Abstracts of the 4th General Scientific Meeting, Society of Intensive Care Medicine (Singapore)

Singapore, 2005

Impact of 24-h intensivist in paediatric critical care

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Critically ill patients are at high risk for death and permanent disability. Their care is also very expensive. During the past 30 years, critical care medicine has matured rapidly in the developed world and there emerged a group of physicians who regarded themselves as critical care specialists or "intensivists", dedicated to the care of the critically ill. Parallel developments and evolution occurred in the field of paediatric critical care.

In many countries there has been a trend to support the role of a full-time intensivist or team of intensivist who often supervise junior doctors in larger institutions. The concept of the "closed unit" is an outgrowth of this phenomenon. Several studies both in adult and paediatric intensive care have shown that changing from an "open" ICU format to a "closed" ICU format led by intensivists was associated with lower severity-of-illness adjusted mortality and morbidity. The team management approach led by a full-time intensivist offers the best prospect for ICU care, and gives practical approaches to team management that affect duration of stay, ventilation management, choice and duration of antibiotics and other issues.

In reality however, in the developing world in particular, where paediatric critical care is not well-established, the "open" unit system is still the norm. The open model may lead to difficulties related to multiple physicians who visit the unit and may fragment care, and there may be conflicts in management among the various consultants.

The microcirculation in critical illness

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There are increasing data demonstrating abnormalities of microcirculatory flow in critically ill patients with sepsis and that persistence of these abnormalities is associated with worse outcome. This has led to the suggestion that therapy should be aimed at resuscitating the microcirculation not aimed at restoring macrocirculatory variables to normal.

These microcirculatory data, however, are somewhat at odds with tissue oxygenation data which suggest that tissue oxygen tension is supranormal in animal models of sepsis and septic patients. This apparent conflict may reflect local microcirculatory control mechanisms. As a result of differential binding of nitric oxide by oxyhaemoglobin and deoxyhaemoglobin this leads to in increased microcirculatory flow in areas of tissue hypoxia and decreased flow in areas of tissue hyperoxia. If this is the case it suggests that the microcirculatory abnormalities are an appropriate response to the increase in tissue oxygenation and do not require treatment.

Antibiotic failure

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Antibiotic failure can be said to be present if there is a lack of response to "adequate" therapy. The may either be empiric therapy or microbiologically guided therapy. When one is faced with such a situation, a systematic approach is needed. The failure may be antibiotic related, microbiology data related or may be due to the fact that the problem, is a noninfectious one.

Drug Related Antibiotic Failure

Drug related "Antibiotic Failure" may be related to the selection of antibiotic or the dose of antibiotic. It may reflect a

problem with tissue penetration, or with the brand of antibiotic selected. Alternatively it may reflect a situation in which the organism is untreatable e.g. a virus infection. Problems with selection of antibiotic could result in therapeutic failure. "Broad spectrum" drugs may fail to cover specific organisms, e.g. 3rd generation cephalosporin will be inactive against MRSA or enterococci, antibiotics will not cover viral infections and the betalactams will not cover unusual infections like legionella or rickettsia.

Another cause of "Antibiotic Failure" is due to inadequate blood or tissue levels of the antibiotic. This may occur when oral treatment is used in patients with poor GI absorption or when a decreased dose is used for economic reasons. This inadequate regime may be due to the use of low doses or due to longer duration between doses. Aminoglycosides do not penetrate lung tissue well and CSF infections and infective endocarditis need high doses of beta lactams. Other situation in which "Antibiotic Failure" due to poor tissue penetration problems occur is when there are undrained abscess or collections or when there is a glycocalyx biofilm or slime around a foreign body. Sequestered infections and those in tissues with poor blood supply, like a diabetic foot, may not respond, as inadequate amounts of antibiotic reach the site of infection. When urological infections like pyelonephritis or prostatitis occur in diseased organs there is poor tissue penetration of antibiotics and in such situations quinolones have better penetration than beta lactams.

Microbiology Related Antibiotic Failure

Microbiology related "Antibiotic Failure" could be due to a discrepancy between in vitro vs in vivo sensitivity or due to a failure to distinguish between colonization from infection.

