Editorials

The teleology of inflammation - doing battle with the selfish gene

Human host-defense systems are calibrated by natural selection against recurrent low-grade tissue incursions by foreign organisms.[1] Without immediate local isolation of tissue invaders and efficient repair of tissue damage, the host becomes dangerously vulnerable. As a consequence, routine host-defense involves explosive, yet contained, and coordinated cellular and humoral responses.

However, the critical end-point here is not individual survival, but rather the best overall chance of successful propagation of the species. In fact it has been argued that we are merely survival machines for our own selfish genes.[2] Certainly host-defense systems are first and foremost products of selection pressure, and less common events lack sufficient evolutionary visibility to have a major impact. From this perspective, overwhelming infection and large-scale tissue damage evidently represent a lesser threat to gene immortality, because responses to these events seem maladaptive, with excessive, prolonged and uncoordinated mediator release. The result is 'malignant intravascular inflammation',[3] which can cause vasodilatory shock, multiple organ dysfunction syndrome and death. The selfish gene may thus allow adverse outcomes for victims of these less common threats, since they are mathematically disadvantaged. As critical care practitioners we find ourselves confronted by the paradox that under certain circumstances, our patients are programmed to die at the hands of what should save them – their own host-defense systems. Trying to rescue victims of evolutionary 'collateral damage' is the more frustrating part of an intensivist's job description.

In this issue of Critical Care and Resuscitation, Drs Corke, Glenister and Watson look closely at one component of tissue and more particularly splanchnic host-defenses which seems to become maladaptive on major stimulus.[4] Following their recent exploration of the relationship between the gastro-intestinal tract and multiple organ dysfunction syndrome, [5] these authors concentrate specifically on secretory phospholipase type A_2 ($sPLA_2$). The $sPLA_2$ enzyme is one of a large group of phospholipases best known for an ability to hydrolyse certain types of phospholipids to produce arachidonic acid, an important precursor in the eicosanoid host-defense pathway. The authors outline the wide variety of $sPLA_2$ subtypes now known, and the various roles attributed to them, ranging from inflammatory mediation to tissue repair and signal transduction. The reasons for their specific interest in $sPLA_2$ can be summarised as follows:

- The $sPLA_2$ enzyme exhibits experimental bacteriocidal activity and promotes phagocytosis.
- The normal substrate is anionic phospholipids, but certain subtypes can act on neutral phospholipids in intact cell membranes, causing tissue damage.
- The gut mucosa is a likely source of most endogenous $sPLA_2$, the expression of which can be up-regulated by endotoxin and platelet activating factor.
- Experimental splanchnic ischaemia-reperfusion releases sufficient gut $sPLA_2$ to cause distant organ injury.
- Administration of $sPLA_2$ to experimental animals causes shock.
- Large quantities of the enzyme are released after cardio-pulmonary bypass, major vascular surgery, sepsis, shock, multi-trauma and pancreatitis.

Because of this profile, the authors suggest that selective inhibition of $sPLA_2$, or one of its sub-types, might be of benefit in critical illness, particularly in situations where there is both inflammatory mediator release and the possibility of occult gut dysoxia. They cite some experimental support for this concept.

Such speculation is of course familiar territory. It should not to be discouraged, although prior to the PROWESS study[6] more than fifty novel therapies showing early promise in the treatment of severe sepsis and septic shock generated disappointment,[7,8] and even adverse outcomes,[9] in Phase II or III trials. There is already speculation that $sPLA_2$ inhibition will go the same way.[8] Possible reasons for the repeated negative findings are many, and have been explored elsewhere along with suggested improvements in the trial process.[10] The very nature of large scale clinical trials of agents such as $sPLA_2$ inhibitors can militate against high quality efficacy data, despite exacting protocols and enthusiastic policing of recruitment criteria by trial coordinators. In particular, one should beware of data originating from units where the prime motivation for patient recruitment is financial.

