has been hard to measure in the absence of objective diagnostic criteria. Dr. David Pearson and colleagues discuss the need for objectivity for surveillance of patients treated by mechanical ventilation, in the context of the U.S. Centers for Disease Control and Prevention's Ventilator Associated Event diagnostic key. It is important that this new tool is validated, to provide objective validated criteria for the diagnosis of ventilator-associated events. Next, Prof. Michael Niederman describes recent findings in the use of aerosolised antibiotics in mechanically ventilated ICU patients, and argues that it may be time to reevaluate their use for therapy of lower respiratory tract infection.

In the final article in our Sepsis series, Prof. Martin Matejovic and colleagues look at the ongoing debate on the role of haemodynamic alterations in sepsis-related renal failure.

In the Matrix section, Prof. Samuel Tisherman reviews the role of therapeutic hypothermia in severe trauma, which may be of benefit for haemorrhagic shock, traumatic cardiac arrest, traumatic brain injury and spinal cord injury. Next, Prof. Terence Valenzuela looks at the potential of ischaemic conditioning, including preconditioning, preconditioning and postconditioning, for neuroprotection in stroke.

In the Management Section, Univ.-Prof. Gernot Marx and Mr. Rainer Beckers discuss the promise of tele-intensive care medicine in improving healthcare outcomes, workflow, efficiency and quality.

As we approach the 100th anniversary of World War I, it is salutary to be reminded of the advances in military medicine. Mobile critical care in combat, and the benefits flowing on for remote critical care and evacuation of civilians in natural disasters, is the subject of the article by Lieutenant Colonel Michael Reade. Next, Dr. Chris Subbe highlights the impact of rapid response teams on the ICU. Such teams improve referral to the ICU and affect rates of admissions. Further improvements may be gained through advances in technology.

Prof. Jan Bakker is well-known for his research on blood lactate. He is interviewed for this issue on this and other interests, which include ethics and end-of-life care.

Our Country Focus is Saudi Arabia. Dr. Mariam Alansari and Prof. A.H. Alzeer discuss the Kingdom of Saudi Arabia's healthcare framework for Haj, the annual mass gathering of pilgrims to Mecca, which brings unique challenges.

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

Jean-Louis Vincent

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ICU Management

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INDUSTRY AND RESEARCH NEWS

New Receptor Holds Clue to New Treatment for Sepsis

A newly discovered nociceptin receptor in the body might be important in the body's response to sepsis, according to researchers.

The body's initial response to sepsis is to produce an intense reaction from the immune system to fight the infection. This involves activation of white blood cells, stress hormones and other substances, known as 'inflammatory mediators', which cause inflammation. It has already been found that nociceptin is involved in inflammation; it affects how white blood cells work. This suggests strongly that nociceptin has an important role in the body's response to inflammation and sepsis.

Professor David Lambert and Dr. Jonathan Thompson of the Department of Cardiovascular Sciences at the University of Leicester in the UK recently published two collaborative research papers. Their theory is that nociceptin makes inflammation or sepsis worse; by blocking the nociceptin system, the symptoms of sepsis could be reduced, which could lead to new treatments.

In the first paper, Professor Lambert, in collaboration with Dr. Zoë Brookes at the University of Sheffield and Dr. Girolamo Calo and Dr. Remo Guerrini at the University of Ferrara, has shown for the first time using fluorescent chemistry, which was designed in Ferrara, that nociceptin receptors are found on blood vessels with no nerve supply and that in a laboratory model of sepsis, blocking these receptors is protective. In the second paper, Dr. Thompson and Professor Lambert have discovered that nociceptin levels in the bloodstream are elevated in patients with sepsis in Intensive Care, demonstrating that nociceptin activation might be important in critically ill patients suffering from sepsis.

Dr. Thompson said, "Clinicians are making progress in the early recognition and treatment of sepsis, but we have no specific drugs that effectively stop the spread of inflammation, or the biological processes involved. We have found that nociceptin, a chemical similar to endorphins produced in the body, is increased in inflammation and sepsis. This suggests that drugs which block the nociceptin receptor could dampen the widespread inflammation that occurs in sepsis, and improve outcome. More work is needed, but these drugs are being developed. If they are effective then we could potentially save many lives."

Professor Lambert added, "I am particularly excited by these findings as they translate many years of laboratory work into a possible target for this disease."

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Do Patient Data Management Systems Affect Revenue in the ICU?

A recent article in BMC Medical Informatics and Decision Making by Ixchel Castellanos and colleagues looked at the financial implications of introducing a Patient Data Management System. This study was a retrospective observational and explorative analysis of cost and reimbursement data of a hospital ICU in Germany for three years before and three years after the system introduction. The authors believe that they are the first to present a ROI calculation for a PDMS based on the actual costs and revenues of an ICU. They note that they were surprised that there are few typical parameters, which may be used to compare different institutions, and hope that their approach may encourage institutions to publish comparable data. They found a considerable increase of costs and reimbursement over six years, which was largely unaffected by PDMS introduction and no net cost savings when comparing the considerable investment costs with the potential effect on revenue. They surmise that the introduction of a PDMS has probably minimal or no effect on reimbursement. They conclude, "In our case the observed increase in profit was too small to amortise the total investment for PDMS implementation. This may add some counterweight to the literature, where expectations for tools such as the PDMS can be quite unreasonable."

Reference

Castellanos I et al. (2013) Does introduction of a Patient Data Management System (PDMS) improve the financial situation of an intensive care unit? BMC Medical Informatics and Decision Making, 13: 107. Available at: http://www.biomedcentral.com/1472-6947/13/107

Best Practices for Tele-ICUs: NEHI Brief

NEHI, a national nonprofit health policy institute published a brief in November, which outlines best practices for tele-ICUs. While the technology used in the tele-ICUs surveyed in the United States is similar, practices vary. The NEHI argues that these emerging new patterns of use have the potential to make tele-ICU coverage more scalable and accessible to more hospitals and more beds.

The brief identifies six critical best practices, including: collecting pre-coverage outcomes prior to tele-ICU initiation; rotation of clinical staff between the monitoring centre and the physical ICU; extending coverage outwith the ICU via wired beds and mobile carts.

"The use of tele-ICU care is entering a second phase of adoption," said NEHI president Wendy Everett. "And as more tele-ICUs are implemented, the need for best practices to guide this expansion is critical."

Reference

Bartolini E, King N (2013) Emerging best practices for tele-ICU care nationally. NEHI Issue Brief. Available at: http://www.nehi.net/publications/82/emerging_best_practices_for_teleicu_care_nationally

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PREVENTION OF VENTILATOR-ASSOCIATED PNEUMONIA

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Introduction

Healthcare-associated infections have become a challenge in public health policy. In critically ill patients, ventilator-associated pneumonia (VAP) is the most frequent healthcare-associated infection. Depending on studies, 10% to 30% of ventilated patients will develop a VAP during their ICU stay (Chastre et al. 2002). VAPs account for heightened morbi-mortality, lengthened stays in intensive care and increased treatment costs. These infections also trigger a rise in the consumption of antibiotics, which favours the development of bacterial resistance. Therefore, decreasing VAP incidence must be a priority in the management of critically ill patients.

Physiopathology of VAP

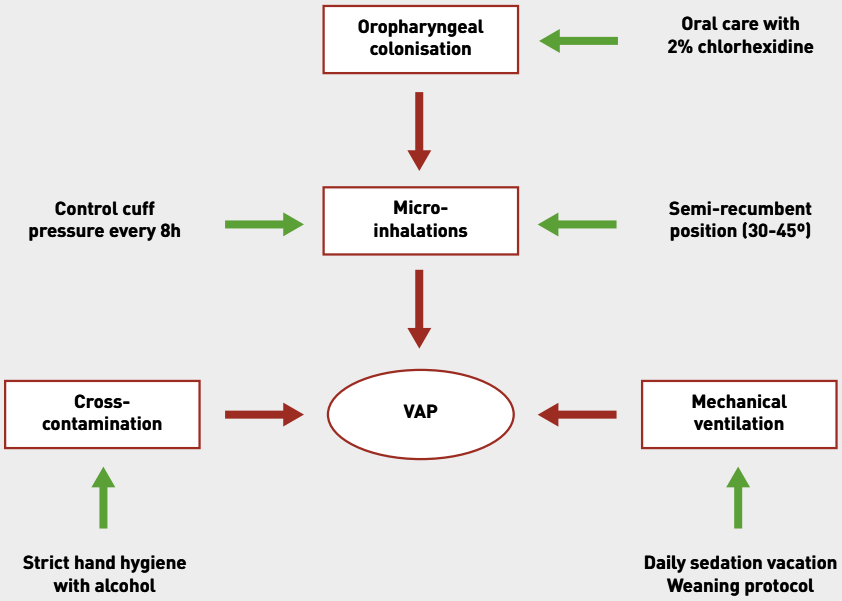
Enhanced knowledge of the complex physiopathology of VAP has led to the development of effective preventive strategies (see Figure 1). Colonisation of the upper and digestive airways by micro-organisms originating in the patient or coming from another patient through cross-transmission is the predominant mechanism of initiation. Fostered and favoured by the presence of a tracheal tube, it is at the origin of tracheal colonisation through the bacterial aspiration resulting from the passage, around the tube cuff, of oropharyngeal secretions in the vicinity of the trachea and the lower respiratory tract (Kollef 2004).

General Rules

Prevention measures are primarily based on the universal principles of standard hygiene. They are meant to prevent cross transmission of pathogens. These measures include basic hygiene: alcohol-based hand rubbing, wearing gloves for one patient - one activity. Screening for carriage of methicillin-resistant Staphylococcus aureus (MRSA) and other multi-drug resistant bacteria according to local ecology, and the use of contact precautions should be utilised to prevent cross-contamination (Siegel et al. 2007). Staff training with regard to these measures helps to ensure respect of their application.

More recently, universal decolonisation with intranasal mupirocin and daily bathing with chlorhexidine-impregnated cloths has been shown to be more effective than screening and isolation to prevent healthcare-associated infections (Huang et al. 2013). However, the lack of impact on the incidence of non-staphylococcus infections and the risk of the development of resistance to mupirocin and/or chlorhexidine with their wide use are limitations

Figure 1. Diagnostic Key for Ventilator-Associated Events



to the generalisation of this practice.

Avoiding Mechanical Ventilation Whenever Possible

While intubation and mechanical ventilation are major risk factors for VAP, recourse to non-invasive ventilation (NIV)is a safe and interesting alternative means of risk reduction. Indeed, its use is safe and effective to prevent VAP compared to the use of invasive mechanical ventilation (Hess 2005; Squadrone et al. 2005).

If intubation and duration of mechanical ventilation are among the most recognised risk factors for VAP, the first days of ventilation are the riskiest of all. As a result, early weaning from the ventilator and extubation should be considered as soon as the clinical situation allows for them. Excessive sedation/analgesia prolongs the duration of mechanical ventilation. Application of a sedation/analgesia algorithm integrating daily interruption of sedative drugs and daily spontaneous breathing trials is to be recommended (Girard et al. 2008). Conversely, failure of weaning leading to reintubation has been identified as a risk factor for VAP, of which incidence is heightened in the event of accidental extubation (de Lassance et al. 2002).

Limiting Micro-Inhalations

Intubation should preferably be orotracheal. Keeping a sufficient level of pressure in the tube cuff of the tracheal tube is of fundamental importance in limiting micro-aspirations. Ideally, pressure should be maintained between 20 cmH_2O (15 mmHg) and 30 cmH_2O (22 mmHg). If it is too low, there exists a risk of inhaling the subglottic secretions accumulated from the oropharynx, which is known to take on a preponderant role in VAP incidence. Regular monitoring of tube cuff pressure is consequently recommended, but its optimal frequency has yet to be clearly determined. To reduce these risks, automatic devices allowing for continuous regulation of tracheal tube cuff pressure have been developed. In a randomised study, the percentage of patients with a micro-inhalation of gastric contents was half lower in the group of patients where tube cuff pressure was maintained by a pneumatic system than in the control group where tracheal tube cuff was maintained by verification and adjustment 3 times a day with a manual manometer (Nseir et al. 2011). Moreover, the microbiologically confirmed VAP percentage had significantly diminished in the intervention group compared to the control group (9.8% vs. 26%; p = 0.032).

The interest of the semi-recumbent position has been assessed in several studies. The randomised and pioneering study by Drakulovic et al. compared the strictly supine rest position to the semi-recumbent position (objective 45°). Whether diagnosis was clinical or microbiological, the authors found a significant VAP reduction. Nevertheless, a recent multicentre prospective study compared the semi-recumbent position (objective 45°) to a position characterised as 'standard' (Van Nieuwenhoven et al. 2006). Notwithstanding monitoring more than once a day by a dedicated staff, the objective of 45° was reached in only 15% of the patients; mean angulation oscillated over the first week between 23° and 29°, while in standard position patients, its oscillation ranged from 10° to 15°. Given these clinical conditions, VAP incidence did not differ from one group to the other. It would consequently appear that even if the principle of a head-up position is accepted, the level of elevation to be reached remains undetermined; either an objective of 45°, which is difficult to attain, or else an objective ranging from 30° to 45°, which is more realistic, should be preferred.

Closed tracheal suction systems have been proposed to limit the risk of VAP. Unfortunately, threemeta-analyses have not found the closed system to be preferable in terms of lower VAP incidence, mortality or duration of stay in intensive care; as a result, it is not recommended(Subirana et al. 2007). The potential benefits of diminished crossed transmissions through this suction system have likewise failed to be demonstrated (Jongerden et al. 2007).

Subglottic secretion drainage is possible through use of a tracheal tube equipped with an orifice located above the cuff. Numerous studies have been conducted, and their findings have been summarised in a meta-analysis (Muscedere et al. 2011), showing that the use of subglottic aspiration is associated with a reduction of VAP risk. In parallel, duration of ventilation and stay in intensive care were significantly reduced, but without any effect on mortality and duration of hospital stay.

> *"Decreasing VAP incidence must be a priority in the management of critically ill patients"*

Limiting Oropharyngeal Colonisation

In intubated patients the modifications of saliva, with reduction of both its amount and the immune factors concentration, facilitates oropharyngeal microbial proliferation (Bonten et al. 1996). To limit this phenomenon, several ways have been proposed. Selective digestive decontamination (SDD), when associated with systemic antibiotic therapy, brings down VAP incidence (D'Amico et al. 1998) and mortality (Vandenbroucke-Grauls et al. 1991), while SDD alone reduces nothing other than the incidence of VAP. In spite of the interest of the aforementioned results, this preventive method is only marginally used and has not been included in the most recent recommendations. The probable reason for this reluctance resides in an ecological risk along with the potential emergence of multi-resistant bacteria(Daneman et al. 2013).

Oropharyngeal decontamination through local application of an antiseptic(chlorhexidine or povidone-iodine) for the purposes of limiting local flora represents another interesting method of VAP prevention. A meta-analysis involving 2481 patients showed some VAP diminution (Labeau et al. 2011). The benefits of chlorhexidine are more substantial in cardiothoracic surgery patients or when a high concentration (2%) is used.

Conclusion

Many specific preventive measures have been studied to reduce the incidence of VAP. The most important include oro-tracheal intubation, maintaining tube cuff pressure between 25 and 30 cmH_2O, use of a sedation-analgesia algorithm allowing for early weaning from ventilation, privileging use of non-invasive ventilation, the semi-recumbent position at 30-45°, and regular nasal and oro-pharyngeal decontamination with chlorhexidine. All these measures must be used in bundles. ■

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1. Lorente, et. al, Influence of an Endotracheal Tube with polyurethane cuff and subglottic secretion drainage on Pneumonia, May 2007. 2. Data on file 510K Clearance K120985. 3. Data on file #R151219. Evaluation of Fluid Leakage Past Tracheal Tube Cuffs: Effects of Tracheal Size and Cuff Pressure.

Kimberly-Clark

VAP, VAC, IVAC AND VENTILATOR-ASSOCIATED EVENTS:

THE NEED FOR OBJECTIVITY FOR SURVEILLANCE

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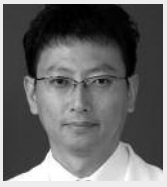

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The novel U.S. Centers for Disease Control and Prevention's Ventilator Associated Event (VAE) diagnostic key will enable sensitive tracking of all significant pulmonary complications of mechanical ventilation. The use of objective, validated criteria will provide more accurate and reliable data for local audit and interhospital benchmarking. We anticipate that it will replace VAP incidence as a quality assurance tool in critical care.