The difference between in vitro and in vivo susceptibility may result in microbiologically meaningless reports. Aminoglycosides will not be active against streptococcus and TMP/SMX will not be active against klebsiella. A "sensitive" report may not reflect MICs. Clues may be obtained by looking for class resistance. For example a report which shows salmonella to be sensitive to ciprofloxacin but resistant to nalidixic acid, suggest an increase in the MIC and the need for high doses of ciprofloxacin. Low level resistance of pneumococcus to penicillin may be similarly missed on disc testing leading to prescription of inappropriately low doses of beta lactam antibiotics.

A failure to distinguish between colonization and infection may lead to "Antibiotic Failure". Certain organisms common colonizers but unusual cause of disease (citrobacter, enterobacter) while other organisms are also common colonizers and may also cause secondary disease (MRSA and pseudomonas). Treating these will allow overlooking another actual pathogen.

On occasion a second organism or a second site of infection (e.g. vascular catheter) or a mixed or polymicrobial infection may result in "Antibiotic Failure".

Noninfectious Fevers

Noninfectious fevers may cause "Antibiotic Failure". These include sepsis mimickers like disseminated malignancy, drug overdoses and poisons, endocrine disorders like thyrotoxicosis, Addisons disease, pheochromocytoma or vascular problems like microangiopathic haemolytic (MAHA) syndromes, cholesterol emboli, and other rheumatological-vasculitic diseases. The presence of noninfected necrotic tissue or collections could mimic sepsis and brain injury could result in noninfective pyrexia.

Other causes of Antibiotic Failure

Other causes of "Antibiotic Failure" include overwhelming sepsis, late presentation of sepsis and sepsis with immune insufficiency. Here, despite "correct" antibiotics use, the balances of host versus pathogen forces is unfavourable, and the sepsis relentlessly progresses to death. Similarly, when the sepsis is only one component of a complex syndrome of MOF or severe pre-existing co-morbidity, appropriate use of antibiotics may not be enough to prevent the progress of the underlying problem. Lastly, an appropriately treated sepsis may relapse due to a sequential infection, and appropriate change of antibiotics may salvage the situation.

Therapeutic hypothermia in neurological injury

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The role of therapeutic hypothermia in neurological injury has been shown to be definitely beneficial in animal experiments. Several studies since the 1990s, particularly single centre trials, have shown efficacy in settings such as after witnessed cardiopulmonary arrest; in patients with severe head injury and raised intracranial pressure; in patients with large middle cerebral artery hemispheric strokes with cerebral edema, and for intra-operative use to reduce neurological deficit in a variety of surgical procedures (cerebral aneurismal surgery; cardiac surgery; spinal cord protection for vascular surgery). Nonetheless, several large clinical trials such as the NABISH 1 and IHAST have reported equivocal outcomes at best. A critique of these studies suggest that well designed treatment goals carried out in the context of experienced centres with established treatment protocols may be important in achieving better outcome. As such, therapeutic hypothermia should not be regarded as a panacea or magic bullet in neuroprotection but as one of several useful tools available in the armamentarium against a worse neurological outcome.

This presentation reviews the key parameters in (1) patient selection and setting, (2) hypothermic temperature targets, (3) induction times to targeted temperature, (4) duration of hypothermia therapy, (5) decision to discontinue and optimal re-warming period, (7) cooling techniques and (6) complications and their avoidance.

ICU delirium: An under-appreciated problem

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Delirium is a disturbance of consciousness with inattention accompanied by a change in cognition or perceptual disturbance that develops over a short period of time (hours to days) and fluctuates over time. Studies have shown that 20 to 80% of critically ill patients experience delirium. Despite this prevalence, delirium often remains unrecognized. Delirium has been reported to be an independent predictor of prolonged ICU and hospital length of stay, as well as a higher 6 month mortality rates. Delirium may also predispose ICU survivors to prolonged neuropsychological deficits.

Early recognition is important in delirium management. The Confusion Assessment Method for the ICU (CAM-ICU) is a validated and reliable serial assessment tool for monitoring delirium in ICU patients. Once delirium is detected, efforts should focus on identifying the aetiology and for the presence of known risk factors. Both prevention and treatment should focus on the minimization and/or elimination of predisposing and precipitating factors.

Risk of delirium may be minimised by the following interventions: repeated reorientation of patients, provisions of cognitively stimulating activities, a nonpharmacological sleep protocol, a pain management protocol, early mobilization and range of motion exercises, timely removal of catheters and physical restraints, use of eye glasses and hearing aids, minimization of unnecessary noise/stimuli.