Just as repeated negative outcomes may reflect the deficiencies of large clinical trials, an isolated positive outcome should also be treated with healthy skepticism. It is not beyond the realms of possibility that the landmark 6% reduction in absolute mortality attributed to the administration of recombinant Activated Protein C was simple type 1 error. In other words, if enough immunomodulation trials with inherent deficiencies are performed, one must eventually produce a false positive

result. Hopefully this was not the case with the PROWESS study, but time will tell.

What seems certain is that there will be no single magic bullet capable on its own of protecting our patients from maladaptive responses to intense inflammatory triggers. In the end, incremental benefits from individual agents such as recombinant activated Protein C will need to be pooled to counteract the legacy of the selfish gene.

Dr. T. J. Morgan
Intensive Care Facility
Royal Brisbane Hospital
QUEENSLAND 4029

REFERENCES

1. Beutler B, Poltorak A. Sepsis and the evolution of the innate immune response. Crit Care Med 2001;29 [Suppl]:S2-S7.
2. Dawkins R. The Selfish Gene. Oxford: Oxford University Press, 1989.
3. Pinsky MR. Multiple systems organ failure: malignant intravascular inflammation. Crit Care Clin 1989;5:195-198.
4. Corke C, Glenister K, Watson T. Circulating secretory phospholipase A_2 in critical illness – the importance of the intestine. Critical Care and Resuscitation 2001;3:244-249.
5. Corke C, Glenister K. Monitoring intestinal ischaemia. Critical Care and Resuscitation 2001;3:176-180.
6. Bernard G, Vincent J, Laterre P, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344:699-709.
7. Carlet J. Immunological therapy in sepsis: currently available. Intensive Care Med 2001;27:S93-S103.
8. Arndt P, Abraham E. Immunological therapy of sepsis: experimental therapies. Intensive Care Med 2001;27:S104-S115.
9. Fisher CJ jr, Agosti JM, Opal SM et al. Treatment of septic shock with the tumor necrosis factor receptor : Fc fusion protein. N Engl J Med 1996;334:1697-1702.
10. Cohen J, Guyatt G, Bernard GR, et al. New strategies for clinical trials in patients with sepsis and septic shock. Crit Care Med 2001;29:880-886.

Treatment options for refractory intracranial hypertention: the evidence-based cupboard is bare

The management of patients with refractory posttraumatic intracranial hypertension remains a difficult and often frustrating clinical problem. This typically occurs in young patients with moderate to severe diffuse axonal injuries, frequently associated with traumatic subarachnoid haemorrhage, occurring 3 - 5 days following injury. The natural progression of this "hyperaemic" or "vasogenic" phase of brain injury is variable and depends on the elastant reserve of the brain.[1] Put simply, if the patient has adequate intracranial volume to absorb increases in intracranial pressure without further compromising cerebral blood flow, then associated neuronal loss should be minimised. The mortality in these patients is high; survivors are frequently left with significant disabilities.

By applying a pathophysiological approach to exhaustion of elastant reserve, it would appear that mechanical therapies such as cerebrospinal fluid (CSF) drainage or decompressive craniectomy would be successful in improving intracranial pressure/volume relationships.[2,3] Many experienced neurosurgeons have anecdotes of "remarkable" recoveries in patients with apparent refractory intracranial hypertension following decompressive craniectomy.[4] Medical therapies such as cerebral volume regulation ("Lund" therapy),[5] or "optimised" hyperventilation,[6] have theoretical merit. However, the plural of anecdote is not data: none of these therapies have been subjected to an adequately powered, outcome based, randomised and controlled trial.

Current management guidelines offer little in terms of providing evidence-based strategies for such patients. Drainage of CSF via an intraventricular catheter is recommended both as an intracranial pressure monitor and as a "first line' method of reducing intracranial pressure.[7] Medical therapies to reduce intracranial hypertension such as hyperventilation, hypothermia, or barbiturates are considered as "second tier" therapies, whilst surgical decompression is mentioned as an option.[8]

The logistics of conducting a randomised trial to assess whether any of these treatments improve outcome are formidable. Traumatic brain injury is a heterogenous process. Outcomes are markedly influenced by primary injury and secondary ischaemic/hypoxic insults; ICU management strategies vary widely between centres, and surgical interventions such as decompressive craniectomy are applied with various levels of enthusiasm. Quantification of outcome is problematic - the extended Glasgow Outcome Score is the most widely used tool, but opinion is inconsistent about the optimal follow up period and the sensitivity and specificity of functional survival.