Background

The incidence of ventilator-associated pneumonias (VAPs) has long been considered the reference benchmark for guiding continuous quality improvement in mechanically ventilated patients. In recent times, however, its validity as a tool for such surveillance has been called into question. This article will discuss the evolution of ventilator-associated pneumonia into the ventilator-associated event (VAE) and the importance of now validating this tool for use in both internal and external quality assurance processes.

Ventilator-Associated Pneumonias

A VAP is diagnosed when a mechanically ventilated patient satisfies certain systemic, clinical and pulmonary criteria (Horan et al 2008). Within these diagnostic criteria scope for subjectivity exists, resulting in an algorithm favouring sensitivity over specificity for VAP diagnosis. As the treatment of VAPs is antibiotics, the knock-on implications for this lack of specificity, in terms of antimicrobial stewardship, are clear. There remains no gold standard for VAP diagnosis in vivo, and, as a consequence, VAP prevalence is very difficult to quantify accurately. Evidence from prevention-targeted randomised controlled trials would suggest that this figure lies somewhere between 16% and 21% (Lorente et al 2012; Rello et al 2002; Rello et al 2013; Barbier et al. 2013; Melsen et al. 2013). Compounding this baseline variation is a lack of objectivity within some of the diagnostic criteria, reflected both in a widespread inter-observer variability in VAP diagnosis (Klompas 2008), and in post-mortem studies revealing that as many as half of all cases are misdiagnosed (Tejerina et al. 2010). Mathematical modelling has also been able to demonstrate that the prevalence of other pulmonary conditions will affect the rate of VAP diagnosis, despite a constant, fixed VAP incidence (Klompas et al. 2008).

Several bodies have attempted to standardise and increase the specificity of diagnostic criteria (Lorente et al. 2012; Torres et al. 2009; Guidelines 2009), of which the Centers for Disease Control and Prevention (CDC)'s version is the most widely utilised. Studies performed at the CDC's prevention epicentres by Klompas and colleagues (Klompas et al, 2011) advanced this by replacing subjective criteria with objective, quantifiable data for pulmonary deterioration where possible. They then applied this modified VAP definition to retrospective data, and were able to demonstrate improved capacity to predict 'hard' outcomes of duration of mechanical ventilation, ICU length of stay and mortality when compared with their traditional VAP definition. Although clearly demonstrating an association between objective data and clinically relevant outcomes, this revised tool did not increase specificity for VAP diagnosis.

Importance of VAP

For the very reasons outlined above, ascribing accurate attributable mortality to VAP is fraught with confounding issues. A recent meta-analysis concluded that the overall attributable mortality of VAP is 13% (Melsen et al 2013). Original patient data were taken from 24 randomised controlled trials assessing a broad range of VAP prevention techniques. VAP incidence was most commonly the primary outcome rather than mortality. Acknowledging that no gold standard exists for VAP diagnosis, the authors grouped included studies into categories, depending upon whether invasive specimens were required as part of the diagnostic key or not, thus allowing for regional variation in practice. Noteworthy here is an Australian-wide study showing little if any use of bronchoalveolar lavage in the diagnosis of VAP (Boots et al. 2005). As suspected, there was a variation between subgroups with higher rates for surgical patients and patients with mid-range severity as expressed by acute physiology and chronic health evaluation (APACHE) and simplified acute physiology score (SAPS) at admission (Melsen et al. 2013). The authors of the meta-analysis concluded that

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the predominant cause of this increased risk of dying was the prolonged exposure to intensive care therapies (Melsen et al. 2013).

Quality Assurance

Any quality assurance marker must be evidence-based, clinically relevant and have optimal sensitivity and specificity. In addition, when used as a surveillance tool, it must be sufficiently common and preventable to have a demonstrable impact upon morbidity and mortality. As a subdivision of nosocomial infection, VAPs fulfill some of these criteria, but what is not often reported is the non-modifiable contribution to their aetiology. As an example, it would be hard to believe that an elective post surgical patient has the same baseline risk profile as a complicated medical patient; so it would not be fair to draw conclusions on standards of underlying care based solely on VAP incidence. Further emphasising the unreliability of this data was a study by Klouwenberg and colleagues (2013), who were able to demonstrate concordance in diagnosis of just 35%, for the same patient cohort, between different personnel responsible for surveillance reporting. As a tool for internal audit, if confounders of personnel and diagnostic criteria can be controlled for, then VAP surveillance may be of use, but when the generated data is used for external inter-ICU comparison then the impact of confounding bias is too great. Many interventions and 'bundles' have targeted VAP prevention (Melsen et al. 2013; Bouadma et al. 2012), with subsequent falls in VAP rates. However, a failure to reliably improve upon 'hard' clinical outcomes such as length of stay and mortality would suggest that in addition to the intervention, surveillance artifact may be present. Although this discordance between VAP rate lowering and static mortality rates may just relate to a failure to power for these outcomes, a more sinister aetiology may be true: in an era where financial disincentives are applied to perceived poor clinical performance, some hospital administrators have been accused of 'playing' the system to avoid penalty (Magill and Fridkin 2012). In the UK, the NHS has placed the responsibility for data integrity firmly at the feet of clinicians, advocating for firm clinician engagement in developing quality assurance tools. In turn, this has led to some campaigning for the abandonment of VAP incidence as a quality assurance tool in favour of newer markers (Shorr and Zilberberg 2012).

In regards to ventilator-associated events, whilst VAPs may be the most frequently documented they are far from the only complication of mechanical ventilation. Barotrauma, atelectasis and pulmonary oedema could all be considered to be common, preventable complications independently associated with poor clinical outcomes. For this reason, their incidence should have a role to play in benchmarking and subsequent quality improvement.

Thus, criticism can be grouped into three broad categories: i) the poor specificity for VAP of commonly used diagnostic tools ii) a multi-factorial lack of concordance in diagnosis between surveillance personnel, and iii) the lack of importance placed upon other, highly morbid, complications of mechanical ventilation in quality control initiatives.

> *"Objective, commonly captured data for all patients on ventilators is a more logical way forward"*

Ventilator-Associated Events and Ventilator-Associated Conditions

Klompas et al. explored the feasibility of purely objective diagnostic surveillance criteria for VAP (Klompas et al. 2012). Thirty-two different candidate definitions were created, composed of different combinations of the following signs: i) three thresholds for respiratory deterioration defined by sustained increases in daily minimum positive end-expiratory pressure or FiO_2 after either 2 or 3 days of stable or decreasing ventilator settings, ii) abnormal temperature iii) white blood cell counts iv) purulent pulmonary secretions defined by neutrophils on Gram stain, and v) positive cultures for pathogenic organisms. They concluded that only definitions requiring objective evidence of respiratory deterioration, detected through documentation of alterations in respiratory support, were significantly associated with increased hospital mortality. Crucially, placing these alterations on the first level of a novel diagnostic key would enable tracking of not only VAPs but also clinically significant non-VAP complications of mechanical ventilation. Collectively, these complications would be termed Ventilator-Associated Events (VAEs). As a surveillance tool, previously privileged pathologies would now be trapped and available for quality control.

Accordingly, in 2013 the CDC National Healthcare Safety Network (NHSN) introduced VAE surveillance, a novel tool for monitoring mechanically ventilated patients. Designed to replace VAP surveillance, VAE monitoring would provide objective, reproducible data tracking all complications of mechanical ventilation leading to an alteration in ventilator settings and an increase in respiratory support. This restratification comprises a three tiered mode (see Figure 1). Entrance into the VAE surveillance tool is through detection of an increase in daily minimum PEEP or FiO_2, objective data that can be reliably trapped by clinical information systems. In this way, all patients with clinically significant pulmonary complications are identified and their data recorded, irrespective of whether a VAP or non-VAP is causative. At this level they are referred to as Ventilator-Associated Conditions (VACs). The second tier, infection-related ventilator-associated complications (IVAC), is reached when VAC criteria are complemented by: i) traditional SIRS (systemic inflammatory response syndrome) signs of leucocytosis and abnormal temperature, and ii) the commencement of antimicrobials. Progression to the third tier occurs when evidence exists of a pulmonary source of infection, a 'possible' pneumonia being differentiated from 'probable' pneumonia on the basis of at least semi-quantitative pathogenic organism culture in the latter.

According to CDC NHSN, the uppermost two tiers, namely VAC and IVAC, are designed to be suitable for use in potential future public health reporting, inter-facility comparisons and pay-for-performance programmes. Requiring only objective data confers adequate external validity for this purpose and will also enable patterns of antimicrobial prescribing to be compared more reliably. Possible and probable VAP diagnosis would be utilised within internal quality control systems to allow for the variation in practice in obtaining the necessary respiratory specimens to confirm diagnosis.

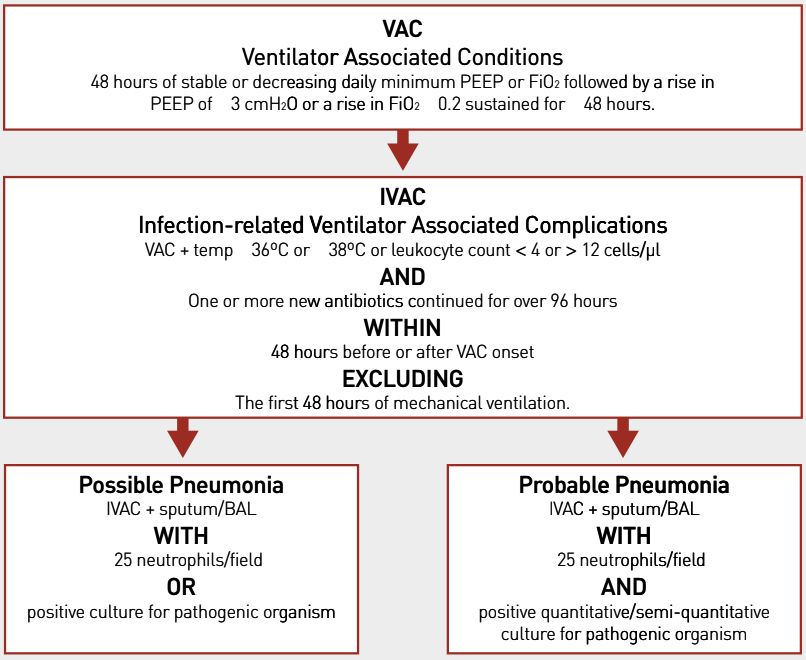
Validation

Hayashi and colleagues performed a retrospective evaluation of VAC (Hayashi et al. 2013). One of the aims of the study was to capture commonly recorded prospectively documented objective data (FiO_2, PEEP). They were able to demonstrate that VAC events were associated with both increased length of stay in ICU and increased days of mechanical ventilation. In addition to these negative outcomes, Klompas et al. (2011) were able to demonstrate an increase in mortality associated with VAC diagnosis compared with traditional VAP criteria. Therefore, a prospective study with a larger sample size is required to evaluate the utility of VAC and IVAC surveillance before its implementation in Australian ICUs. The introduction of a common clinical information system platform in South East Queensland will help to facilitate more efficient multi-site data collection and collaboration for this purpose.

Summary and Conclusion

At the bedside there is no doubt that there is sporadically a need to treat respiratory tract infections in patients on a ventilator with antibiotics. Exactly when this is required and how this is defined is being questioned, as there is not a uniform, unequivocal diagnostic set of criteria for the diagnosis of VAP. This makes comparisons, incidences and outcomes difficult to compare and to track. Especially as regards a quality indicator, objective, commonly captured data for all patients on ventilators is a more logical way forward. VAC has been put forward to address this concern. All patients on a ventilator will have FiO_2, PEEP and PaO_2 regularly recorded, and with clinical information systems now permitting realtime tracking and recording of incremental changes in these parameters we believe VAC will replace VAP as a quality assurance tool. The incorporation of antimicrobial use into the IVAC tier will also permit more reliable comparisons of stewardship models, and by differentiating between probable and possible VAPs, the final tier of the VAE key will also allow for local variations in diagnostic specimen sampling. ■

Figure 1. Diagnostic Key for Ventilator-Associated Events



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INHALED ANTIBIOTICS IN THE ICU

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New delivery methods have been developed for aerosolised antibiotics in mechanically ventilated ICU patients. This therapy can reduce the need for systemic antibiotics in the therapy of gram-negative pneumonia.

Introduction

Inhaled antibiotics have been available for use in patients with a wide range of respiratory infections, but their role in mechanically ventilated patients has not been routine, and has been primarily as adjunctive salvage therapy for difficult infections. With the emergence of multidrug-resistant (MDR) pathogens as a cause of lower respiratory tract infection in the ICU, the need for new therapeutic approaches is acute. Inhaled antibiotics address this need in a variety of ways. They can be effective against emerging MDR pathogens, including Pseudomonas aeruginosa, Acinetobacter spp, and the Enterobacteriaceae, primarily because they achieve high local concentrations at the site of infection. In addition, they do so without increasing the risk of systemic drug toxicity. Although the concept of inhaled antibiotics is not new, the technology of drug delivery has improved in recent years, while the availability of systemic antibiotics that are effective against MDR pathogens has declined, and there are few new drugs being developed for infection with gram-negative pathogens.

> *"Based on recent findings it may be time to re-evaluate the use of aerosolised antibiotics in the ICU for therapy of lower respiratory tract infection"*

Historical Perspective

Topical antimicrobial therapy for ICU patients was popularised in the 1970s with a series of investigational interventions to prevent ventilator-associated pneumonia (VAP) (Klick et al. 1975). Although the intervention was successful in preventing many pneumonias, the patients who did develop pneumonia, in spite of this effort, were infected with highly resistant organisms, and the resulting infections had a high mortality, so that the net effect was no change in ICU death rate. The observation about the emergence of resistance was so concerning that interest in using topical antibiotics for pneumonia in the ICU declined rapidly. Since then, usage has been primarily sporadic and anecdotal, being applied in situations of infection with MDR pathogens, but never as routine adjunctive therapy of VAP (Hamer 2000).

For example, one recent report described a retrospective, matched case-control study of 43 patients in Greece with MDR VAP, treated with either IV colistin alone or combined aerosol and IV colistin. The population included 77% of patients having A. Baumanii as the pathogen. Although there was a trend to more clinical cure with adjunctive aerosol therapy, there was no difference in mortality, clinical success or bacterial eradication (Kofteridis et al. 2010). Other investigators have applied aerosol therapy as a last ditch salvage effort for patients with MDR pathogens, who were either failing systemic therapy, or who had infection with pathogens that were not susceptible to any available therapy. In these reports, some patients did recover, suggesting a role for aerosol therapy in this dire circumstance (Hamer 2000). In addition, some investigators have shown the efficacy of inhaled therapy for patients with ventilator-associated tracheobronchitis (Palmer et al 2008).

In all of these early studies the aerosol was delivered by either routine nebulisation, a jet nebuliser, an ultrasonic nebuliser, or no specific delivery system was specified. In general, all of these approaches were inefficient, sometimes with little drug getting into the patient, and even less being delivered to the distal lung, at the alveolar site of infection. Recently, nebulisation techniques have improved, with a better understanding of how to optimise delivery to ventilated patients, and these developments have opened up new possibilities for aerosol therapy of VAP.