The patient's current medications should be assessed for any offending agents (e.g. sedatives or analgesics) that may be causing or exacerbating the delirium. If possible, these drugs should be removed or decreased in dose. There are currently no drugs with FDA-approval for the treatment of delirium. Haloperidol is often used for the treatment of delirium, though this is based on sparse outcomes data from nonrandomized case series and anecdotal reports. Prospective randomized controlled trials are needed to evaluate the effectiveness and safety of haloperidol and other antipsychotics/neuroleptic agents (e.g. droperidol, risperidol, quetiapine, olanzapine).

Antibiotic strategies: Looking beyond the antibiogram.

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Although the results of antibiotic sensitivity testing are crucial in determining the choice of antibiotic to treat an organism that has been isolated from a patient, there are several other factors which should be considered. These include tissue penetration, pharmacokinetic-pharmacodynamic relationships, adverse effects and induction of resistance.

Clearly tissue penetration is an important consideration as the antibiotic has to reach the site of infection in order to be effective. The difference in tissue penetration between vancomycin and linezolid may explain the preliminary findings suggesting that the latter may be a more effective treatment for methicillin-resistant *Staphylococcus aureus* pneumonia.

Pharmacokinetic-pharmacodynamic relationships describe the association between certain pharmacokinetic parameters (eg ratio of peak serum concentration:minimum inhibitory concentration) and outcome (usually mortality). An understanding of these relationships is important in determining the appropriate dose and dosing interval, with the pharmacokinetic parameter being used as a surrogate end-point. A logical extension of this is to use the relationship to determine the suitability of a particular agent for treating a particular organism. The example of the use of quinolones to treat pneumococcal pneumonia will be used. The pharmacokinetic parameter most closely associated with good outcome is the ratio of area under the concentration- time curve to the minimum inhibitory concentration (AUC:MIC). For pneumococcal infections the cut-off value for microbiological cure is 33.7. Using this figure, pharmacokinetic data derived from critically ill patients and the MICs for pneumococci in different Asian countries, it is apparent that treatment of pneumococcal infection with quinolones may be sub-optimal in some Asian countries, even when the isolate is reported as being sensitive to quinolones.

Induction of resistance is also an important consideration. For example there are data suggesting that use of third generation cephalosporins may result in emergence of extended spectrum ß lactamase producing strains.

Infection control in the Intensive Care Units

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Intensive Care Unit (ICU) patients are at the greatest risk of acquiring heatlhcare-associated infections (HAIs) because of the severity of their underlying condition, length of ICU stay and usage of invasive devices. They are at 5 to 10 times greater risk of acquiring HAIs than the general hospital population as reported in United State. The majority of these infections are primary bloodstream infections, pneumonia and urinary tract infections, which are associated with the invasive devices. Removal of the devices as earliest as possible is the general principle used in reducing HAIs. Other strategies such as use of antibiotic-impregnated invasive devices, sub-glottis aspiration and closed suctioning system have been shown to reduce the incidence of HAIs. Technology, however, cannot substitute for sound core system processes designed to minimize the risk of HAIs. Consistent use of Standard Precautions such as hand hygiene between patient contact and strict compliance with appropriate isolation procedures must be followed.

Surveillance for HAIs is an important element of the infection control programme in the ICU. Successful surveillance focuses on system-level change and linking disseminated data with prevention efforts. The infection control team can provide information, education and intervention tools to the ICU to reduce host-risk factors of infection. The infection control team together with the ICU care providers can achieve in reducing HAIs, impacting morbidity, mortality, cost of care and length of stay and ensuring patient safety through targeted surveillance and intervention.

The hypothalamic-pituitary-adrenal axis in the critically ill

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The adrenal or suprarenal glands secrete multiple hormones. The adrenal medulla secretes adrenaline and noradrenaline which form part of sympathetic (flight, fright and fight) response. This hormone secretion is controlled by the sympathetic nervous system. The adrenal cortex secretes cortisol, aldosterone and sex hormones. 90% of the minarelocorticoid response is exerted by aldosterone, which results in maintenance of fluid status and blood pressure. This response is regulated by BP and volume status via kidney and RAA system. 95% of the glucocorticoid responses mediated by cortisol. This primarily results in mobilization of fuels and an anti-inflammatory effect.