These logistic hurdles do not however mean that future studies are impossible. Recent interest in revisiting the role of decompressive craniectomy has increased around the world, particularly in Europe

following a specific survey conducted by the European Brain Injury Consortium and in Australia following a positive study in children.[4] Decompressive craniectomy is an inconsistently and infrequently performed procedure, largely influenced by surgical preference. To demonstrate an absolute reduction of mortality by 10 - 15% from baseline mortality of 30%, a sample size of 350 patients would be required. This would mandate a multicentred, probably multinational, trial requiring a standardised management approach.

Patient selection is an interesting issue as the role of decompressive craniectomy in patients with raised intracranial pressure due to extra-axial or intradural haematomas is different to those with primary diffuse axonal injury. Consequently, patients would need to be identified, or stratified according to underlying cerebral pathology determined by CT scan.[9] Treatment thresholds could be determined by the degree of intracranial hypertension, assessed using a standardised method of intracranial pressure measurement, such as ventricular drainage. Thereafter, surgical methods of decompressive craniectomy (unilateral vs bilateral) and medical therapy will need to be standardised. Finally, mortality and functional outcomes will need to be assessed at six and 12 months using a standardised method. Such a study would require an adequately funded, cohesive and committed study group.

The allocation of funding and research resources directed at a high mortality and morbidity condition such as traumatic brain injury have been questioned by some. Studies directed at injury prevention and early quantification of functional outcome are considered to be better cost-effective research initiatives. Concerns have been addressed that such "aggressive" interventions such as decompressive craniectomy, or cerebral volume regulation may reduce mortality, but increase vegetative survivors. These are valid comments particularly when the significant funding, design, coordination and conduct of such a trial may provide an answer for only one question.

However, given the persistently high mortality and morbidity associated with traumatic brain injury, research at all facets of this global epidemic is a priority. Evidence-based guidelines, such as those promulgated by the Brain Trauma Foundation, highlighted the paucity of evidence upon which many units base their practice. In many ways, these guidelines have laid the foundation to address future questions, rather than provide definitive answers. The next challenge is to answer them.

Dr. J. A. Myburgh
Intensive Care Unit
St George Hospital
NEW SOUTH WALES 2217

REFERENCES

1. Martin NA, Patwardhan RV, Alexander MJ, et al. Characterization of cerebral hemodynamic phases following severe head trauma: hypoperfusion, hyperemia, and vasospasm. J Neurosurg 1997;87:9-19.
2. Guerra WK, Piek J, Gaab MR. Decompressive craniectomy to treat intracranial hypertension in head injury patients. Intensive Care Med 1999;25:1327-1329.
3. Guerra WK, Gaab MR, Dietz H, Mueller JU, Piek J, Fritsch MJ. Surgical decompression for traumatic brain swelling: indications and results. J Neurosurg 1999;90:187-196.
4. Munch E, Horn P, Schurer L, Piepgras A, Paul T, Schmiedek P. Management of severe traumatic brain injury by decompressive craniectomy. Neurosurgery 2000;47:315-322.
5. Grande PO, Asgeirsson B, Nordstrom CH. Physiologic principles for volume regulation of a tissue enclosed in a rigid shell with application to the injured brain. J Trauma 1997;42:S23-S31.
6. Cruz J. The first decade of continuous monitoring of jugular bulb oxyhemoglobinsaturation: management strategies and clinical outcome. Crit Care Med 1998;26:344-351.
7. The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Recommendations for intracranial pressure monitoring technology. J Neurotrauma 2000;17:497-506.
8. The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Critical pathway for the treatment of established intracranial hypertension. J Neurotrauma 2000;17:537-538.
9. The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Computed tomography scan features. J Neurotrauma 2000;17:597-627.