New Understanding to Improve Aerosol Delivery to the Lung

Attention to delivery of aerosolised antibiotics to the infected lung has prompted investigators to define

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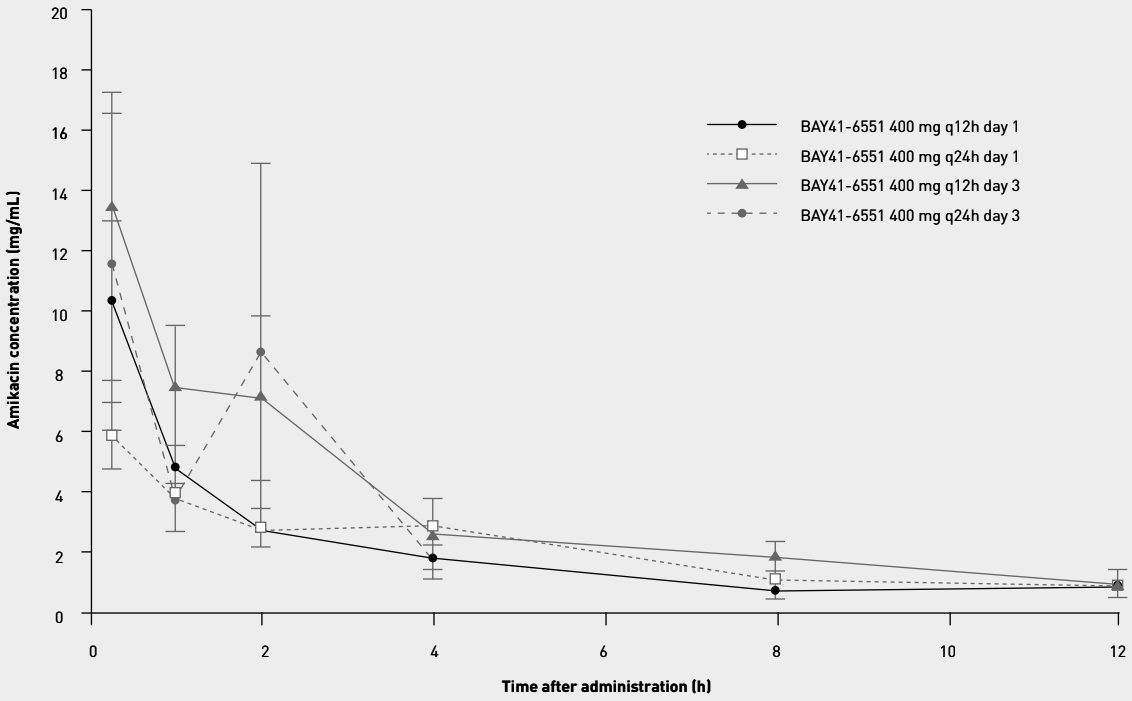
the optimal criteria for drug selection and drug delivery. The drug that is used must have high intrinsic activity against the most resistant pathogens causing respiratory infection. At the same time a limited systemic absorption from the respiratory site could minimise systemic toxicity. With both of these considerations in mind, recent studies have focused on inhaled use of aminoglycosides and colistin.

In considering how to deliver antibiotic to the lung, there are several issues that are relevant for mechanically ventilated patients with pneumonia. First, a delivery device should be able to generate small particles (< 5 microns) that are capable of reaching the alveoli, and not just depositing in the upper airway. In addition, whatever device is selected should be positioned in the ventilator circuit to maximise retention by the patient while minimising environmental contamination, which occurs if delivery is coordinated with the inspiratory cycle. In addition, it is important to consider whether an inhaled antibiotic can penetrate the pneumonic lung, or whether the presence of consolidation will prevent the deposition of antibiotic at the most affected site.

Deposition of inhaled agents in pneumonic lung is possible, but is not as effective as in non-consolidated tissue. Goldstein and colleagues studied piglets with bronchopneumonia from E. coli intrabronchial instillation, who were treated with amikacin given by an ultrasonic nebuliser (Goldstein et al. 2002). In the study 38% of the nebulised dose was retained in the lung, with higher concentrations in the lung areas that were less severely affected by the pneumonia. However, when lung concentrations were compared for aerosolised versus intravenous therapy, more drug was delivered, even to the severely bronchopneumonic area, with aerosol therapy than with intravenous therapy. However, there was more systemic drug absorption from the pneumonic area than from the non-pneumonic areas. Thus, the findings of this study suggested a utility for aerosol therapy, even for pneumonic lung, provided that serum levels were monitored to avoid too much systemic absorption.

Rouby and colleagues have conducted a number of animal and human studies of aerosol therapy of pneumonia, and have suggested ways to optimise drug delivery to the lung in mechanically ventilated patients (Rouby et al. 2012). They have generally advocated for the use of a new type of vibrating mesh plate nebuliser, rather than a jet nebuliser, although they have also suggested some value with the use of an ultrasonic nebuliser. Vibrating mesh plates are able to generate a uniform particle size, keeping all

Figure 1. Tracheal aspirate amikacin concentrations (mean + standard error) over time on day 1 and day 3 (all treated patients). Values are for all treated patients with tracheal aspirate amikacin concentrations at the relevant time point. q12h every 12h, q24h every 24 h



With kind permission from Springer Science+Business Media: Intensive Care Medicine, BAY41-6551 achieves bactericidal tracheal aspirate amikacin concentrations in mechanically ventilated patients with Gram-negative pneumonia, Vol. 38, 2012, 263-71, Michael S. Niederman, Jean Chastre, Kevin Corkery, James B. Fink, Charles-Edouard Luyt, Miguel Sánchez García, figure 2.

the particles less than 5 microns. In the studies by Rouby et al., the nebuliser is placed in the inspiratory limb, before the Y connector , and it can be synchronised with inspiration, so that at least 60% of the reservoir dose is deposited in the lung. In selecting the nebulised dose, they recommend using the systemic dose of the antibiotic, plus the amount of drug that is estimated to deposit in the tubing and expiratory filter. They also recommend using a tidal volume of 7-9 cc/kg, in a controlled ventilatory mode, with the patient sedated, using constant inspiratory flow, at a 1:1 inspiratory to expiratory ratio. They suggest using an inspiratory pause of at least 20% of the duty cycle, and to do the nebulisation with the heat moisture exchange filter removed.

We have recently completed a trial of nebulised amikacin for patients with gram-negative ventilator associated pneumonia (VAP), using a vibrating mesh plate nebuliser, and our delivery method was not exactly the same as specified by Rouby et al. In our study, the nebuliser was placed distal to the Y connector, before the origin of the endotracheal tube, and delivery was only in the inspiratory cycle (Niederman et al. 2012). Delivery was coordinated by a pressure control module that sensed the pressure in the inspiratory limb of the ventilator tubing, and delivery could be optimised by stopping nebulisation in the last 25% of the inspiratory cycle, to 'wash in' the inhaled agent to the deep lung. Using this method, any mode of ventilation was allowed, and patients did not need sedation to facilitate drug delivery. In the study, 71% of the patients were on assist-control ventilation, with the rest being on pressure support. The goal of the delivery system was to achieve a tracheal aspirate concentration of amikacin of > 6400 micrograms/ ml (> 25 times an MIC of 256 micrograms / ml). Using a dose of 400 mg amikacin every 12 hours, this high concentration was achieved in 50% of the patients. Tracheal concentrations were higher after twice daily administration than after once daily administration. Tracheal concentrations were higher at day 3 than on day 1, but at both times serum concentrations remained < 10 micrograms/ml, and generally much lower than this level, with a mean of 3.16 micrograms/ml (see Figure 1).

Recent Findings With Inhaled Antibiotics

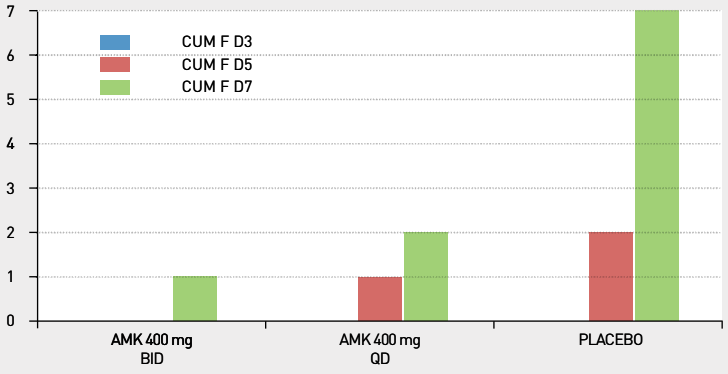
With the advent of new aerosol delivery methods, it is necessary to re-evaluate the efficacy and trial design of inhaled antibiotics for patients with gram negative pneumonia, treated with mechanical ventilation. When an inefficient nebuliser is used, along with too low a dose, efficacy is unlikely. For example, in one study of 100 patients with gram-negative pneumonia, a jet or ultrasonic nebuliser of 75 mg of colistin was added to systemic therapy, every 12 hours, with no benefit on clinical outcome (Rattanaumpawan 2010). Future trials may need to consider endpoints other than cure or mortality. These trials should probably focus on a patients with an enhanced risk of infection with MDR gram-negatives, use aerosol as an adjunct to systemic therapy, and look at endpoints such as early failure, without adjunctive aerosol therapy, and the ability of aerosol therapy to lead to clinical success with the use of less systemic therapy, than without adjunctive aerosol. Some of these ideas have been tested in recent trials.

One recent study has shown the value of inhaled high dose colistin in treating pneumonia caused by MDR pathogens. In this study 43 patients with ventilator-associated pneumonia (VAP) caused by Acinetobacter baumanii or Pseudomonas aeruginosa were treated with high dose inhaled colistin (5 million units every 8 hours with a vibrating mesh plate nebuliser) either with or without (n=28) systemic antibiotics. The clinical cure rate was 67%, virtually identical to the success in treating 122 patients with VAP caused by sensitive strains of the same pathogens, that had been treated exclusively with intravenous antibiotics (Lu et al 2012). In areas of confluent pneumonia, the use of aerosolised colistin led to an increase in thoracic gas volume.

In another study by the same group of investigators, a randomised comparative trial was conducted in 20 patients with sensitive or intermediate strains of P. aeruginosa who were treated with inhaled amikacin plus inhaled ceftazidime, and a group of 20 patients with similar organisms who were treated with only intravenous ceftazidime plus intravenous amikacin or ciprofloxacin (Lu et al. 2011). After 8 days both groups had similar rates of treatment success, but acquired antibiotic resistance only occurred in those getting intravenous therapy. There were 4 patients with intermediately sensitive organisms who had bacterial eradication from the use of only aerosol therapy. Drug delivery by aerosolisation was efficient, with over 60% of the nebulised dose being retained in the lung. This study suggested that aerosol therapy alone, and not just as adjunctive therapy, was effective to treat VAP, although the use of this approach is not likely to be widespread.

In another recent study Niederman et al. examined whether the use of adjunctive aerosolised amikacin could have a clinical benefit other than clinical or microbiologic cure rates (Niederman et al. 2012). In a randomised trial of 69 mechanically ventilated patients with gram-negative pneumonia (with more than half having either P. aeruginosa or Acinetobacter spp), amikacin was given with a vibrating mesh plate nebuliser at either 400 mg twice daily, 400 mg once daily, or a placebo was given via aerosol. All patients received systemic antibiotics, and at the end of a week, in this blinded trial, the patients receiving the highest dose of amikacin were receiving less systemic therapy than the patients receiving either placebo or lower dose amikacin. In addition, systemic therapy was escalated (more or broader spectrum agents used) in 14% of the high dose inhaled amikacin patients, 38% of the lower dose inhaled amikacin patients and in 58% of those receiving inhaled placebo. Clinical failure was defined by serial measurement of the Clinical Pulmonary Infection Score, with failure defined as a rise >2 points at day 3, a failure to fall

Figure 2. Cumulative number of clinical failures at day 3, day 5 and day 7 for each of 3 treatment groups. Clinical failure was defined by serial measurement of the Clinical Pulmonary Infection Score.



CUM= cumulative, F= failures, D= Day, AMK= amikacin, BID= every 12 hours, QD= every 24 hours.

by >1 point at day 5 or >2 points at day 7. By this definition, there were fewer failures with the amikacin twice daily dosing than with other regimens (see Figure 2). Thus, the use of adjunctive aerosol therapy had the benefit of leading to less systemic antibiotic exposure, by leading to a more rapid clinical response than in those patients receiving only systemic antibiotics, and leading to less clinical failure, suggesting a possible role for aerosol therapy to reduce systemic antibiotic exposure in the ICU therapy of pneumonia.

Is It Time for Routine Use of Inhaled Antibiotics as Adjunctive Therapy for VAP?

Based on recent findings, it may be time to re-evaluate the use of aerosolised antibiotics in the ICU for therapy of lower respiratory tract infection. While they may be useful as adjunctive therapy of pneumonia caused by MDR pathogens, they may also have a role as routine adjunctive therapy, to reduce the duration of systemic antibiotic therapy of pneumonia. Chastre et al. have demonstrated that 8 days of antibiotic therapy may be as effective as 15 days in VAP, but when non-fermenting gram-negatives are present, 8 days of therapy may lead to more microbiologic failures (Chastre et al 2003). The use of routine adjunctive aerosol therapy may address this issue by providing more 'up-front' therapy, thereby permitting short duration of systemic therapy, even for non-fermenting gram-negatives.

More data are needed to determine if nebulised antibiotics should be used routinely in the therapy of gram-negative pneumonia in ventilated patients. If the data are positive,we may be able to extend this approach to non-ventilated patients, since the same aerosol technology is becoming available for this population as well. Other targets of aerosol therapy in the ICU are patients with ventilator-associated tracheobronchitis, which may be a predecessor of VAP, and which may be effectively treated with topical tracheobronchial antibiotics, without the use of systemic therapy. In the conduct of future studies, it is also important to evaluate the efficacy of current inhaled agents on gram-positive pathogens, where they may have efficacy, or it may be necessary to combine the current agents with another agent active against MDR gram-positives such as methicillin-resistant S. aureus, since many patients have mixed gram-negative and gram-positive infections. ■

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KIDNEY ATTACK IN SEPSIS
THE ROLE OF HAEMODYNAMICS

For decades, textbooks have suggested that renal hypoperfusion and tissue ischemia are the primary pathogenic event in sepsis-induced acute kidney injury (S-AKI). Although paradigms are actively changing, there is still a shortage of data clarifying the pathogenic role of renal circulation in the development of S-AKI.

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The kidney is a common 'victim organ' of sepsis. A number of pathological processes have been postulated for S-AKI, including alterations of renal global and microvascular (both glomerular and peritubular) haemodynamics and changes in immunological, inflammatory and bioenergetic pathways. However, the causative contribution of each to kidney dysfunction in sepsis remains enigmatic. This is particularly true for the role of renal circulatory alterations, which is still a subject of inflammatory debate (Wan et al. 2008; Prowle et al. 2012). The fuel for this fire lies in the fact that almost all our knowledge is derived from various animal models with rather limited clinical relevance, because online recording of renal haemodynamics, oxygenation, and a clear-cut detection of evolving pathology is lacking for the human kidney during the development of S-AKI. It has been postulated for almost 60 years that AKI in sepsis is largely an ischaemic form of AKI and that renal vasoconstriction is the first and major pathogenetic event there (Schrier 2004). This might certainly be valid for prolonged unresuscitated sepsis. By contrast, only relatively recently, an Australian group of researchers challenged this old-fashioned view, and showed in a sheep model that renal vasoconstriction is not necessarily a prerequisite for AKI to develop during resuscitated, hyperdynamic sepsis (Langenberg et al. 2006;2007). They demonstrated that AKI can develop despite significant renal vasodilatation and increased renal artery blood flow and the paradigm of renal hyperaemia in S-AKI has been introduced (Wan et al. 2008). The persisting controversy regarding the role of renal haemodynamics in sepsis has nicely been illustrated by an extensive review of available human and experimental evidence performed in 2005 (Langenberg et al. 2005). The analysis documented that renal blood flow reported mostly in experimental studies is markedly heterogeneous (decreased, increased or unchanged), and that cardiac output appears to be the dominant predictor of both renal blood flow and renal vascular resistance in sepsis. It should be stressed, however, that the majority of studies reporting a reduction in renal blood flow were derived from short-term and mostly hypodynamic models characterised by a reduced cardiac output, which clearly limit the inference that could be drawn. Nevertheless, even after eight years since this publication, we still do not know the dynamic behaviour of renal circulation during S-AKI, in particular due to the lack of reliable methods allowing continuous renal blood flow measurement in critically ill patients.