The physiological role of cortisol is to mobilize fuels to counter stress. It does this by increased gluconeogenesis, increased liver glycogen stores and blood sugar and increase liver production from amino acids. There is a protein catabolic effect with decreased peripheral synthesis and increased breakdown. Fat metabolism is also stimulated with increased mobilization of fat stores. Any increase in fat deposition is secondary to increased hunger and increased food intake. Cortisol also has a haemodynamic effect, as it is one of the components of cardiovascular reactivity. It has a permissive effect on the catecholamines receptor and is also needed for synthesis of catecholamines, Na, K-ATPase. It decreases production of Nitric Oxide which then modulates vascular tone and permeability. It has complex and multiple effects on inflammation with a net effect of suppression of inflammation at multiple levels. The physiological control is via the CNS. Stress of any sort stimulates hypothalamic release of Corticotropin-Releasing factor (CRF), with subsequent increased ACTH release from pituitary and increased adrenal production of cortisol. This response occurs rapidly. A feed back control exists and an increase in serum cortisol level inhibit both CRF and ACTH release.

A reversible and variable response of the HPA axis is noted with SIRS and sepsis, with full recovery post illness. There may be inhibition or stimulation of cortisol release and also changes in protein binding changes and cellular level receptor resistance. This often leads to a blunted cortisol response in critical illness.

ICU patients may have primary adrenal failure if they have had prior steroid therapy or a primary disease of the adrenal gland. Drugs like ketokonazole or etomidate may suppress adrenal function. Secondary adrenal failure may occur with pituitary disease.

There are several unanswered questions when evaluating the stress cortisol response in ICU patients as against a stable patient with an endocrine problem. To further confound matters, 90% of cortisol is protein bound and is it difficult to measure free cortisol, yet the activity depends on free cortisol levels. There appears to be decreased binding and increased free fraction in critically ill.

For ICU patients an acceptable baseline appears to be 25 mics/dl, while for other normal patients,18 mics/dl is regarded as adequate. One can additionally use an ACTH stimulating test for further information a high dose HD-ACTH stimulation test with 250 mic.gms or a low dose LD-ACTH test with 1-2 mic.gms may be used. The response is conventionally measured after 30-60 minutes and either a rise of > 9 mics/dl from base line or a post stimulation value of > 25 mics/dl is considered adequate. The delta max value or the change pre and post stimulation is more a reflection of adrenal reserve than function. Absolute values are more clinically relevant. It should be noted that the ACTH stimulation test only tests adrenal function and does not test HPA axis integrity. This HPA axis can be evaluated by noting the response to physiological stress like hypotension, hypoxia or hypoglycaemia. In situations of such physiological stress a low cortisol value is indicative of HPA axis failure and suggest the need for cortisol replacement. In situations there is no additional value of an ACTH stimulation test.

A pragmatic approach to evaluating the HPA axis is as follows. A random level should be > 25 mics/dl. One does not need samples to be collected at a specific time of day in ICU patients. In normotensive critically ill patients, a normal response to a LD-ACTH is a cortisol level of > 25 mic/dl. Adrenal insufficiency exists if the LD-ACTH results in a value of < 25 mics/dl, and one could consider replacement doses as per clinical context. In hypotensive patients with < 25 mics/dl, a high dose and low dose ACTH tests help further evaluation. Primary adrenal insufficiency may be diagnosed if the cortisol value is < 25 mics/dl baseline and post LD and HD-ACTH. HPA axis failure is considered when the baseline value is < 25 mics/dl and increases to >25 mics/dl with both LD and HD-ACTH stimulation. ACTH resistance will manifest as a low baseline cortisol which remains < 25 mics/dl with LD-ACTH stimulation but increases > 25 mics/dl with HD-ACTH stimulation. The Adrenal Exhaustion Syndrome is seen in chronic critical illness where there is normal adrenal function test on admission but later in the illness there is an acquired adrenal insufficiency.