Rare and emerging infections

Most intensive care specialists are aware of the emergence of antibiotic resistant bacteria in critical care units and the risks of cross infection via hands of hospital personnel or contaminated equipment, of resistant gram positive and gram negative bacteria and even Candida. Methicillin resistant S. *aureus*, vancomycin resistant enterococcus, extended spectrum ß lactamase (ESBL) producing *Klebsiella sp*., multiresistant *Pseudomonas sp*. and, most recently, vancomycin intermediate *S. aureus*[1] all represent major therapeutic challenges in critically ill patients.

However in this months Journal, Hore describes the

'hazards outside' – an eclectic collection of rare but potentially devastating infectious diseases that may require critical care management.[2] Many other emerging or severe and unusual infections such as Hendrah (equine morbillivirus) and the related Nipah virus, Aeromonas, Melioidosis, Flinders Island spotted fever and new strains of influenza virus could have been described, but those selected are illustrative of a number of points.

Firstly, all the infections discussed are associated with exposure to either marine or soil environments, arthropods or vertebrate hosts and are thus often associated with travel or leisure activities. More adventurous travel, environmental and climate changes may change the frequency at which these emerging and re-emerging infections occur. Thus an accurate history of potential exposure remains the key to diagnosis. This may be problematic when patients are critically ill or if the incubation period, as is the case for Lyssavirus infection, may extend for several years. A further difficulty is that a history of arthropod or other exposure may never be obtained. For example, a recent analysis of the epidemiology of rabies acquired in the USA found that 80% had no definite history of an event associated with transmission.[3]

Secondly, most physicians will be unaware of these infections and their virulence potential. If acquired and established, infection with marine Vibrios and *Capnocytophaga sp.* may present in the fulminant manner normally associated with overwhelming meningococcal infection.

Thirdly, diagnostic difficulties (even if the infection is considered) arise because of the fastidious nature of the bacteria or limited availability of reliable serological assays. When exposure is common and severe symptomatic disease unusual, positive serological responses may be misleading. For example, almost 20% of healthy dairy farmers in the Gippsland have leptospirosis antibody titres by microagglutination of $\geq$ 1:50.[4]

Finally, these infections may require antibiotics not generally considered for empirical regimens in hospitalised patients. The best example of this is rickettsial infection, which is refractory to penicillin and cephalosporins but responds promptly to oral tetracycline. *Chromobacterium violaceum* also has an unusual antibiotic profile, with resistance to penicillins and cephalosporins common.

It is inevitable that the infections discussed by Hore and other new, or reemerging diseases, will continue to appear or their geographical distribution will change as a result of behavioural and environmental changes. Detection of these diseases requires continuing clinical and laboratory vigilance and close liaison between intensive care and infectious diseases specialists and diagnostic laboratories.

The Infectious Diseases Society of America has established an Emerging Infections Network (http://www.idsociety.org/EIN/AboutEIN.htm#Purposes &Functions) for the reporting of rare infections and unusual clinical events that may indicate the presence of new infectious diseases. The establishment of a similar network in Australia should be considered.

Assoc. Professor D. Gordon
Department of Microbiology and Infectious Diseases
Flinders Medical Centre
SOUTH AUSTRALIA 5042

REFERENCES

1. Ward PB, Johnson PDR, Grabsch EA et al. Treatment failure due to methicillin-resistant Staphylococcus aureus (MRSA) with reduced susceptibility to vancomycin. Med J Aust 2001;175:480-483.
2. Hore. C Important unusual infections in Australia: a critical care perspective. Critical Care and Resuscitation 2001;3:262-272.
3. Noah DL, MPH; Drenzek CL, MS; Smith JS, et al. Epidemiology of Human rabies in the United States, 1980 to 1996. Ann Intern Med 1998;128:922-930.
4. Skilbeck MW, Miller GT. A serological survey of leptospirosis in Gippsland dairy farmers. Med J Aust 1986;144:565-570.

Is endotracheal suctioning an art or a science?