> *"a gradual shift from 'haemodynamically-based' theories to more complex approaches has occurred in recent years"*

Generally speaking, we have two contradictory concepts in renal circulatory responses in sepsis: the theory of renal ischaemia despite systemic vasodilatation and the concept of renal hyperaemia with the renal circulation participating in sepsis-induced vasoplegia and low systemic vascular resistance. Physiologically, both renal vasoconstrictive and vasodilatory profile is compatible with a reduction in glomerular filtration as a result of reduced glomerular filtration pressure. Note, however, that AKI affects

40-50% of all septic patients (Zarjou and Agarval 2011). Hence, the relevant question arises whether renal circulation behaves differently in patients developing AKI as opposed to those without AKI. To address this issue, we studied the dynamic renal circulatory changes using two porcine models of severe sepsis (peritonitis and IV infusion of live Pseudomonas aeruginosa) (Benes et al. 2012). This modelling allowed us to generate two distinct groups of septic animals, those with and without the development of S-AKI, thereby enabling us to isolate and study both haemodynamic and non-haemodynamic factors discriminating AKI from non-AKI. We observed that 50% of all animals developed S-AKI despite comparable septic insult and totally identical supportive treatment. Interestingly, despite identical systemic haemodynamic profiles characterised by well-maintained cardiac output and systemic vasodilation, a different renal circulatory pattern was observed in AKI and non-AKI subjects. Whereas a consistent link between well-maintained cardiac output and preserved renal blood flow was documented in septic animals that remained AKI-free, the animals complicated by the development of S-AKI showed progressively increased renal vascular resistance accompanied by reduced renal blood flow suggesting an apparent renal vasoconstriction.

Figure 1. Different global renal hemodynamic phenotypes: cause or consequence of S-AKI?

These results allow for several important considerations. First, renal circulation behaves differently in sepsis with AKI as opposed to sepsis alone. Second, renal haemodynamics in septic subjects developing AKI cannot reliably be predicted from systemic haemodynamics. Finally, septic AKI may be accompanied by an uncoupling between systemic and renal vascular resistance, supporting the existence of the phenomenon of selective renal vasoconstriction even in a well-resuscitated large animal model with sepsis-induced systemic vasodilation. It should be noted, however, that a wide inter-individual variability in renal vascular resistance was observed in S-AKI animals, ranging from highly increased to unchanged or even slightly reduced. Such a variability might question a causative link between renal global circulatory changes and kidney dysfunction, at least in early, well-resuscitated, and normotensive large mammals sepsis. Regardless of causation, our results suggest that S-AKI can occur within the setting of two different renal haemodynamic phenotypes: vasodilatory and vasoconstrictive (see Figure 1) (Lipcsey and Bellomo 2011), i.e. that both haemodynamic paradigms exist. The fact that renal circulatory changes appear to be independent from systemic haemodynamics implies that S-AKI develops as a consequence of kidney-specific pathophysiology. The underlying mechanisms that determine which phenotype predominates remain unknown. Theoretically, the type of infection, stage, and severity of sepsis or even genetically driven imbalance in vasomotor control and yet undefined disharmony of glomerular vascular balancing mediators may dictate the renal haemodynamic phenotype. These relationships are amenable to direct investigation.

New data on the renal haemodynamics in S-AKI has emerged from a recent clinical study by Prowle et al. (2012). The authors assessed renal blood flow using cine phase-contrast magnetic resonance imaging in ten adult patients with established S-AKI. In this cohort of patients, median renal blood flow was significantly lower compared to the renal blood flow in healthy individuals. Moreover,

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despite a wide range of cardiac output, renal blood flow was consistently reduced as a fraction of cardiac output (less than half normal). Finally, a majority of patients had markedly increased renal vascular resistance when compared to healthy volunteers. Collectively, these data suggest that renal vasoconstriction might be a feature of established S-AKI, independent from systemic haemodynamics. Although larger studies with serial measurements are necessary to inform us about the exact fate and the role of renal blood flow in sepsis and AKI, this study is undoubtedly a welcome step further.

It is essential not only to understand the complex behaviour of global kidney perfusion, but also its intrarenal distribution as well as changes in local microvascular blood flow. Certainly, the damage to the renal microcirculation and resulting tissue hypoxia may constitute early critical steps in the development of S-AKI. However, lack of techniques enabling direct visualisation of the unique architecture of the kidney microcirculation both in the cortex and medulla and exact real-time measurements of oxygen tension in the corresponding areas represent the main impediments to the study of intrarenal oxygenation in man (Matejovic 2011). Nonetheless, several experimental studies have provided evidence for the causative role of peritubular microvascular injury in S-AKI (Mayeux and MacMillan-Crow 2012). Age is one of the factors that may markedly influence not only the pattern of global renal haemodynamic profile (Seely et al. 2011), but also the vulnerability of renal microvasculature to the inflammatory stimuli (Wulfert et al. 2012). Recent experimental research has also reinforced interest in glomerular pathobiology during S-AKI. Xu et al. suggested an important role of TNF-alfa-mediated degradation of the glomerular endothelial surface layer and loss of glomerular endothelial fenestration in the development of S-AKI in mice (Xu et al. 2013). Another attractive, yet speculative, concept of glomerular bypass shunts permitting renal arterial blood to bypass the process of filtration has recently been discussed (Bellomo 2013).

Conclusions

In conclusion, there is still an ongoing debate whether or not the global renal haemodynamic alterations (regardless of the phenotype) are a primary pathogenic factor or if they are just a consequence rather than a cause of renal injury. Over time, as information accumulates and our understanding increases, a gradual shift from 'haemodynamically-based' theories to more complex approaches has occurred in recent years. Undoubtedly, further intensive mechanistic studies and solid reproducible research are warranted. ■

Acknowledgements

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THERAPEUTIC HYPOTHERMIA IN SEVERE TRAUMA

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Uncontrolled, exposure hypothermia is associated with worse outcomes in trauma patients. In contrast, laboratory studies suggest benefit of controlled, therapeutic hypothermia for haemorrhagic shock, traumatic cardiac arrest, traumatic brain injury and spinal cord injury. Well-designed, prospective studies are needed.

Introduction

Spontaneous, uncontrolled hypothermia occurs in many victims of major trauma. Shock, alcohol and drug intoxication, sedation, and anaesthesia limit the ability of trauma patients to maintain normal temperature homeostasis. Exposure for evaluation and operative interventions can increase heat loss. Cooling is further exacerbated by the administration of room temperature intravenous fluids and blood products. In the end, hypothermia may just represent the result of energy depletion from shock. The more severe the injury, the greater the risk of hypothermia (Gregory et al. 1991).

Several studies have demonstrated a strong association between the development of hypothermia and mortality in trauma patients (Jurkovich et al. 1987; Luna et al. 1987). Since the development of hypothermia is multifactorial and many of these factors may directly increase mortality, it has been difficult to clearly define the independent impact of uncontrolled hypothermia on trauma outcomes. Utilising a large state-wide trauma database, Wang et al. (2005) demonstrated an independent association between the development of hypothermia and mortality, controlling for age; sex; injury severity score; head, abdominal, and skin abbreviated injury scale; systolic blood pressure; mechanism of injury; intravenous fluids; and route of temperature measurement. All of these factors were independent predictors of hypothermia. The adjusted odds ratio for death in patients who became hypothermic (≤35ºC) was 4.04 (95% CI: 3.34–4.89). Similarly, the odds ratio for death in patients with isolated traumatic brain injury who became hypothermic was 3.14 (CI: 2.12–4.67).

Based upon the current clinical literature, the standard of care for severely injured patients remains active rewarming to maintain normothermia. Consideration for therapeutic hypothermia is challenging for investigators because of this current dogma.

Haemorrhagic Shock

Therapeutic, controlled, mild hypothermia (32-34ºC) has been studied in laboratory experiments using haemorrhagic shock models, with or without significant tissue trauma. Hypothermia has beneficial effects on the heart, liver, and skeletal muscle. More importantly, hypothermia consistently improves survival (Wu et al. 2005; George et al. 2010). For example, using a porcine model of prolonged haemorrhagic shock and trauma with intensive care life support throughout, Wu et al. (2005) demonstrated improved 24-hour survival.

Why is there such a dichotomy between the beneficial effects of hypothermia demonstrated in the laboratory and the strong clinical association between hypothermia and worse outcomes in patients? First, and perhaps most important, is the physiologic difference between uncontrolled, exposure hypothermia in patients, which can be associated with energy depletion, shivering and catecholamine responses, as compared to controlled, therapeutic hypothermia, during which shivering and stress can be prevented with sedation. Second, coagulopathy may play a role, though coagulation studies at 34ºC and experience with therapeutic hypothermia after cardiac arrest or traumatic brain injury do not suggest clinically relevant coagulation abnormalities at this temperature (Resnick et al. 1994; Watts et al. 1998). Third, it is possible that the amount of tissue trauma commonly seen in trauma patients may not be well replicated in the laboratory. Fourth, patients receive allogeneic, banked blood, while animal models typically include reinfusion of fresh, autologous blood.

No prospective, randomised trials of therapeutic hypothermia have been conducted in trauma patients. The only prospective, randomised trial related to temperature management in trauma patients compared standard rewarming with a novel continuous arteriovenous rewarming technique in a small number of patients who were already hypothermic (Gentilello et al. 1992). There was a suggestion of short-term (but not long-term) survival ben-

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efit with faster rewarming.

As mild, therapeutic hypothermia during severe haemorrhagic shock may delay or prevent cardiac arrest and may improve survival, a randomised clinical trial seems warranted.

Cardiac Arrest

Mild hypothermia has become standard therapy for comatose patients after non-traumatic cardiac arrest. Recommendations from the American Heart Association suggest that patients who remain comatose after resuscitation from an out-of-hospital cardiac arrest caused by ventricular tachycardia/fibrillation should be cooled to 32-34ºC for 12-24 hrs (Peberdy et al. 2010). They further suggest that there may be benefit of therapeutic hypothermia after in-hospital cardiac arrest and after cardiac arrest from other causes, possibly including trauma. For comatose trauma patients, without traumatic brain injury, who have suffered a cardiac arrest, therapeutic hypothermia should be considered if there is no clear contraindication, such as coagulopathy (Tuma et al. 2011).

For patients who exsanguinate from trauma, surgeons have little time to obtain haemostasis and adequately resuscitate patients before cardiac arrest is irreversible. Typically, these patients undergo emergency department thoracotomy, but survival is less than 10% (Rhee et al. 2000). Emergency Preservation and Resuscitation (EPR) has been developed as a novel approach to managing such patients by rapidly cooling them to allow tolerance of a prolonged period of circulatory arrest, during which haemostasis is achieved, followed by delayed resuscitation using cardiopulmonary bypass (CPB) (Tisherman 2004).

For induction of hypothermia (10-15ºC) for EPR, the fastest methods seem to be either a flush of cold saline directly into the aorta (Tisherman 2004) or use of a CPB circuit with ongoing low flow (Sailhamer et al. 2007). Delayed resuscitation then requires full CPB. The longer the period of hypothermic circulatory arrest that is desired, the deeper the level of hypothermia that is required. Profound hypothermia (10ºC) with glucose and oxygen in the flush can allow good neurologic recovery after even up to 3 hours of circulatory arrest (Wu et al. 2008). The optimal fluids and drugs for EPR still need to be developed. Clinically relevant dog and swine models with complex injuries have demonstrated that EPR has the potential to allow injury repair and neurologically-intact survival (Wu et al. 2006; Sailhamer et al. 2007).

Based on the preclinical studies, investigators at the University of Pittsburgh have developed the EPR for Cardiac Arrest from Trauma (EPR-CAT) feasibility trial (University of Pittsburgh). The study will enrol victims of penetrating trauma who suffer a cardiac arrest within 5 minutes of arrival at the trauma centre, but do not respond to initial resuscitation, including emergency department thoracotomy. The aorta will be cannulated with an arterial CPB cannula to enable rapid flush of ice-cold saline until tympanic membrane temperature is less than 15ºC. At that point, the patient can be rapidly transported to the operating room for resuscitative, damage-control surgery and delayed resuscitation with CPB. The protocol will require a coordinated effort by emergency physicians, trauma and cardiac surgeons, perfusionists, anaesthesiologists and operating room staff trained in the EPR technique. The primary outcome variable will be survival to hospital discharge without major neurologic disability. As the study progresses, the criteria and the technique may be revised.

Traumatic Brain Injury

Laboratory studies have demonstrated that early induction of mild to moderate hypothermia can improve many physiologic parameters, particularly intracranial pressure, and outcome after traumatic brain injury (TBI). Clinically, one single-centre randomised, controlled trial of early, post-TBI hypothermia (33ºC for 24 hours) demonstrated benefit at 6 months, but not 12 months, in a subset of patients with initial Glasgow Coma Scale (GCS) of 5 to 7 (Marion et al. 1997). The first, multi-centre North American Brain Injury Study: Hypothermia (NABIS:H) failed to demonstrate benefit of hypothermia at 33ºC for 48 hours (Clifton et al. 2001). There was a suggestion that hypothermia is detrimental to subjects >45 years of age, but possibly beneficial for patients who were ≤45 years of age and who were hypothermic on admission. There was also significant variability amongst centres, particularly smaller centres.

Based on the subset analysis from NABIS:H, NABIS:H II was designed to enrol subjects who were 16-45 years old at select, experienced centres (Clifton et al. 2011). The intent was to induce hypothermia as early as possible after injury. This study did not demonstrate benefit of therapeutic hypothermia. Subset analysis of this study suggested that subjects with surgically-removed haematomas may have reaped greater benefit from hypothermia than those with diffuse brain injury.

Future studies may include stratification of patients by type of injury (focal vs diffuse). Previous studies have controlled temperature by protocol and found that intracranial pressure sometimes increased during rewarming. Titration of temperature based upon intracranial pressure during rewarming may be appropriate. Regardless of whether future studies demonstrate benefit of the induction of hypothermia, it is clear that hyperthermia should be avoided as any fever can worsen neurologic outcomes. Controlled normothermia has become standard.

Spinal Cord Injury

Benefit of systemic, therapeutic hypothermia has been demonstrated in laboratory models of spinal cord injury (Inamasu et al. 2003). Clinically, hypothermia has been used for spinal cord protection during aortic surgery (Okita 2011). For traumatic, spinal cord injury, a randomised, clinical trial of therapeutic hypothermia is in progress (University of Miami).

Future Directions

A recent workshop sponsored by the U.S. National Institutes of Health and U.S. Army recommended additional studies to better understand the mechanisms of benefit of hypothermia, clinical impact of exposure hypothermia, and interactions between hypothermia and potentially-beneficial drug therapies (Alam et al. 2012). Clinical trials are needed to explore the trauma settings for which hypothermia may have benefit, including haemorrhagic shock, cardiac arrest from trauma, traumatic brain injury, and spinal cord injury. ■

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ISCHAEMIC CONDITIONING FOR NEUROPROTECTION IN STROKE

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Introduction

Worldwide, stroke remains the second leading cause of death after heart disease. Since the 1970s there has been a 42% decrease in stroke mortality in high-income countries and a 100% increase in low-income countries (Norrving and Kissela 2013). These trends are multifactorial; however, a significant component is due to a less robust infrastructure for tertiary prevention of stroke i.e. rapid diagnostic imaging, thrombolytic medication and endovascular thrombus-removal interventions. These remain largely limited to the 'developed' world. Ischaemic conditioning, a simple, inexpensive, and non-invasive therapy applicable to thrombotic stroke promises to be feasible throughout the world.

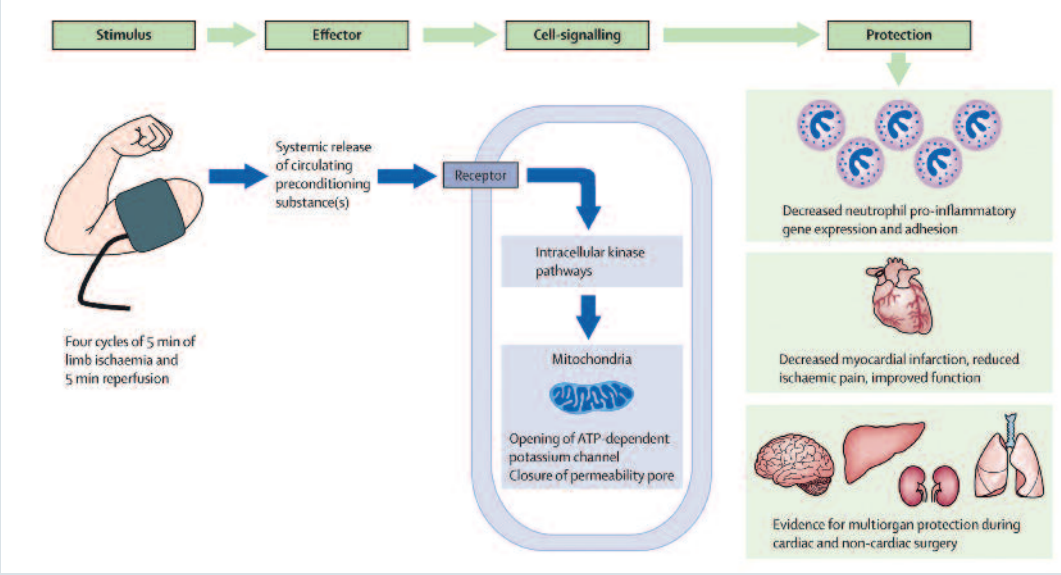
Reperfusion Injury and Ischaemic Conditioning

Ischaemia due to impaired blood flow produces within cells a reduction in ATP, an increase in lactate concentration and impairment of cell membrane-based ion transporters. Decreased cytosolic pH, cell and mitochondrial oedema are the sequelae. Cell death and necrosis follow. While reperfusion must occur to salvage ischaemic but potentially viable cells, reperfusion itself causes cell damage distinct from the original ischaemic insult (Hearse et al. 1973).