Incidence of adrenal insufficiency in ICU patients has been variably reported as follows:

- Elective surgery: 5%
- SICU patients with ventilation or hypotension: 37%
- Hypotensive elective surgical patients: 95%
- Medical/mixed ICU: 0-30%
- Septic patients: 8-65%

Cortisol has therapeutic potential in inflammation in that it may blunt the hyper-immune response. This may be beneficial or detrimental. Used in the hypo-inflammatory phase of a critical illness, it will probably be detrimental. It may benefit haemodynamics by improving cardiovascular reactivity. Steroids should be used in ICU patients on long term or recent steroids or any other classical medical indication. It is probably useful in sepsis with poor fluid response needing catecholamine inotrope or vasopressors therapy.

A review of literature shows that most trials have not shown an overall decrease in mortality with steroids but have shown some improvement in surrogate endpoints like blood pressure, inotrope requirements and LOS. Similarly meta-analysis has not shown a decrease in overall mortality with steroids. A study by Annane and colleagues suggests a mortality benefit may exist in a sub group of septic patients who are ACTH non-responders. A meta-analysis by the same author suggests that long courses of low doses of corticosteroids reduced 28 days and hospital morality.

An ongoing RCT (CORTICUS) may give a clearer answer to the actual role of steroid replacement in these septic patients. Till then it appears prudent to follow the Surviving Sepsis Campaign which has recommended 3 practice guidelines.

Steroids guideline: 1
(Grade C)
1a,b,c,d (Grade E)
Use IV Hydrocortisone 200-300mg/day in 3-4 divided doses for 7 days in septic shock refractory to fluids and requiring pressors

Other additional expert comments regarding this guideline included
1a: Use 250 mcg ACTH stimulation test
Identify non-responders if cortisol rise < 9mcg/dl
1b: Decrease dose after resolution of shock
1c: Taper steroid dose at end of therapy
1d: Add fludrocortisone 50 mcg OD orally

This guideline was based on the following references
1. Briegel (1999) Crit Care Med 27:723-732
2. Bollaert (1998) Crit Care Med 26:645-650
3. Annane (2002) JAMA 288:862-871

Steroids guideline: 2
(Grade A)
Do not use high dose steroid (> 300 mg hydrocortisone/day)

This guideline was based on the following references
1. Bone (1987) NEJM 317:653-658
2. Cronin (1995) Crit Care Med 23:1430-1439
3. Veterans study group (1987) NEJM 317:659-665

Steroids guideline: 3
(Grade E)
Do not use steroid if no shock unless on prior steroid or endocrine deficiency

Critical care aspects of dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS)

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Caused by the four serotypes of the dengue flavivirus and transmitted by *Aedes aegypti*, dengue affects an estimated 50-100 million people annually around the world, principally in tropical and subtropical regions. Dengue virus (DEN) causes a spectrum of clinical disease ranging from dengue fever to dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), which when untreated may lead to death. The infecting serotype and an individual's previous exposure to other DEN serotypes are known to influence disease severity.

Previously thought to be a childhood disease, recent epidemiologic data shows that the highest incidence of dengue is in the older children to young adult age group where data is still scanty. Although no specific treatment is available, an early diagnosis at a time when thrombocytopenia is absent and dengue serology likely to be negative is essential for adequate follow-up of a febrile patient. Early clinical and laboratory indicators in children with dengue are anorexia, nausea and vomiting, a positive tourniquet test and a lower total white count, and absolute neutrophil counts and a higher plasma alanine and aspartate aminotransferase levels. Defervescence, defined as an axillary temperature of less than 38^{o}C, is a defining point in dengue. Plasma leakage with a resultant rise in haematocrit differentiates DHF from DF. By this time thrombocytopenia and dengue serology will be positive and the diagnosis of dengue becomes firmer. Significant and sudden plasma leakage causes hypovolaemic shock which is very amenable to intravenous fluid therapy.