Tracheobronchial suctioning 2 - 4-hourly (or when large airway sounds are heard) is performed in intubated intensive care patients to remove airway secretions and reduce the incidence of atelectasis, lung collapse and pneumonia. Generally, it is performed by two people, with the patient monitored using an ECG recording and pulse oximetery. One person ventilates the patient manually using 100% oxygen, a reservoir bag and assembly, increasing the patient's tidal volume by 1.0 - 1.5 L for 3 - 6 breaths, before removing the endotracheal tube connector for suctioning (i.e. 'open' system suction technique).[1] Pre-suction saline instillation is also used by some, particularly in paediatric practice. A sterile suction catheter (usually a 12 - 14 French gauge catheter in an adult) is inserted, by the other person, into the airway until a resistance is felt, it is then withdrawn 2 - 3 cm before suction is applied.[2] The catheter is then withdrawn completely with negative pressure interrupted momentarily throughout

the 15 second suctioning interval. A minimum of one minute is usually required between suctioning episodes.[2]

The suction catheter is connected by a large diameter extension tube to a collection bottle and a vacuum system. The apparatus provides a free air flow rate of no less than 40 L/min at the end at which the catheter is attached.[3] While negative pressures of 100 - 170 mmHg are suggested as safe suctioning pressures (particularly in paediatric patients),[4] the Australian Standards for suction systems require suction units that can generate negative pressures of 450 mmHg or greater when occluded.[3]

In an adult, the catheter normally extends up to 10 cm beyond the end of the endotracheal tube and is 45 - 50 cm long to enable the correct length of insertion. The catheter should be free of sharp edges, contain an end hole and two or more side holes. There is an air entrainment hole at the other end of the catheter to allow intermittent suctioning. If an angled tip is used, one of the side holes should be placed at the convex side of the angle,[5] and an external marker should indicate the direction of the tip.

As flow is proportional to the pressure difference, viscosity of the fluid being removed, and length and 4th power of the internal radius of the catheter, it is clear that the internal radius of the catheter (which should be as large as possible) has the greatest effect on efficiency of suction. However, to allow gas to return to the airway during suctioning, the outer catheter diameter should be no greater 0.6 times the inner diameter of the endotracheal tube (e.g. 14 French gauge for an 8 - 9 mm tube).[6]

A 'closed' system has also been used for tracheo-bronchial suctioning, with the postulated advantages including a multiple-use single-catheter system (changed every 24 hr), reduction in environmental contamination[7] and allowing continuous mechanical ventilation during suctioning to reduce hypoxia and hypercapnoea.[8-11] However, the benefits of a 'closed' system suction technique have been disputed, as hand contamination from showering of the condensate from the flush port, pooling of the catheter irrigation saline within the connectors, difficulty in cleansing the inner tube after use, ineffective secretion removal, catheter infection and sticking of the suction catheter in the endotracheal tube have all been reported.[12,13]

In this edition of the journal, Frengley *et al*,[14] report the effect of a closed tracheal suction system in adults (using a 14 French gauge catheter inserted for 5 seconds in an 8.0 mm internal diameter endotracheal tube and a negative pressure of 368 mmHg) on mechanical ventilation. They found that the effect varied depending on the ventilatory mode used. For example, in volume control ventilation the end expiratory pressure increased following catheter insertion and subatmospheric airway pressures were recorded during suctioning. During continuous positive airway pressure/pressure support ventilation, the 'closed' suction system had no effect on end-expiratory pressure following catheter insertion and subatmospheric airway pressures were largely avoided during suctioning.[14]

In general, suctioning is an art, particularly as surveys of techniques used by nurses, physiotherapists and respiratory therapists reveal that the techniques used vary widely.[15,16] There are no prospective, randomised controlled studies that have demonstrated an advantage of any technique (e.g. presuction hyperventilation, saline instilation, angle tip catheters, suctioning only on the way up, etc) in reducing the incidence of atelectasis, lung collapse and pneumonia, while minimising the adverse effects of airway trauma, hypoxia, hypercapnoea and haemodynamic instability. Indeed, many of these techniques continue to be used even though some have been shown to be hazardous (e.g. a five fold increase in bacterial contamination of the lower airway has been reported when presuction saline instillation is used, compared with standard suctioning techniques).[17]

The 'closed' system suction techniques that have emerged as an alternative to the conventional 'open' system suction techniques are another 'art' form, and as disadvantages of this technique are now being reported, they must also undergo rigorous investigation before being accepted into clinical practice.