Ischaemic conditioning is the creation of brief and repeated cycles of non-lethal ischemia alternating with reperfusion in a selected organ or tissue. This 'conditioning' reduces damage from later, prolonged ischemia.

Murry and Reimer in 1986 reported a canine model of acute myocardial infarction designed to measure the size of infarction resulting from interruption (forty minutes) of flow in the circumflex coronary artery (LCX). Animals so treated were maintained for four days, sacrificed, and the extent of infarction in the LCX vascular bed measured by histochemical techniques (Murry et al. 1973). An experimental group underwent four cycles of five minute LCX occlusion, each reversed by five minutes of reperfusion, before the prolonged occlusion of the artery. Infarct size in the experimental group was 25% that of dogs that did not receive pulsatile ischemia/reperfusion. This discovery, termed 'ischaemic conditioning', was later extended by Przyklenk in a similar experiment wherein conditioning of the circumflex vascular bed reduced infarct size and contractile dysfunction after subsequent sustained coronary occlusion of the left anterior descending artery

Figure 1. Biological effects of remote ischaemic preconditioning
Transient ischaemia of the arm liberates a circulating effector that induces remote cellular adaptation to a subsequent, extended, and potentially lethal period of ischaemia in remote tissues.



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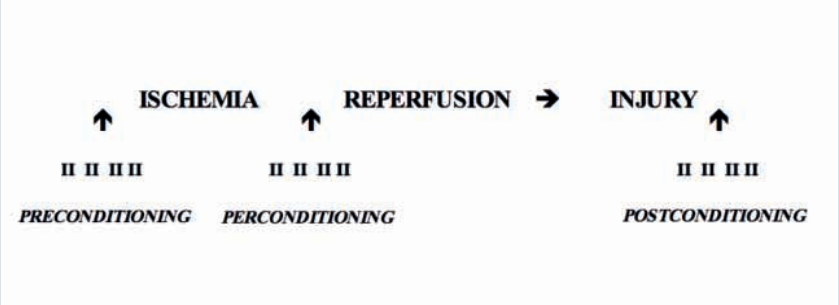
(Przyklenk et al. 1993). Ischaemic conditioning (IC) thus appeared to generate humoral factors transported in the circulation. Ischaemic conditioning remained an interesting, but not clinically useful, phenomenon until the discovery that ischaemic conditioning of an extremity could induce protection in internal organs such as heart, brain, lung and kidney (Kharbanda et al. 2002). This 'remote' ischaemic conditioning (RIC) effect makes possible the use of an arm or leg for timed pulses of brief ischemia/reperfusion with a standard sphygmomanometer (see Figure 1).

The mechanism of ischaemic conditioning has been intensively studied over the past 25 years and involves humoral, neurogenic, and immune factors (Hess et al. 2013). Moreover, there are two phases to the protection: the first lasts approximately four hours, after which the magnitude of protective effect subsides. This initial phase is likely mediated through 'triggers' - small molecules such as adenosine, bradykinins, opioids, and reactive oxygen species. Dialysate, obtained with a 15 kilodalton-cutoff membrane from the plasma from ischaemic-conditioned human subjects, generated protection against infarction by coronary artery ligation when perfused through isolated rabbit hearts. Partial characterisation of the plasma ischaemic conditioning factor by column chromatography demonstrated a hydrophilic nature (Shimizu et al. 2009). Using proteomic methods, Lang confirmed the humoral factor of ischaemic conditioning to be of small molecular weight (less than 8 kd) (Lang et al. 2006). Subsequent transcription of DNA and protein synthesis produces distinct mediators at 12 to 24 hours (Hausenloy and Yellon 2010; Loukogeorgakis et al. 2005). Research has shown that a significant proportion of the protective effect of RIC is mediated through stabilisation of the mitochondrial permeability transition pore (mPTP) (Hausenloy et al. 2009). In unconditioned tissue reperfusion results in a flooding of small molecules into the mitochondrion followed by subsequent oedema and dysfunction of the organelle.

Ischaemic conditioning may be applied before ischemia (prior to elective procedures such as percutaneous coronary artery stenting), during ischaemia (the interval between onset of thrombotic myocardial infraction or stroke and reperfusion therapy) or after reperfusion. These periods are termed respectively: 'preconditioning', 'perconditioning' and 'postconditioning'.

Figure 2.



Since the 1980s, large clinical trials have demonstrated rapid thrombolytic therapy to be effective in reducing mortality and morbidity in two major thrombotic emergencies: ST-T segment elevation acute myocardial infarction (STEMI) and acute thrombotic stroke. STEMI established itself first, initially with intravenous thrombolytic drugs (GUSTO investigators 1993), and advancing to percutaneous coronary artery intervention (French et al. 2003). Later, treatment of thrombotic stroke followed a similar path: initial intravenous pharmaceutical thrombolysis to endovascular techniques (Hacke et al. 2004). Both conditions share a similar course: unpredictable initial arterial thrombosis followed by a period of ischaemia then therapeutic restoration of blood flow to the ischaemic organ. In both STEMI and thrombotic stroke, a large number of symptomatic individuals must be screened to identify a genuine acute thrombotic event. Theoretically, the ischaemic interval of both conditions affords an ideal opportunity for application of remote ischaemic conditioning, specifically perconditioning, (see Figure 2) to ameliorate reperfusion injury. Remote ischaemic perconditioning has the additional advantage that personnel with minimal training may administer it prior to a confirmed diagnosis. Finally, the procedure poses a miniscule risk of harm to patients who are not experiencing a thrombotic event.

Bøtker investigated this possibility by randomising symptomatic STEMI patients, transported by ambulance to hospital, for coronary revascularisation. Patients were randomised prehospital to either five cycles of brief ischaemia/reperfusion, administered to an upper arm by blood pressure cuff, or to no ischaemic conditioning. On arrival, Single Positron Emission Computed Tomography (SPECT) delineated the area of ischaemic myocardium (area at risk). The study called for repeat SPECT thirty days later at which time the area irreversibly infarcted was measured. The primary outcome was the myocardial salvage index defined as (initial ischaemic area of myocardium)/ (initial ischaemic area of myocardium) – (area infarcted at 30 days). Of those completing the study protocol, the median myocardial salvage index in conditioned patients was 0.75 versus 0.55 in the unconditioned group; a difference not statistically significant (Bøtker et al. 2010). In a subgroup analysis of patients with anterior myocardial infarction (therefore, a large area of ischaemic myocardium) from the same study, the investigators suggested a trend toward greater myocardial salvage and long term left ventricular function (Munk et al. 2010; Sloth et al. 2013). Interpretation of these results must take into consideration the large number of randomised patients who did not meet inclusion criteria on hospital arrival, did not return for 3 month imaging or were lost to follow-up. Of 333 randomised patients, only 142 (43%) completed the study protocol, and it was these patients in whom the degree of myocardial salvage could be determined. This study established the feasibility and safety of prehospital conditioning; but did not demonstrate a significant benefit from remote ischaemic perconditioning in clinically relevant outcomes.

Remote Ischaemic Perconditioning and Stroke

The current standard therapy for thrombotic stroke is intravenous tissue plasminogen acti-

vator (tPA) (within 3 to 6 hours of symptom onset) to re-establish perfusion. Successful treatment also causes reperfusion injury to the previously ischaemic brain. In a rat model of ischaemic stroke (occlusion of the middle cerebral artery), Hahn studied mice preconditioned and perconditioned with a hind leg tourniquet, The conditioned mice manifested significantly smaller stroke volumes after 120 minutes of cerebral ischemia compared with an unconditioned control group (Hahn et al. 2011; Tropak et al. 2011). Of interest was the observation that perconditioned (conditioning of hind limb during cerebral ischaemia but before reperfusion) developed stroke volumes significantly smaller compared to the preconditioned (conditioning before cerebral ischaemia). Results of the first prospective phase three human trial of remote perconditioning in acute thrombotic stroke were reported by Hougaard and others in 2013. The study design was similar to that of Bøtker, intended to determine whether remote ischaemic conditioning performed as an adjunct to thrombolysis would improve salvage of ischaemic but viable brain during thrombotic stroke. Patients with stroke-like symptoms, en route by ambulance to hospital, were randomised to either perconditioning (administered by blood pressure cuff to the arm) or no perconditioning. Patients whose stroke or transient ischaemic attack were confirmed by MRI and received tPA were enrolled and followed up by MRI 30 days later. One hundred and forty nine subjects completed the 30 day follow-up. The primary endpoint was salvage of ischaemic but viable brain tissue as determined by initial and 30 day MRI (Hougaard et al. 2013). Analysis revealed no significant statistical difference in preservation of ischaemic cerebrum between the two groups. The secondary clinical endpoints of infarct growth from 0-24 hours and on clinical performance instruments also did not achieve statistical significance (Meng et al. 2012).

> "Ischaemic conditioning, a simple, inexpensive, and noninvasive therapy applicable to thrombotic stroke, promises to be feasible throughout the world"

Post Conditioning

Less well understood, but potentially exciting, are reports that post-ischaemic conditioning (five brief cycles of bilateral upper extremity ischemia followed by reperfusion, twice daily for 300 consecutive days after cerebral haemorrhage) with atherosclerotic intracranial arterial stenosis reduced the incidence of recurrent stroke in control subjects at 90 and 300 days from 23.3% and 26.7% respectively, to 5% and 7.9% (p=0.01). Time to recovery was shorter and cerebral perfusion status improved also in the post-conditioned group (Meng et al. 2012).

Ischaemic conditioning is a unique physiologic process that may be seen across species, suggesting that it arose early in evolutionary history. Early prospective human trials have been disappointing; however, increasing knowledge of the bimodal timing of protection - a rapid, short-lived state followed by a later, longer-lasting one - and of the multiple effector pathways offer the hope that combining perconditioning and postconditioning will yield immediate benefit to victims of thrombotic stroke. Ischaemic conditioning for prolonged periods after stroke appears to reduce the rate of reoccurrence and enhance the rapidity and extent of rehabilitation. In any case, the simplicity, low cost, and safety of ischaemic conditioning merit continued clinical study in humans. ■

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TELE-INTENSIVE CARE MEDICINE
HIGH POTENTIAL OF ENHANCING HEALTHCARE OUTCOMES

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Ageing society will lead inevitably to a shortage of intensivists. Tele-intensive-medicine as an innovative solution grants future provision of care, addressing quality of care, outcome, and economics in intensive care.

Introduction

Intensive care medicine is facing an increasing demand for healthcare. Due to longer life expectancy, consecutively increasing morbidity, growing burden of chronic disease and refined treatment options demand is increasing on the one hand, while on the other hand the availability of intensive care professionals and graduates from medical universities constantly decreases. This will lead to shortages in the intensive care sector, due to scarcity of resources. In order to solve those problems intensive care specialists are striving for innovative solutions, of which one can be found in telemedicine.

Telemedicine is defined as the use of information and communication technology, in order to transfer medical services - independent of time and space - from healthcare professionals to patients. It is used if participants of medical services are separated by distance (Field and Grigsby 2002). It has the potential to positively influence this situation by transferring intensive care expertise to rural areas, with an additional supporting character for smaller intensive care units. Furthermore, this telemedical connection will lead to higher chances of success in terms of treatment as well as in saving more lives.

Aim of Tele-intensive Care Medicine

Tele-intensive care medicine has the capability of providing high-quality intensive care for patients and their families irrespective of where they live (EU 2008; Merkel 2012). Especially low volume intensive care units will benefit from an association with a telemedicine centre with higher volume, wide spectrum of 24/7 available subspecialities and a wide catchment area, Furthermore, tele-intensive care medicine interventions will prevent shortcomings in the number of intensive care professionals and will assure necessary standards. Therefore, the aim of tele-intensive care medicine is provision of high standards of care in every region, especially in rural areas, independent of the actual number of intensive care professionals and demographic situations.

Improved Outcomes by Telemedicine in Intensive Care Medicine

By means of telemedical solutions hospitals are supported by a university hospital or a telemedicine centre. These centres not only share routine and clinical expertise in uncommon diseases, but also an emphasis on standard preventive measures and care bundles. Furthermore, local hospitals and telemedicine centres amalgate into a virtual high-volume centre by connecting their units. As a consequence formation of such networks in intensive care units enables participants to achieve through tele-intensive care:

- decreased mortality;
- decreased morbidity;
- decreased length of stay;
- decreased number of readmissions;
- improvement of diagnosis and therapy by interdisciplinary exchange;
- increased quality of after-ICU life;
- potential cost savings.

Coherent interaction of different technologies like audio-video-conference systems, continuous transfer of vital patient data, information exchange through patient data management systems, or automatically generated alarms lead to a holistic solution. Standardised therapy plans and consistent application of prevention policies (e.g. peptic ulcer prophylaxis, ventilator bundles) are certainly crucial factors for the positive effects mentioned above (Lilly et al. 2011). Telemedical intervention improved compliance with cardiovascular protection by 24%, and compliance with effective VAP-bundles (ventilator-associated-pneumonia) was improved by 54%. Of outstanding importance is the fact that additional, long-term effects of telemedicine led to a higher proportion of patients discharged to their own homes (53.4% instead of 45.9%) and less demand for long-term care, e.g. rehabilitation facilities or nursing homes (Lilly et al. 2011)

Currently, identification of individual factors contributing to favourable outcomes is a matter of ongo-

ing research (Kahn et al. 2011). However, better availability of intensive care experts can be one conclusive explanation for better outcomes. Another potential success factor is participation via telemedicine in the expertise and routine of high volume centres. In conventional organisational models of intensive care, this factor was clearly identified as a determinant of success (Kahn et al. 2011; Kanhere et al. 2012; Peelen et al. 2007).

telemedicine in intensive care medicine. Another study by Zawada et al. (2009) reported a reduced mortality by 3.7% (from 9.6% to 5.9%).

All studies show a significant decrease in mortality and thus positive effects of telemedicine on intensive care units. Those effects and the above described clinical improvements and success factors, should lead to realistic cost savings in intensive care medicine.

> *"Tele-intensive medicine as a new model of cooperation seems to be a promising way to influence outcome, workflow, efficiency and quality of care"*

In established tele-ICU bases in the United States positive effects were observed not only during pilot projects but also in permanent operation. This could be demonstrated in small intensive care units as well as larger units with more than ten beds and within academic institutions (Lilly 2011). A reduction of mortality was found in several studies. McCambridge et al. (2010) stated a reduction by 4.3% (from 15.8% to 11.5%) of intensive care unit mortality. Risk-adjusted mortality could be significantly lowered by 29.5% compared to the control group (McCambridge et al. 2010). Lilly et al. (2011) discovered a significant reduction from 10.7% to 8.6%, which shows the positive effects of

Economic Effects of Tele-intensive Care Medicine

Tele-intensive care medicine can influence the cost of intensive care delivery in several perspectives. Resources will be used more efficiently, which in consequence will lead to a clear reduction of costs in intensive care medicine. Follow-up costs of ICU survivors will decrease due to higher quality of delivered care and fewer post-ICU sequelae including dependency on long-term care.

High additional implementation costs will decrease during dissemination of tele-ICU. On a mid-to long term view significant first-year costs can be compensated by a positive effect resulting in $3000 per patient savings. Besides the reduction of mortality, which is difficult to measure in monetary terms, telemedicine will result in more efficient use of resources in this sector and safeguard future access to and quality of care for the whole population. Capacity problems and scarcity of resources will be tackled effectively. Possible savings caused by decrease of complications are substantial as well. For instance, early detection of complications leads to fewer renal replacement therapies and less mechanical ventilation.