The physician caring for a patient suffering from DHF/DSS faces one of the most acute and dramatic management problems in tropical medicine. The sudden and massive increase in capillary permeability coincides with defervescence, the return of normal body temperature. One of the major challenges in DSS is to correct hypovolaemia and achieve adequate fluid replacement without precipitating fluid overload. Unlike non-dengue patients in the intensive care unit (ICU) who may have invasive monitoring to guide therapy, the physician has only his clinical expertise and some simple laboratory tests to guide therapy in dengue patients. Indeed, in the majority of cases, a careful assessment of the haemodynamic circulation based on the peripheral circulation, distal pulses, blood pressure, heart rate, level of consciousness and urine output together with serial measurements of haematocrit is all that is necessary to make a decision about the type and quantity of fluid therapy. The ideal fluid in DHF/DSS has yet to be found although there are some suggestions that colloids such as dextran 70 and gelafundin may be more beneficial to DHF patients with a pulse pressure of > 10 mmHg. The vast majority of DHF/DSS patients especially those receiving early infusion, will recover using electrolyte solutions alone. The second challenge in DSS is the management of patients with prolonged shock and massive haemorrhage where immediate transfusion with blood products is essential. Haematocrit values are confusing in this situation where continued plasma loss due to capillary permeability may lead to a stable or even a rising haematocrit reading despite active haemorrhage. Vital signs, serial measurements of arterial lactate and direct estimates of blood loss provide the best indicators of transfusion adequacy. Approximately 15% of DSS patients will require blood transfusion.

Oxygen: How much does one need

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The normal oxygen delivery from the left ventricle to the tissues (DO2) is 1 L/m. This may be increased by raising the PO2 / SO2 to more than 60-90 mmHg / 90-95%, the haemoglobin to more than 10-15 gm/dl or the cardiac output (CO) to more than 5 L/m.

A quick survey of dying patients in an ICU will show that the commonest cause of mortality are sepsis, severe co-morbidity, immune compromise, advanced chronic organ failure, malignancies, circulatory collapse, brain death or severe brain injury. It is rare to see isolated hypoxaemia secondary to acute reversible non inflammatory disease cause death. This observation makes one question the actual role of hypoxia in causing mortality in ICU patients.

When evaluating the problem of hypoxaemia, DO2 and mortality, we need to ask if mortality is due to a failure to use oxygen, rather than a decrease of supply. If so, correction of hypoxaemia and increasing DO2 may not be the answer. It must be

realized that the cellular store of energy is ATP and that oxygen is not a direct supplier of energy. It is only one component of energy production.

Hypoxia represents a situation where there is inadequate O2 for cellular metabolism. This may be hypoxaemic hypoxia, stagnant hypoxia, anaemic hypoxia or histotoxic hypoxia. A brief look at hypoxaemic situations, like those seen in adult congenital cyanotic heart disease (PO2 < 40-60 mmHg), natives living at 15,000 ft, (PaO2 = 43 mmHg) or intrauterine life (22-25 mmHg) clearly demonstrates that isolated hypoxaemia is not in itself dangerous.

The next question involves the supranormal DO2 issue. This is based on two flawed hypothesis, one that VO2 has two phase relation with DO2 (VO2 dependent DO2 and VO2 independent of DO2) and second that the failure of cardio-respiratory reserve is directly responsible for MOF. The delivery of blood and O2 depends on the tissue needs. When a tissue needs more O2, there is either an increased O2 extraction or an increased autoregulatory vasodilation and blood flow. This will cause redistribution or increase in global cardiac output. The VO2 controls the DO2 and not vice versa.

The second flawed hypothesis recognizes the fact that critical illness is associated with increased O2 requirements. The hypothesis that failure of cardio-respiratory reserve is directly responsible for MOF is flawed. A look at exercise physiology will demonstrate a huge reserve that is many time greater than the hypermetabolic demands of a critical illness.

The problem is not failure to deliver O2 but failure to use the delivered O2. Multiple experimental studies in humans and animals have demonstrated this inability to use O2 as the main cause of energy failure, and demonstrate that it is not due to the lack of O2 delivery to tissues.

Multiple studies have given conflicting results but has led experts to state "Do not aim for predefined elevated cardiac output" (Surviving Sepsis Campaign: Guidelines, G: Inotrope therapy: Recommendation 2 (Grade A), Aim for adequate O2 delivery. Gattinoni NEJM 1995;333:1025-1032, Hayes NEJM 1994;330:1717-1722)

Ultimately, aiming for supra-normal oxygen delivery is an example of chasing the wrong parameter and getting nowhere.

Non-invasive ventilation in the Intensive Care Unit

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Introduction

While non-invasive ventilation (NIV) has been shown to improve outcome in patients with acute exacerbations of chronic obstructive pulmonary disease (COPD), cardiogenic pulmonary oedema and immunocompromised patients with acute respiratory failure, many questions about its applications remain unanswered.

Recent studies have shown benefit for its use in post-extubation respiratory failure and postoperative hypoxia as well.