Dr. L. I. G. Worthley
Department of Critical Care Medicine
Flinders Medical Centre
SOUTH AUSTRALIA 5042

REFERENCES

1. Riegel B, Forshee T. A review and critique of the literature on preoxygenation for endotracheal suctioning. Heart Lung 1985;14:507-518.
2. Brown SE, Stansbury DW, Merrill EJ, Linden GS, Light RW. Prevention of suction-related arterial oxygen desaturation. Comparison of off-ventilator and on-ventilator suctioning. Chest 1983;83:621-627.
3. Australian standards for suction systems for mechanical use in hospitals. AS 2120, 1977.
4. Singh NC, Kissoon N, Frewen T, Tiffin N. Physiological responses to endotracheal and oral suctioning in paediatric patients: the influence of endotracheal tube sizes and suction pressures. Clin Intensive Care 1991;2:345-350.
5. Lomholt N. Design and function of tracheal suction catheters. Acta Anaesthesiol Scand 1982;26:1-3.
6. Ehrhart IC, Hofman WF. Loveland SR. Effects of endotracheal suction versus apnea during interruption of intermittent or continuous positive pressure ventilation. Crit Care Med 1981;9:464-468.

7. Cobley M, Atkins M, Jones PL. Environmental contamination during tracheal suction. A comparison of disposable conventional catheters with a multiple-use closed system device. Anaesthesia 1991;46:957-961.
8. Bodai BI. A means of suctioning without cardiopulmonary depression. Heart Lung 1982;11:172-176.
9. Carlon GC, Fox SJ, Ackerman NJ. Evaluation of a closed-tracheal suction system. Crit Care Med 1987;15:522-525.
10. Belling D, Kelley RR, Simon R. Use of the swivel adaptor aperture during suctioning to prevent hypoxemia in the mechanically ventilated patient. Heart Lung 1978;7:320-322.
11. Kerr DR, Vonwiller JB, Abrahams N. The Stocks suction bullet. Anaesth Intens Care 1978;6:185-199.
12. Blackwood B. The practice and perception of intensive care staff using the closed suctioning system. J Adv Nurs 1998;28:1020-1029.
13. Blackwood B, Webb CH. Closed tracheal suctioning systems and infection control in the intensive care unit. J Hosp Infect 1998;39:315-321.
14. Frengley RW, Closey DN, Sleigh JW, Torrance JM. The effect of closed system suction on airway pressures when using the Servo 300 ventilator. Critical Care and Resuscitation. 2001;3:230-235.
15. Brooks D, Solway S, Graham I, Downes L, Carter M. A survey of suctioning practices among physical therapists, respiratory therapists and nurses. Can Respir J 1999;6:513-520.
16. Buglass E. Tracheostomy care: tracheal suctioning and humidification. Br J Nurs 1999;8:500-504.
17. Hagler DA, Traver GA. Endotracheal saline and suction catheters: sources of lower airway contamination.Am J Crit Care 1994;3:444-447.

Further reflections on clinical trials in critical care

In a recent editorial in this Journal, we drew attention to some potential problems of the reporting of trials involving group sequential methods.[1] In particular, i) we cited evidence from the statistical literature that, as a consequence of group sequential methodology, point estimates of treatment effects of such trials are inflated and confidence intervals are inappropriately narrow, and ii) in a hand-search of 16 trials in the New England Journal of Medicine from January 2000 to March 2001, using group sequential methods, no trial was found to include a statement of, or actual adjustment for, these biases in treatment estimates.