Conclusion

Tele-intensive medicine as a new model of cooperation seems to be a promising way to influence outcome, workflow, efficiency and quality of care. Supported by outcome and economic studies we expect that quality aspects will enrich the intensivist's armamentarium by an additional organisational model of care. Promising results as well as progress in telemedical methodology will pave the way to routine use of tele-ICUs. It can be expected that consensus found in debate about preferable ICU organisational structure in terms of closed vs. open ICUs will repeat itself. Growing evidence of sound quality data will demonstrate efficiency and benefit of the tele-ICU. ■

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MOBILE CRITICAL CARE

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Rapid evacuation of critically ill patients is central to modern military medicine. Here, evidence underpinning various aspects of 'mobile critical care' in Afghanistan is discussed, highlighting several lessons for civilian systems.

Introduction

The essence of military combat casualty care is rapid evacuation from the combat zone to progressively safer and better resourced areas, facilitating consolidation of advanced technological healthcare into small numbers of secure hospitals. Rapid transit distinguishes military trauma care from that delivered by civilian hospitals in war zones, which generally must treat patients in one location until they recover or die. Military trauma systems have always focused on rapid evacuation. Many aspects of the structure (if not function) of the modern NATO (U.S.-led) Joint Trauma System in Afghanistan would look familiar to a medical officer of the First World War (see Table 1). The differences would be speed of transit, the ability to bypass steps if a patient requires a surgical specialty (most commonly neurosurgery) only available at a larger hospital, and the complexity of en route medical care. The ability to provide this 'mobile critical care' has facilitated a revolution in modern combat healthcare. Robust epidemiological analysis of the Joint Trauma System in Afghanistan has facilitated rapid system- and practitioner-level improvements, and holds lessons for all trauma systems, both military and civilian.

Speed of Transit

Many people know of the dramatic reduction in time from battlefield to initial wound surgery facilitated by the helicopter, first used in substantial numbers during the Korean War. Less appreciated is the dramatic fall in time from initial wound surgery to the most sophisticated multidisciplinary care outside the combat zone that has occurred since 2001 (see Table 2). In the Vietnam War, the average time a wounded casualty took to return to the United States was 45 days (Carlton, Jr. and Jenkins 2008), as no transport capability existed that could provide even the rudimentary

Figure 1. Royal Air Force Medical Emergency Response Team aboard a CH-47 Chinook.

Reproduced by permission.

Table 1. Levels of Combat Casualty Healthcare Facility, World War I – Present

WWI healthcare facility	WWI staff	WWI function	Differences in the modern Joint Trauma System
Battlefield first aid	Stretcher bearers with rudimentary medical training	Tamponade of haemorrhage; removal from the battlefield	Every combatant has training and equipment to deal with the commonest causes of preventable death: extremity haemorrhage, airway obstruction, and tension pneumothorax.
Role 1: Battalion Aid Station (US) or Regimental Aid Post (UK & Commonwealth)	A non-specialist doctor with the assistance of medics and stretcher bearers	Collect casualties for onward movement, confirm haemorrhage tamponade, provide non-trauma primary care and occupational medicine	Moderate- to severe- trauma patients usually bypass Role 1 facilities unless they are in close proximity to the casualty (e.g. in a Forward Operating Base)
Role 2: Field Ambulance	Surgeons and supporting medical officers; medics and transport personnel to move patients to Role 3 hospitals after stabilisation	First level at which surgery could be performed; limited to life-preserving operations.	Remains the first facility at which limited surgery is possible. Very small inpatient holding capability; relies heavily on rapid patient evacuation and responsive logistic support. Imaging limited to plain radiology and ultrasound. Staffed by a general +/- orthopaedic surgeon and an anaesthetist. "Role 2 Enhanced" facilities have emerged in the last 15 years, which add an ICU capable of mechanical ventilation, larger blood & medication stores, +/- CT scanning. Usually staffed by a general surgeon, orthopaedic surgeon, anaesthetist & intensivist, specialist nurses, and sometimes by an emergency physician.
Role 3: Field Hospital. The largest healthcare facility deployed in the Area of Operations.	Surgeons, physicians, nurses, paramedical personnel	More complex surgery possible, in order to stabilise a patient for prolonged evacuation by land or sea. Substantial ward holding capacity.	The first hospital with a mixture of surgical specialists (including neurosurgery, cardiothoracic surgery, maxillofacial surgery, ophthalmology) complementing general and orthopaedic surgeons. CT scanning +/- MRI scanning. Larger ICU capable of all critical care interventions with the usual exception of renal replacement therapy and extracorporeal membrane oxygenation. Much smaller ward holding capacity.
Role 4: General Hospital	Similar staff to a large civilian hospital. Placed a 'safe' distance from the conflict; for expeditionary forces, in the country of origin.	The full range of surgical and medical acute care.	No different.
Role 5: Repatriation / convalescent hospital	Similar staff to a civilian rehabilitation hospital	The full range of surgical and medical sub-acute and chronic care.	No different.

critical care organ supports available at the time. In contrast, modern Critical Care Aeromedical Transport Teams (CCATTs) (also known as Military Critcare AME Teams (MCATs) in Australia and Critical Care Air Support Teams (CCASTs) in the UK) are able to transport patients on every form of organ support, including extracorporeal membrane oxygenation (Neff et al. 2013), which allows patients to arrive in a Role 4 hospital (currently located in Germany for US and Australian casualties, and in Birmingham for UK patients) within as little as 36 hours or less after wounding. This has dramatically changed the configuration of hospitals in the area of operations. For example, the ratio of ICU to ward beds in a typical NATO Role 3 hospital in Afghanistan in 2013 is 1:2.5, in comparison to 1:16 at the 1st Australian Field Hospital in Vietnam. Modern combat hospitals can only continue to function with effective 'mobile critical care'.

Complexity of En Route Care

a. From point of wounding ("Forward AME")

Understanding the optimal cost-benefit relationship in aeromedical evacuation (AME) assets is still evolving, driven largely by excellent data capture and epidemiological analysis in the current conflict. Two landmark studies demonstrated mortality benefit associated with more sophisticated care at the point of wounding. The first took advantage of the 'natural experiment' when a rotation of U.S. National Guard paramedics (who were flight paramedics in civilian life) replaced active-duty army medics (full-time military personnel with comparatively basic medical training) as clinicians on MEDEVAC helicopters retrieving patients from the point of wounding. (Mabry et al. 2012) Mortality at 48 hours fell from 15% to 8% without any other obvious explanation. A related international study compared hospital or 30-day mortality associated with retrieval by the British Medical Emergency Response Team (MERT), comprising a critical care physician, emergency nurse, and two paramedics transported in the relatively roomy CH-47 Chinook, with that of U.S. Army 'Dustoff' medics (with relatively basic training and scope of practice), transported in a comparatively small UH-60 Blackhawk, and U.S. Air Force Parachute Rescue PEDRO paramedics (trained to a more advanced level than army medics, and transported in a dedicated HH-60 Pavehawk). For the most minor and most severe wounds transport method had no effect, but for patients with an Injury Severity Score (ISS) of 16 – 50, mortality associated with the MERT (12.2%) was significantly (p=0.035) less than the composite mortality with the other two teams (18.2%) (Morrison et al. 2013). Possible confounding limits the certainty of this conclusion: for example, MERT patients were more likely to be from NATO countries, and were more commonly wounded by blast, neither of which is captured by ISS. The MERT frequently performed procedures in transit: for example in patients with ISS 16-50: chest decompression 24.9%, advanced airway intervention 40.5%, and prehospital blood transfusion 32.2%. Unfortunately, no comparative U.S. data was collected. MERT patients had a shorter time between hospital admission and operating theatre arrival, suggesting many emergency department-level interventions had already been performed, or that clinical planning and handover by a physician in flight led to expedited transit to surgery. A later study using the same database found that mortality of more severely wounded patients (ISS 20-29) associated with the MERT was significantly lower than that of those associated with the well-trained PEDRO medics (4.8% vs. 16.2%) (Apodaca et al. 2013), suggesting the size of the team and airframe influenced outcome.

b. Between role 2 – 3 – 4 hospitals ('Tactical AME' within the operational theatre; 'Strategic AME' outside the operational theatre)

The military is not unique in being able to provide critical care organ support in large fixed-wing aircraft, but the experience of >16,000 interhospital patient transports over the last 13 years (Blackbourne et al. 2012) using highly configurable platforms such as the C-17 Globemaster has placed modern air

Table 2. Speed of Transit through the Evacuation Continuum

	Time to first surgical care	Time spent in Area of Operations	Case Fatality Rate
World War I	12-18 hours	1-2 months	22%
World War II	6-12 hours	1-2 months	19.1%
Korean War	2-4 hours	--	23%
Vietnam War	65 minutes	45 days	15.8%
Iraq/Afghanistan Wars	1-2 hours	2-3 days	9.4%

forces at the leading edge of this practice. Nations have slightly different approaches to this task (see Table 3), but there is no evidence that these produce different results. These teams can provide all aspects of 'conventional' critical care, and can be supplemented to facilitate extracorporeal support. (Neff et al. 2013)

Command and Control Systems for Mobile Critical Care

The variability of capabilities in en route care, the tactical vulnerability of evacuation platforms, the varying eligibility of patients for different levels of care and the different services available at Role 2 and 3 hospitals all necessitate a sophisticated system that can appropriately allocate assets to tasks. In Afghanistan in 2013 this is the role of regionalised Patient Evacuation Coordination Cells (PECCs) staffed by clinicians (usually critical care-trained nurses with advice from physicians as required) and aviation officers in much the same way as in advanced civilian aeromedical retrieval systems. While anecdotally the performance of the PECCs is excellent, curiously this is one aspect of the deployed medical system that has not been the subject of a published performance evaluation.

Figure 2. Evacuation of civilian critical care patients from Cairns Base Hospital, Australia in a RAAF C-17 Globemaster, in anticipation of Cyclone Yasi. 2011.

Australian Defence Force photograph, reproduced with permission.
Source: http://www.defencejobsbroadcasts.gov.au/health/articles/cyclone-yasi-mercy-mission/

Evacuation Platforms

While developing effective systems and competent personnel is the main challenge in establishing a mobile critical care service, availability of appropriate evacuation platforms remains important. Some of the advantage associated with the British MERT may be simply the greater amount of space available in a CH-47 Chinook (see Figure 1) compared to a UH-60 Blackhawk. Strategic AME is considerably easier (and perhaps even safer) in a C17 Globemaster (see Figure 2) than in the slower, noisier and more cramped C130 Hercules. Table 3 outlines characteristics of common military aircraft. There is debate in most militaries over whether aircraft evacuating from the point of wounding should be dedicated to the AME role, but modern air forces have mostly abandoned dedicated strategic fixed wing aircraft in favour of multi-role platforms fitted as required with critical care equipment, such as the RAAF Deployable Aeromedical Retrieval and Transport System (DARTS) package. Civilian critical care AME generally involves fewer patients, transported either in small aircraft or in a reconfigured space on a commercial airliner. The time and expense of configuring civilian airliners has meant that almost all large-scale critical care air evacuations have been performed using military aircraft.

Clinical Considerations in Aeromedical Evacuation

Many textbooks (such as Hurd et al. (2003)) discuss the clinical considerations in aeromedical evacuation of the critically ill, and this is not the place to reproduce their content. It is sufficient to note that the problems of lower atmospheric pressure at altitude (even in pres-

Table 3. Examples and Characteristics of Common Military Aeromedical Transport Platforms in Common Use

	Range; Cruising speed	Patient capacity	Medical Crew	Medical interventions that can be performed
Tactical evacuation from point of wounding and between hospitals in the Combat Zone				
CH-47F Chinook (as operated by the Royal Air Force MERT)	400nm; 130 knots	Up to 24 litters; up to 9 requiring critical care, but most often 1-2 in the MERT role from point of wounding.	1 physician, 1 nurse, 2 paramedics	All prehospital interventions likely to be required, incl. blood transfusion, rapid sequence intubation, video laryngoscopy
UH-60 Blackhawk (as operated by the Australian Army and US Army DUSTOFF)	368nm; 150 knots	Up to 6 litters, or typically one requiring critical care	2 emergency medical technicians	Basic interventions incl. needle thoracostomy, supraglottic airway devices & IV therapy, but not rapid sequence intubation or blood transfusion
HH-60 Pavehawk (as operated by the US Air Force PEDRO)	373nm; 159 knots	Up to 6 litters, or typically one requiring critical care	2 paramedics	All prehospital interventions likely to be required, incl. blood transfusion, rapid sequence intubation, video laryngoscopy
Strategic evacuation from hospitals in the Combat Zone to those in secure countries				
C-130J-30 Hercules (operated by the USAF, RAF and RAAF, amongst others)	2835 nm; 348 knots	Up to 97 litter patients in stacked racks (but up to 50 if carrying staff and equipment); or up to 5 (but usually only 2) in RAAF critical care configuration	USAF CCATT has 1 physician, 1 CCRN and one respiratory therapist, in addition to general duties AME nurses, for up to 6 critically ill patients. RAAF MCAT has 1 physician and 1 nurse in addition to a general duties AME team for every critically ill patient.	All critical care interventions, but usually not extracorporeal therapy
C-17A Globemaster (operated by the USAF, RAF and RAAF, amongst others)	2420 nm; 450 knots	Up to 36 litter patients; or up to 5 (but usually only 4) in RAAF critical care configuration		All critical care interventions. In USAF practice, when augmented with suitable personnel and equipment, this has included renal replacement therapy, extracorporeal CO_2 removal and extracorporeal membrane oxygenation.

surised cabins if they are not kept at sea level, as is commonly the case), lack of space, noise, vibration, temperature, vulnerability (for example to a delirious patient) and the lack of consumables all require detailed planning by clinicians familiar with this environment. Clinical 'pearls of wisdom' include the particular value of invasive arterial pressure monitoring in small aircraft in which vibration interferes with oscillometric devices, the utility of Heimlich (or similar) valves rather than water-seal chest drains, the use of endotracheal cuff manometers to prevent tracheal mucosal damage, and running infusions in syringe drivers rather than in bags hanging over volumetric pumps. A major obstacle in aeromedical critical care is the time many authorities seem to require to clear modern medical devices for use in flight, which commonly leaves the patient dependent on equipment that has long since been superseded in regular practice.

> *"The capacity to perform 'mobile critical care' has transformed the modern combat health-care system, and changed the standard of care afforded to many remote civilian populations and those affected by natural disasters"*

Future Technology for Mobile Critical Care

Future mobile critical care should be made considerably safer and easier through the application of technologies that currently exist. If patient monitoring can be wirelessly streamed to a device the clinician either carries (or wears, as a head-mounted display (Liu et al. 2009)) in the airframe, the same information could be transmitted to a senior physician at the destination hospital – perhaps with a view of the patient from a helmet-mounted camera. Relatively inexperienced transporting clinicians are often capable of lifesaving interventions such as intubation, but are reluctant to make the decision to do so; prompting by telemedicine is a promising means of overcoming this (Skorning et al. 2012).

Conclusion

The capacity to perform 'mobile critical care' has transformed the modern combat healthcare system, and equally has changed the standard of care afforded to many remote civilian populations and those affected by natural disasters. Clinical practice only improves with constant experience, and systems only improve when the feedback loop to those writing policy is short. Having demonstrated these facts admirably in the last 13 years of conflict, many experienced military clinicians will soon return to civilian practice. This affords an opportunity to transfer and also to build upon knowledge. With the anticipated reduction in military clinical activity, strategic alliances with civilian critical care transport services also offer a system-level opportunity to improve on the lessons learnt in conflict. U.S. military responsibility for civilian prehospital transport in southwest Texas is an excellent example of such a partnership (Bailey et al. 2013), as is the regular work of UK military personnel with the civilian London Helicopter Emergency Medical Service. Investments in improving care prior to arrival in large hospitals and in more rapid transport are the greatest opportunities to reduce preventable mortality from trauma and other critical illnesses. ■

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IMPACT OF RAPID RESPONSE TEAMS ON ICU

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Rapid Response Systems (RRSs) improve timely referral to ICU, rate of unscheduled admissions and readmissions rates. Reliability of RRSs might be improved in future by automated monitoring devices that can support recognition and response.