Attempts have also been made to improve the patient interfaces with devices such as the helmet to reduce discomfort, skin complications and non-compliance.

Obstructive diseases

There have been many studies showing improved outcome with the use of NIV in patients with acute exacerbations of COPD. Recently, there have been several meta-analyses which have supported the earlier findings.

Cardiogenic pulmonary oedema

Both continuous positive airway pressure (CPAP) and bilevel ventilation have been shown to improve physiological variables. However, the studies comparing these 2 modes have had differing results in terms of mortality and rates of myocardial infarction.

Facilitation of weaning

Controversy persists for the application of NIV in weaning. Ferrer et al's study demonstrated shortened duration of intubation and hospital stay, reduced nosocomial pneumonia and reduced mortality in patients weaned to NIV compared to conventional weaning on a ventilator. However, in Esteban et al's study, his group of patients with post-extubation respiratory failure treated with NIV had a higher ICU mortality and the study was terminated prematurely.

Learning curve for NIV use

Successful use of NIV requires the close attention of a skilled caregiver especially in the initial period of its utilization. As the caregiver team gains experience in the use of NIV, outcomes may also improve. Girou et al's retrospective review of NIV use in a French University referral hospital showed a significant increase in NIV use and a concomitant decrease in mortality and ICU-acquired infection rates over the study years. The authors speculated that improvement in the delivery of NIV over time was associated with the reduction in mortality and nosocomial infections.

Do-not-intubate (DNI) patients

NIV has been used in some centres to reduce dyspnoea and treat reversible processes such as acute pulmonary oedema or COPD exacerbation in DNI patients. Its use remains highly controversial as it is not non-invasive and may actually increase discomfort. As such it is important that patients are fully informed about the implications of the treatment.

Abstracts of
The 12th International Symposium on Shock and Critical Care, Bali, 2005

Echocardiography 2005 for the critically ill patient

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Echocardiography is of immense value in the evaluation of heart disorders. It plays a vital role in unravelling the cardiac contribution to circulatory failure in the critically ill patient. One third of patients admitted to an Intensive Care Unit with a noncardiac primary diagnosis have additional cardiac pathology. Therefore, evaluating the heart rapidly and preferably noninvasively at any time of night or day becomes important in the delivery of optimal care, hopefully with a good quality outcome. Studies on a haemodynamically unstable patient need to be performed in a skilled and focused manner.

Major challenges impede the widespread use of echocardiography in Intensive Care Units. These include educating the intensive care community as to the potential of the modality, developing echocardiographic examinations that are relevant to the critically ill patient, and producing quality studies. Expanding the routine elective echocardiographic study to one beneficial in the haemodynamically unstable patient with multiorgan failure, has led to research of clinical tools that are most beneficial to the intensivist. Techniques used for stable patients with only cardiac disease, require vigorous evaluation to assess their efficacy in the shocked or deteriorating patient. Assessment of left ventricular function (whilst on inotropic therapy), measuring left atrial pressures (as an indicator of left ventricular preload), evaluating right heart and pulmonary interactions, are but a few of the specialised areas relevant to the intensivist. Also, the value of a non-invasive diagnostic technique identifying unsuspected cardiac pathology, which is contributing to a patient's clinical instability, should not be underestimated.

Increasing numbers of Intensive Care Units around the world have or are obtaining their own dedicated echocardiographic equipment. This trend will be accentuated as cost considerations become more favourable with the marketing of smaller and less expensive machines. The research opportunities in the critically ill population are enormous. Replacing potentially dangerous invasive modalities of assessing cardiac function with a safer and more adaptable method provides considerable research opportunities on a heterogenous group of patients.

Training and credentialing are pivotal to the development of quality echocardiographic studies. Training guidelines and standards developed by respected national and international groups provide guidance to intensivists performing echocardiography. Future specific training and credentialing programmes specific to Intensive Care Medicine need to be developed.