Background

Co-location of patients with life-threatening illness allows for pooling of resources and expertise. Since the 1950s polio epidemic this has happened in Intensive Care Units. With the development of new technologies and drugs to support failing organs the management of critical illness has become more specialised, thus widening the gap between the level of care provided in ICU and that provided on general wards.

At the same time there is increasing evidence that early intervention in acute illness is associated with better outcomes in myocardial infarction, stroke, sepsis, acute kidney injury and other conditions. The better outcomes are probably both clinical (reduction of mortality and morbidity) and financial (shorter length of hospital stay and greater degree of self care on discharge from hospital). The timely delivery of appropriate interventions to patients with time sensitive pathology has therefore become a priority for health service delivery worldwide.

Unfortunately, however, delays in recognition of acute deterioration and treatment are frequent and widespread: international studies examining physiology prior to cardiopulmonary arrests or unplanned ICU admissions show a depressingly uniform picture of prolonged periods of physiological instability prior to adverse events (McQuillan et al. 1998). The causes for these delays are multi-factorial, and include poor knowledge of the physiology of acute illness, mental modelling of data leading to incorrect interpretation, cultural barriers to activate help across professional and hierarchical barriers and unavailability of experienced staff or ICU capacity. The resulting behavioural patterns impact on clinical outcomes of patients referred or admitted to ICU.

Rapid Response Systems: Afferent & Efferent Limb

Rapid Response Systems attempt to improve recognition of critical illness and response to patients at risk of catastrophic deterioration outside ICU on general wards. These two functions are labelled as the afferent and efferent limb.

The afferent limb identifies patients at risk, usually with the help of a structured system of assessment of physiological bedside observations. Vital signs are classified as normal or abnormal, either by using checklists to diagnose a significant abnormality for each parameter, or by scoring each parameter of a set of observations against a scoring table (see Table 1) and adding abnormalities into a summary score, which is then compared against a threshold value to trigger an alert (Subbe et al. 2001; Prytherch et al. 2010).

The efferent limb is a usually ICU based individual or team with critical care skills called the Rapid Response Team, Medical Emergency or Critical Care Outreach. The team can include critical care physicians, nurses and respiratory physiotherapists. If activated the RRT will attend to the patient on the general ward, perform an assessment of physiological abnormality, underlying diagnosis and feasibility of ICU interventions and then initiate treatment and, if needed, transfer to critical care.

The impact of the service on patient-related outcomes depends on a 'chain of survival' (Subbe and Welch 2013) (see Figure 1) with reliable recording of vital signs, reliable recognition of abnormalities, reliable reporting of these by bedside staff to RRTs and a reliable response by the RRT. Failure of any of the elements of this chain will lead to a 'failure to rescue' deteriorating patients and worse measures of severity of illness on arrival in intensive care (Oglesby et al. 2011).

Impact on Intensive Care Services

The on the whole positive evidence from the literature for the impact of Rapid Response Systems on patient safety is somewhat hampered by the large amount of heterogenous interventions that are being summarised under the label of RRS (Winter et

al. 2013). RRTs can interact with ICU patients prior to admission and after discharge back to general wards. There is evidence for a reduction in unscheduled admissions from a range of publications, especially from Australia. In the UK literature there is additional evidence that some of this reduction is achieved by proactive discussions with patients and families around limitations of care and implementation of Do-Not-Attempt-Resuscitation orders (Morris et al. 2013).

Critical care outreach services provide follow-up of patients discharged from ICU, thus ascertaining that seemingly stable physiology at time of transfer is maintained. CCOs help to re-acclimatise patients to the lower levels of staffing on general wards after a time in ICU with its much higher level of nursing support. There is evidence that this sort of service might reduce re-admissions to critical care (Ball et al. 2003).

In 2000 the Service Development Organisation in the UK funded a detailed examination of the impact of the introduction of CCOs on the performance of ICUs. An interrupted time-series analysis of the database of the Intensive Care National Audit and Research Centre (ICNARC) with ICU data matched at unit level against data about the timing of implementation of RRSs showed statistically significant reductions in the number of patients admitted to ICUs after cardiopulmonary arrests and a lower severity of illness on admissions to ICU following the introduction of RRTs (Gao et al. 2007). Outcomes related to utilisation of ICU bed days were confounded by an increase in intensive care funding with a concomitant rise in the number of ICU beds around the same time as the introduction of outreach services.

The only large scale multi-centre randomised controlled trial of Medical Emergency Teams showed little effect on the primary outcomes, which included unscheduled admissions to ICU, but results were confounded by the rather variable compliance with monitoring and escalation protocols in the intervention group (Hillman et al. 2005).

Future Directions

Given that the philosophy of RRSs is compelling it is disappointing that data supporting the impact on critical care services is relatively weak. Given the persistence of 'failure to rescue' and under utilisation of RRTs in patients with obvious physiological abnormalities it is clear that the search for system improvements has to continue.

> *"Given that the philosophy of RRSs is compelling it is disappointing that data supporting the impact on critical care services is relatively weak"*

Low reliability is often related to human factor issues (Leonard 2004), and reliability can be improved by automating processes with the potential of reducing error rates.

Electronic systems to record bedside observations lead to more reliable recording of vital signs. This concerns the completeness of the set of vital signs, including the key respiratory rate as well as an improvement in the frequency of recordings in line with agreed monitoring plans. A subsequent study analysing nearly one million sets of vital signs showed, however, that despite the support that electronic systems provide, clinical staff did not repeat highly abnormal vital signs in nearly a quarter of all patients affected at night thus indicating ongoing human factor issues (Smith et al. 2013).

Similar observations were made after the introduction of spot-check monitors that have the ability to calculate Early Warning Scores, and are able to advise clinicians by suggesting investigations or interventions in response to abnormal values of physiology on their screen. Implementation of these systems in a clinical trial enrolling nearly 20.000 patients in the U.S., UK and Australia led to a more reliable recording of respiratory rate and a reduction in the number of abnormal sets of vital signs prior to a call out of the RRT. In the group of patients with abnormal vital signs a reduction in the need for inotropes was observed. The impact on ICU utilisation was inconsistent, with an increase in the U.S. and a reduction in Australia and the UK (Bellomo et al. 2012).

The more advanced systems are able to cover most of the 'chain of survival'. In addition to the automated recording of vitals signs with wireless sensors, Early Warning Scores are automatically calculated and the frequency of automated measurements can vary with the degree of abnormality. Notifications about abnormalities can be sent to a central con-

Table 1. Early Warning Score (Subbe et al. 2001) Every set of vital signs is scored and parameters are added to achieve a summary score. .

	3	2	1	0	1	2	3
Systolic Blood pressure (mmHg)	<70	71-80	81-100	101-199		>=200	
Heart rate (bpm)		<40	41-50	51-100	101-110	111-129	>=130
Respiratory rate (bpm)		<9		9-14	15-20	21-29	>=30
Temperature (°C)		<35		35-38.4		>=38.5	
AVPU score				Alert	Reacting to Voice	Reacting to Pain	Unresponsive

Figure 1. Chain of Survival: it is crucial for patient safety that each element of the chain performs reliably.

sole on the ward, in Critical Care or to members of the RRT. In principle recording, recognition, reporting and response should therefore all be improved. Clinical trials are currently in progress to assess how this form of monitoring affects patient-related outcomes, behaviour of human teams at the bedside and, last but not least, admissions to critical care.

Conclusions

RRSs can facilitate the flow of critically ill patients from general wards into and out of the ICU. For optimisation of the impact of RRSs on patient outcomes improvements in system reliability are required. ■

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AUTHOR GUIDELINES

ICU MANAGEMENT

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THE ROLE OF LACTATE

AN INTERVIEW WITH PROFESSOR JAN BAKKER

Professor Jan Bakker is Professor of Medicine and Vice-chair of the Department of Intensive Care Adults at Erasmus Medical Centre in Rotterdam in the Netherlands. He is Visiting Professor at Columbia University - New York Presbyterian, U.S. and a Visiting Professor at the University Hospital Pontificia Catolica de Chile.

Can you explain the significance of lactate monitoring in critically ill patients and what it means in practice for the intensivist?

From the very first description in 1843 increased lactate has been associated with dying patients or patients that go on to develop morbidity like organ failure. The initial level, the trend, the time it takes to decrease to normal levels have all been associated with mortality and morbidity as long as intensive care medicine has existed. When Max Harry Weil did his first studies in the 1960s he found that between 4 and 5 was associated with 50% mortality. When we looked a few years ago, we found this level was associated with 45% mortality. Over the last 40-50 years nothing has changed in the relationship between lactate level and mortality.

For intensivists, the question is firstly, if I have this problem of high or non-decreasing lactate, what should I do? Secondly, if I could change it will my patient benefit? There have been few studies addressing this topic. The Pölönen study showed that there was less morbidity when they chased lactate levels to remain normal or be normal as soon as possible (Pölönen 2000). Our multicentre study accepted that increased lactate is not a good sign, especially in the early phase (8 hours) of ICU admission (Jansen et al. 2010). In this phase there is more likely a haemodynamic cause of increased lactate, so low perfusion, low tissue saturation/perfusion, whatever you want to call it, there is a time window where optimisation of the circulation should lead to a decrease in lactate. We tested how to get adequate tissue oxygenation. I think it's the only study ever that incorporated oxygen demand and oxygen delivery into a resuscitation protocol. We said if you want to optimise tissue oxygenation and do something about the need for oxygen and the amount of oxygen going to the tissues, do this very aggressively for maximum 8 hours and then the goal should be to decrease lactate rapidly. What's a significant amount of lactate decrease? About 10% an hour. We measured every two hours. You've done all your stuff and everything seems ok, but your lactate is not coming down, then what? That's a question that's never been addressed in critical care. That could be microcirculatory dysfunction, maldistribution of blood flow in the tissue, so mandatory in the protocol was the use of a vasodilator. With this array of interventions, we showed a risk reduction in mortality by 20%, but to our surprise, there was no effect on lactate at all. In the control group they didn't know lactate for 8 hours, just the first level in order to randomise the patient. In the protocol group every two hours they got a signal, but the actual decrease in lactate was exactly the same. Without knowing the lactate level, it decreased to a similar amount in the control group, despite the fact that the absolute mortality was almost 20% higher [it was absolute 10% difference and relative 20% difference] in this group. The only explanation we could find was that if the lactate was in the very high levels (5-10), if you compare the groups there was about a 30% absolute difference in mortality.

We speculated that especially in this group of patients with very high lactate levels if you don't know the lactate when the patient comes in, then you have no clue what you're doing, because you don't get the signal that you are doing the right stuff, e.g. stop giving fluids or dobutamine. In the lactate group you have the signal that this is going the right way - it was 10 now it's 6, then it's 4, and the patient is improving. This signal was completely lacking in the control group, so we think that this contributed to the difference in mortality. In the post-hoc analysis, we found that the real decrease in lactate occurred in the first two hours of resuscitation not in the first eight hours. Also not studied yet is what the lactate that is not decreasing tells you.

In most patients, lactate is a marker of disease and adequacy of resuscitation, where we have doubt what the specific place is of the circulatory optimisation in lactate. We think there is absolutely a signal that your circulation is inadequate, but it's probably in the very first hours. We just submitted a study with Glenn Hernandez from Chile, where we looked at the bi-phasic change in lactate. I think there is a bi-phasal change, so that very early it drops dramatically, and then it trends down a little. We have an indication in the study we just finished that this indeed is present, but the interval of measurements was very large, so it's a bit difficult, so the first significant rapid drop is circulation, and the next is metabolism. This is optimisation of the balance between oxygen demand and oxygen delivery and the rest is marker of disease.
Lactate is not an easy parameter, it's a

mixed bag of signals. I always say to my residents, "Lactate means trouble." You have to go to the bedside and find out what the message is.

Do you think we have enough data from RCTs to answer the question you have posed on the routine use of lactate as a resuscitation endpoint?

I don't think there is convincing evidence that decreasing lactate levels should be a target of therapy in ICU patients. When lactate is decreasing, that is a good signal, but when lactate is not decreasing, whether you should then optimise or more aggressively treat the circulation I don't think there is enough evidence. Especially we lack evidence for when should we stop 'chasing the circulation' and look at lactate as a marker of metabolism, a marker of something wrong with the patient, but which won't be fixed by giving fluids or dobutamine or whatever. A recent dramatic case we had was a patient with severe septic shock, due to melioidosis, he was on ECMO (extracorporeal membrane oxygenation), and he had a lactate of 12 for three days. His circulation was optimal, as far as we could optimise his circulation, but due to the severe disease and the diffuse intervascular coagulation, his hypermetabolism, he had very high lactate levels, but it came down after three days. He made an uneventful recovery and went home, without any macro organ failure. He was on renal replacement therapy and he was off when he left the ICU. In that particular case it was a marker of disease at very high levels but couldn't have been fixed by circulatory management.

You have suggested that we need to define the correct context for use of fluids for brain injury, sepsis, haemorrhage etc. Could you expand on this?

There is an incredible amount of evidence that HES products have negative effects on a large proportion of ICU patients, in, for instance, renal function. We use a lot of HES products in our brain injury patients to lower intra-cranial pressure. In our study on a marker of kidney injury (de Geus et al. 2011) in almost 800 critically ill patients. there were around 30 patients with isolated brain injury, but none developed renal failure, despite our use of HES products.

Asking why we should use something where we have not shown that the patient will benefit is very valid. But crystalloids in brain oedema are risky. In the context in which you use these HES products, for example colloids are frequently used in surgery and they all improve outcome, maybe the signal is too weak in this population. If you have a huge outcome difference, then some harm is not bad. The context question is good, because basically we do not understand why HES products 'kill' your kidney. I could stop using it, but then let's research the adequate context, or the mechanism of harm in order to understand why we should not use HES products. It's important to know the possible side effects and before we introduce something new to do adequate studies on what's the mechanism of action and what's the safety issue. That's a day-to-day problem in the current ICU, because we have no definitive clues about the endpoint of resuscitation. Fluid unresponsiveness is a strange endpoint of resuscitation, because we are all fluid responsive. Fluid unresponsiveness by definition means the patient is fluid overload. What amount of stroke volume variation is safe, we don't know, we only know when you are not fluid responsive any more you are very unlikely to be hypovolemic. We don't know when it's going to harm you. What's a clinical problem that's going to be solved with fluids is one. If you have a clinical problem that's going to be solved, should you drive for fluid unresponsiveness? We don't know.

Our study in Critical Care Medicine on sepsis vs tamponade, lowering cardiac output to the same amount in both models, then resuscitating the animals clearly showed you needed more fluids and a higher cardiac output to resuscitate the septic microcirculation. However, in a study we just submitted with Glenn Hernandez we showed that the microcirculation may not be an adequate endpoint of survival. Non-survivors to a large extent have abnormal microcirculation so I wonder about the endpoint. To what point should we resuscitate with fluids? In order to risk assess fluid responsiveness, what is hypovolaemia, I have no clue what hypovolaemia is. There's much more to gain, because that's what we do daily on our patients.

An important problem during the night in many ICUs: many patients are treated with fluid because their blood pressure drops when they sleep (I hope mine does when I sleep!), so probably that is normal physiology that doesn't require fluids. When do we need an increase in cardiac output brought about by fluids? We don't really know, we have no clear answers.

> *"Lactate is not an easy parameter, it's a mixed bag of signals"*

What do you see as challenges for critical care in the Netherlands?

The challenge will be to develop our specialty into a primary specialty like anesthesiology, internal medicine etc., and not be a subspecialty of anaesthesiology. That will be extremely hard, because everyone is fighting to keep their territory. Especially for anaesthesiology, it's a good variation of their daily routine to mix between OR and ICU. There are various reasons other then money to keep intensive care in the 'wrong' specialty. I don't think it will happen in the next 10 years in the Netherlands, although I would like it to.

Also, it's very difficult to translate research results from other countries into practice. We are very restrictive in the patients we admit, and there has to be a clear benefit for ICU admission. It's very different in the U.S. and the South of Europe and difficult to translate results. I would favour physiologic, mech-

anistic studies because that data is the same as in the Netherlands. Now we focus on fixing the patient more in a surgical type of way - you have a tumour, we get it out, you're fixed, you have hypotension, we give you volume and drugs, now it's fixed. When you turn it around to ask why the patient has hypotension, what is adequate blood pressure, go from there, then recovery is the result and not the goal. That's a completely new area of research.