The diagnosis and treatment of hypertensive crises

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Hypertension is an exceedingly common disorder in Western societies and as such, health care practitioners of most clinical specialties are likely to encounter patients with acute severe elevations of blood pressure. In particular, hypertensive emergencies and hypertensive urgencies are commonly encountered in the emergency department, operating room, post-anaesthesia care unit, obstetrical suites and intensive care units. The most important factor that limits morbidity and mortality from these disorders is prompt and carefully considered therapy. Unfortunately, hypertensive emergencies and urgencies are among the most misunderstood and mismanaged of acute medical problems seen today. Indeed, the visceral reflex of rapidly lowering an elevated blood pressure is associated with significant morbidity and death. Clinicians dealing with hypertensive emergencies and urgencies need to be familiar with the pathophysiology of the disease and the principles of treatment.

Patients with hypertensive crises may require the immediate reduction of the elevated blood pressure to prevent and arrest progressive end-organ damage. The best clinical setting to achieve this blood pressure control in the intensive care unit with the use of titratable intravenous hypotensive agents. There are several antihypertensive agents available including esmolol, nicardipine, labetalol and fenoldopam. The appropriate therapeutic approach of each patient will depend upon the clinical presentation of the patient. Agents such as nifedipine, nitroprusside and hydralazine should be abandoned as these agents are associated with significant toxicities and/or side effect profile.

Ischemia-reperfusion injury of the lung: role of surfactant

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Although lung transplantation is an accepted treatment option for patients with end stage pulmonary diseases, the one (80%) and five (<50%) year survival remains limited. The major impediment to short-term survival is the development of primary acute graft failure. Clinical symptoms will usually occur within the first 72 hours after lung transplantation and consist of non-cardiogenic lung edema, increased pulmonary artery pressure and resistance, decreased lung compliance and hypoxemia, resulting in increased utilization of intensive care resources, extended hospital stay and/or eventually death.

Lung ischemia-reperfusion injury (LIRI) is an important contributor to primary acute graft failure and occurs during lung transplantation as a result of the cessation of blood flow during transplantation (ischemia). When the lung vessels and main bronchus are reconnected to the receiving patient, blood and oxygen flow to the lung is restored (reperfusion). Although approximately 97% of the recipients show some degree of reperfusion injury on chest X-ray, severe LIRI occurs in 15-30% of lung transplant recipients. Severe LIRI may progress into the acute respiratory distress syndrome (ARDS) within a couple of days after the onset of LIRI. Survival after ARDS is below 50%, thereby contributing to the poor 1-year survival after lung transplantation.

Although complex, the pathogenesis of LIRI can be described by accumulation of intracellular Ca^{2+} and Na^{+} and the subsequent formation of reactive oxygen species, eicosanoids, proteolytic enzymes and (phospho)lipases, which cause damage to the lipid membrane of the cell, resulting in increased cellular permeability, formation of cellular edema and eventually cell death. Finally, all these pathways lead to a disturbed surfactant (*surf*ace *act*ive *a*g*ent*) system.

Up to years after clinical lung transplantation and in ARDS patients, it has been shown that the surfactant system is damaged. Surfactant, which consists of phospholipids and surfactant-associated proteins, is essential for normal breathing, since it lowers the surface tension at the alveolo-capillary membrane, thereby keeping the lung open at the end of expiration. Lowering the surface tension is also important for fluid homeostasis across the alveolo-capillary membrane. Furthermore, surfactant serves as a functional barrier in the alveolus, so that the transfer of molecules across the alveolo-capillary membrane is limited, and it protects the lung against micro-organisms.

Surfactant inactivation after LIRI occurs due to flooding of serum proteins in the alveoli, which dose-dependently inhibit surfactant, and surfactant components into the bloodstream. Furthermore, the aforementioned formation of (phospho)lipases, proteolytic enzymes and reactive oxygen species after LIRI, can directly damage surfactant components.

To restore the damaged surfactant system after LIRI, several authors have investigated the effect of surfactant replacement therapy. Although administration of surfactant after the development of LIRI seems beneficial, it has been shown that pretreatment of the lung with surfactant could be more beneficial. This can be explained by diminished cell membrane damage during ischemia and an enlarged surfactant phospholipid pool before transplantation, thereby preventing deterioration of the entire endogenous surfactant pool due to LIRI. Also, surfactant given to the donor may result in a more homogeneous distribution in the lung as compared to treatment after reperfusion, when alveolar damage has already occurred.

The beneficial effects of surfactant therapy are probably the result of reduction of the inhibitory activity of serum proteins, the reinstatement of surfactant components and possibly of its anti-oxidant and anti-inflammatory effects.