What research are you working on currently?

I am still pursuing lactate, looking at where it's coming from, why is there lactate, why is it not coming down, what is the role of the liver, and the liver perfusion in lactate.

In ethics I'm interested in end-of-life care, futile/ disproportionate care, these difficult terms that are used interchangeably. The differences between the U.S. and Netherlands systems are clear. My U.S. colleagues are not allowed to do much without family consent. They have to keep patients alive when there is no chance of reasonable recovery. I'm interested in the financial and economic aspects. It's very difficult to study, to compare these two different moral/ ethical systems. My sense is that it costs an enormous amount of money. We argue about what an added Quality Adjusted Life Year (QALY) costs, but we never discuss what futility may cost. In the Netherlands the intensivist cannot be forced to continue care, if he thinks it's inappropriate. By law you have to stop treatment that doesn't make any sense. We are liable if we go on with treatment and the family changes their mind. That's to do with communication, informing (we do not ask for permission in the Netherlands!) the family to stop life support and continue to comfort care and explain what will happen. I would love to study something like that, but it's tricky.

> *"It's very difficult to translate research results from other countries into practice"*

You've written about the ethics of using data from patients who die before consent was given. Can you comment about this?

We convinced our ethics committee that if you're running a resuscitation study, you cannot allow patients or relatives to think for 24 hours whether to participate. They agreed we could start the study, then ask permission and, when the patient survives, ask again. We found that if the patient dies in the middle of the night, and the family left, it's difficult and maybe even unethical to contact them. We asked the committee about the data we had without consent, and the committee said we couldn't use it, as it's unethical. We explained that this would introduce bias, as the sickest patients die in the early hours of admission. If we remove the sickest patients from our study, we could end up in a negative study, when it should be positive. So we went to the national ethics committee, which took another approach. There is a file of data that you gathered ethically, as you had permission from the ethics committee. The data no longer belong to the patient, because he's dead. There is no law in the Netherlands to say these data automatically transfer to the relatives. The data is from the hospital. As long as you anonymise the data, you can do what you want with the data from that patient. Problem solved.

This interview will be in our Winter issue, which has a cover story on severe pulmonary infections. What do you see as the challenges of these?

In the Netherlands we have a debate with authorities and insurance companies over the use of extracorporeal membrane oxygenation (ECMO). It's extremely easy to use ECMO to solve the problem of oxygenation or hypercarbia or a combination. There are very scarce data that this is really good or should be a regular intervention in patients with pulmonary failure. If you are young, have H1N1 it works fine, because you know it's a transient disease and if there's not a lot of lung destruction then it's ok, but what about immune system diseases such as Lupus, Wegener's disease, necrotising diseases that destroy the lung, should they be on ECMO, if so, how long to try? We found that after 1-2 weeks, we doubted whether we should go on. Other centres go on for longer, a month to six weeks, then decide it hasn't worked. Should you go from ECMO to the waiting list for lung transplantation? We do it for patients with heart disease. Should we put in new lungs in a 26 year old with necrotising pneumoccal disease? The authorities are not interested to regulate, and would rather wait for guidelines from the national society. The insurance companies don't want to pay, saying there is no evidence. It's an expensive treatment, the incremental costs are significant. We found because you keep these lung patients alive much longer than before, they develop complications like fungi, candida infections in the lung that are very expensive to treat. It's a big question mark. Easy to do, so effective when you start, but you don't have a good endpoint, we don't have a good start point, so that's an open area of a new device looking for clear indications. ■

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Stat Strip LAC

Whole Blood Analyser for Point-of-Care Lactate Testing

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

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

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Easy to Use

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"PILGRIMAGE TO MECCA" IN SAUDI ARABIA

A MODEL FOR HEALTHCARE FOR MASS GATHERINGS

In this article we describe the response of the Saudi Ministry of Health and Hajj authorities to the unique problems of one of the largest annual mass gatherings in the world.

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Introduction

The Hajj or pilgrimage to Mecca with its associated rites is one of the five pillars of Islam. It is a ritual that is undertaken by Muslims once in their lifetime if they are physically and financially capable of doing so. All Muslims worldwide aspire to perform this important act of worship.

The Hajj occurs each year in the 12th lunar month; therefore, its timing varies by approximately 11 days each solar year. For example, in 2013, or 1434 Hijraa in the Islamic calendar, the Hajj took place during October 13-18, while in 2012 Hajj occurred during October 24-29. Umrah is a similar pilgrimage that can be undertaken at any time of the year, but it is likely to be more crowded during certain months of the year in the Islamic calendar, such as the whole month of Ramadan.

The Hajj is one of the largest mass gatherings (MG) in the world, with up to four million pilgrims performing its ritual each year (Khan 2010). In 2012, for example, over three million pilgrims performed Hajj, of which 55% came from outside Saudi Arabia. Of the more than 180 countries from which 'Hajjis' originate, approximately 45,000 are from countries in Europe (Memish 2010). Pilgrims of international (non-Saudi) origin tend to be older, with many pre-existing health problems. They are usually poorer than participants in other mass gatherings, with poor access to advanced pre-Hajj health care (Memish 2010).

Government Preparations

Hajj presents enormous challenges to the authorities in Saudi Arabia. It requires coordinated planning from all government sectors in the Kingdom of Saudi Arabia (KSA) the whole year prior to Hajj time. They annually update a comprehensive programme, to ensure that all aspects of Hajj are conducted safely and without major incident. It is no less than organising an Olympics every year. Arrangements includes healthcare services with more than 17,600 specialised personnel to provide state-of-the-art healthcare to all pilgrims free of charge (Memish 2010).

The Kingdom of Saudi Arabia is continually diligent in responding to logistic issues and health risks that are associated with this assembly of millions of pilgrims in an area of <3 square miles in the environs of Mecca. The Saudi government has spent billions of dollars on measures to reduce crowding and its associated risks, which reached disaster proportions as recently as 2006 (Ahmed 2006). Improvements in crowd management, and establishing facilities and services designed to decrease the physical burden of Hajj, including providing efficient transportation via elevated railways and fabricating more comfortable accommodations, have been its priority.

Trauma is a major cause of morbidity and mortality at the Hajj. Stampede is perhaps the most feared trauma hazard. Particularly dangerous for stampedes is the Jamarat area, where crowds surge around the pillars. To reduce such crowds, and in view of previous Hajj-related disasters, a four-level Jamarat bridge (with 12 entrances and 13 exits) was built with a capacity of 5 million pilgrims over six hours at an estimated cost of $1.1 billion. Each Hajj-related disaster results in some type of policy change, and extra efforts are made. Many such policy changes have cost billions of dollars to prevent reoccurrence of future incidents. By doing this, KSA has decreased deaths due to stampede from more than 1400 in the 1990 Hajj season to 250 in another similar stampede in 2004 (Qanta 2006).

Travel Precautions

KSA was able to achieve a lot in advancing global health in the largest MG (Shuja Shafi 2008). However, more can be achieved by increasing awareness among individual pilgrims and the authorities in their country of origin. The battle against the spread of travel-related infections is a shared responsibility.

Protection of the pilgrims begins before they leave their home countries. Countries sending pilgrims should coordinate preventive measures by healthcare professionals and community groups. Requirements linked to the issuance of entry visas for pilgrims are updated annually by the Saudi Ministry of Health (MOH) (Kingdom of Saudi Arabia 2013), which include universal vaccination of meningococcal poliomyelitis, yellow fever immunisation and other requirements for pilgrims from specific countries (Memish 2013). A recent study showed a decrease in meningitis cases as well as the case fatality ratio after implementing the immunisation requirement, leading to the conclusion that the vaccination policy has had a positive effect an invasive meningococcal disease (Memish 2013). Morever, upper respiratory tract

infection is extremely common when Hajj falls during the winter months. For this reason influenza vaccination is recommended for pilgrims, particularly for persons in at-risk groups. (Alzeer 2009)

Infectious Diseases and Disease Burden

The extreme congestion of people and vehicles during this time amplifies health risks, such as those from infectious diseases that vary each year. In the midst of an emotionally and physically demanding environment with extreme temperatures that may reach 45°C, noncommunicable and communicable diseases pose a genuine risk to pilgrims (Memish 2010). While most will travel and return safely, crowds and mass gatherings in Hajj and Umrah are associated with unique health risks such as transmission of infections, diarrhoeal disease, cardiovascular disease, heat stroke and trauma. Those given specific attention every year include both mild and severe respiratory diseases, food poisoning and gastroenteritis syndromes, haemorrhagic fevers, and meningococcal diseases. Reports of all diseases, particularly those with worldwide immediate effect, like severe acute respiratory syndrome (SARS) and meningitis, are immediately reported to the WHO epidemiologists. These work closely with Saudi authorities to analyse information and coordinate a response.

This year the problem is a disease caused by a new virus — Middle East respiratory syndrome, which is caused by a novel coronavirus (MERS-CoV). Most people infected with MERS-CoV had severe illness and pneumonia, and about half of them have died. This virus was first identified in a patient in Saudi Arabia who died in June 2012. It has so far affected nine countries, most of which are countries from which pilgrims would be travelling for Umra and Hajj. The virus has been shown to spread from person to person through extended close contact, so pilgrims living and travelling in close quarters may be at risk. There is no vaccine currently available to protect against MERS-CoV.

Because of the risk of MERS-CoV, the Saudi Arabian Ministry of Health has put forward some recommendations (Memish 2013), which are supported by the CDC's travel recommendations as well (http://www.who.int/ith/updates/20130725/en/). Both recommend that the following groups should postpone their plans for Hajj and Umrah this year:

- People over 65 years old;
- Children under 12 years old;
- Pregnant women;
- People with chronic diseases (such as heart disease, kidney disease, diabetes, or respiratory disease);
- People with weakened immune systems;
- People with cancer or terminal illnesses.

However, compliance with these voluntary recommendations may not be ideal, particularly considering that the one-time achievement of the qualifications for making Hajj may not occur until later in life, when the prevalence of chronic illnesses is increased. For example, during the 2009 H1N1 pandemic, similar recommendations were issued (Memish 2009). A survey of 406 French pilgrims revealed that one-third were > 65 years of age and one-fifth had diabetes (Gautret 2012). Fewer had chronic respiratory (5.2%) or cardiac (3%) disease. Similar surveys of French pilgrims in 2012 and 2013 revealed that 59% and 48% respectively had a condition for which postponing Hajj was recommended (Gautret 2013).

These recommendations, along with strict immigration rules, have resulted in a reduction of pilgrims coming from both within Saudi Arabia as well as abroad by 35% this year. These efforts will certainly diminish the likelihood of spread of MERS, but will not eliminate it. Ongoing disease surveillance and data analysis is necessary to better understand health risks and strengthen the evidence base for health policy and prevention. No new cases of MERS-CoV have yet been reported after the 2013 Hajj season in KSA.

Previous studies have shown that the prevalence of H1N1 among pilgrims was extremely uncommon (Memish 2012). No viruses were significantly more prevalent in either arriving or departing pilgrims. In addition to concern for transmission of emerging infections, diligence is also warranted in monitoring re-emerged respiratory diseases such as tuberculosis. In the 1994 Hajj season, Alzeer et al. studied pneumonia during Hajj, and they found that mycobacterium tuberculosis was the aetiologic agent in 28% of cases, who were primarily elderly pilgrims, followed by gram-positive bacteria (Alzeer 1998). Although housing and crowding improvements can help control the spread of diseases such as tuberculosis, the potential spread from previously infected pilgrims remains, and more research is needed in this area.

In addition, in 2004 severe sepsis or septic shock was treated in 42 pilgrims with the mean age of 65±14 years (Baharoon 2009). These patients comprised 25% of ICU admissions, and most (71%) had an underlying respiratory disease, which was thought to be the source of sepsis in over half.

> *"Hajj…is a useful model to understand the nature of risk management of any mass gatherings and the benefits of international collaboration and cooperation"*

A review of the burden of cardiovascular disease during Hajj reported that, for the 2002 Hajj, cardiovascular diseases were responsible for 46% of deaths in that study group, with 14% attributable to respiratory causes (Al-Shimemeri 2012). In response to this serious health issue, a Strategic Cardiac Hajj Interventional Programme (SCHIP), which provided three 24-hour cardiac catheterisation laboratories, launched in 2009 (Al Faraidy 2012). In the three years preceding SCHIP introduction, cardiac death rates were approximately 50%. However, during the 2009 through 2011 Hajj seasons that followed implementation of SCHIP, cardiac death rates were substantially reduced to 27%, 33% and 22%, respectively.

Healthcare Provision

The Ministry of Health (MOH) has always been a major contributor to planning for the wellbeing of the pilgrim guests. Infection

Control and Preventive Medicine Policies are established every year, based on knowledge of epidemiology of infectious diseases and global outbreaks. Around 40 preventive medicine teams (stationary and mobile) rotate through the different pilgrim camps to oversee all key public health and preventative matters during the Hajj. These teams report directly to the command centre on communicable diseases (like influenza and influenza-like illness, meningococcal disease, food poisoning and so on), using an electronic surveillance form to be submitted via mobile phones.

The Saudi response to the global H1N1 pandemic in 2009 in preparation for this MG alerted the world to the complex implications and opportunities afforded by similar MGs (Khan 2010). In addition, the KSA government mobilises large resources to areas involved in Hajj. For example, the MOH has in total 5185 hospital beds (permanent and seasonal hospitals). Thirty percent of these beds are considered ICUs, which run as closed units with on-site 24-hour intensivist coverage. To meet this demand, healthcare professionals are mobilised from all over the country (Arabi 2006). Moreover, for the management of heatstroke, all hospitals involved in Hajj are well equipped with special cooling units. Other services provided during this MG include security services and crowd control to ensure that there will be no major incident throughout the 6 days of Hajj.

The MOH continually enhances its ability to manage health issues that may affect Hajj; services are free, regardless of the sophistication of the treatment or intervention. Several hospitals are allocated to receive thousands of pilgrims each day. In 2013 there were 95 new mobile intensive care units that placed a doctor, nurse and essential technology in crowded areas where they are most needed. In the upcoming years from now Hajj will fall during summer months. Accordingly, the Saudi MOH will face another challenge, which is heat-related illnesses, particularly heat stroke and heat exhaustion.

Hajj: Implications for International Clinicians

Hajj presents a unique challenge that impacts international public health. World wide clinicians must be aware of potential risks for disease transmission. Appropriate strategies should then be applied before the departure of pilgrims. Practitioners must also be aware of the risks presented by the returned pilgrim and the potential post-Hajj illnesses. In addition, international collaboration in planning vaccination campaigns and managing health hazards has become essential. Such collaboration should cross all political considerations. The Saudi MOH every year publishes the Hajj requirements for the upcoming Hajj season (in collaboration with the WHO), which is a good guide for the required precautions to ensure safe Hajj for all pilgrims (WHO, 25 July 2013).

In addition to the effort by the Saudi MOH, countries from which pilgrims originate should be diligent in providing appropriate surveillance of returning pilgrims for possible domestic transmission of contagious illnesses including MERS, which may not have been symptomatic at the time the pilgrims departed from Saudi Arabia (Khan 2010). This can be challenging, considering that two-thirds of the pilgrims will be returning to countries where healthcare capacity is limited.

Conclusion

Protection of the health of pilgrims making Hajj to Mecca is an important and often challenging responsibility of the Kingdom of Saudi Arabia. Improvements in the environment and services provided are being made continuously. Pre-Hajj efforts focus on promulgating specific health requirements, which are updated annually, and recommendations for pilgrims to implement personal protection measures. During the Hajj are provided expanding, free MOH healthcare specialised clinics, dedicated hospitals, and mobile intensive care units. More epidemiological research is needed, as is diligent surveillance, as appropriate, of Hajjis after they return to their countries.

After decades of planning for the annual event of the Hajj MG, Saudi Arabia's experience is now well developed. Previous lessons learned added tremendously to this experience. Hajj, which is not the only MG (though the largest), is a useful model to understand the nature of risk management of any MG and the benefits of international collaboration and cooperation. Hajj poses complex challenges that require a broad expertise. No doubt, Saudi Arabia has the experience and infrastructure to provide unique expertise with respect to MGs. ■

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