It is now of some interest to review the results of a trial by Van den Berghe and co-workers in a recent edition of the New England Journal of Medicine.[2] The trial involved 1548 patients in a prospective randomised controlled protocol investigating the utility of intensive versus conventional insulin therapy (targeted to blood glucose concentration), with the primary outcome measure as death from any cause during the intensive care stay. The 4.6% intensive care mortality in the intensive-treatment group vs the 8% in the conventional-treatment group represented an apparent risk reduction of 42% (95% CI: 22-62%). The final treatment-effect estimate was subsequently adjusted for the four interim analyses undertaken in the study: the median unbiased estimate giving a value of 32% reduction in mortality with adjusted 95% CI of 2-55%. Obviously a substantial inflation of the treatment-effect had occurred as a result of the use of sequential group methodology and the trial by Van den Berghe *et al* is one of the few reports in the literature where an appropriate adjustment has been made.

Such adjustments are not post-hoc but derive from the trial structure and the number of interim analyses.[1] All the reader may infer, in the absence of these adjustments, is that the trial treatment estimates are not as good (or as bad) as presented. There are three other recent trials in the literature reporting positive intensive care unit (ICU) treatment interventions where interim analyses have been performed and no adjustment of treatment estimates have been made.[3-5] We note that in recent updates to site-information on the two software packages providing facility for use of unbiased estimators (EaST 2000[6]and S+SEQTrial[7]) that the United States FDA has acquired both these packages. Such may herald, in the future, more regulatory attention to these matters.

At this time, when a number of positive trials of ICU interventions are appearing in the medical literature, it is perhaps relevant to canvas some other issues of trial methodology. The accompanying editorial[8] to the Van den Berghe *et al* and Rivers *et al* papers points to problems of interpretation of unblinded and single-institution trials. With respect to:

a) the impact of "unblindedness": we may assess the effects of this on treatment efficacy by use of the Mann-Whitney statistic, as an alternative to the more traditional estimates such as risk ratio or risk difference. The Mann-Whitney statistic[9,10] estimates the probability (0 to 1.0) that a randomly selected patient given an innovative therapy will respond better than a randomly selected patient given "standard" treatment. That is, for a value of the statistic of say 0.6, the interpretation is that there is a 60% probability that the (next) randomly selected patient (or, more correctly, one of a pair of patients) on therapy will improve compared with no therapy. In the presence of non-blinded randomised studies, it

is suggested that the statistic be decreased by 0.1 to 0.15. In the current context, two[2,4] of the ICU trials were non-blinded and a third[5] was partially blinded. Table 1 shows the Mann-Whitney statistic for the 4 trials mentioned previously (i.e. ARDS net, PROWESS, Van den Berghe and Rivers) and the positive, but non-blinded trial of Amato *et al*[11] which reported a protective-ventilation strategy in ARDS. What is apparent is the increased unadjusted probability of better response in the smallest study (Amato *et al*[11]) and the non-blinded studies compared with the large blinded PROWESS study;[3] but, after "adjustment", the response probabilities, at least for the larger 4 studies, are reasonably comparable. This comparability of responsiveness may say something of future expectations of therapeutic success in the ICU.

Table 1. Mann-Whitney statistic for various ICU trials

Study	*Blinded*	*Total n*	*MW stat*	*MWstat, adj*
Amato et al[11]	no	53	0.67[a]	0.52 to 0.57
ARDS net[4]	no	861	0.54 [h]	0.39 to 0.44
PROWESS[3]	yes	1708	0.47 [a]	0.47
Van den Berghe *et al*[2]	no	1548	0.52 [h]	0.37 to 0.42
Rivers et al[5]	no	263	0.58 [h]	0.43 to 0.48

Total n = total study patient number, MW stat = Mann-Whitney statistic, MW stat, adj = adjusted Mann-Whitney statistic, [a] = MW stat, adj related to 28 day mortality, [h] = MW stat, adj related to hospital discharge mortality.

b) single versus multi-institutional trials: that the results of a single-institution trial may reflect, uniquely, the local structure of care has been previously attested to,[12] but the interpretations(s) of the results of multi-institutional trials may also be a cause for some controversy, if we are to believe the exchanges in current mailing lists. What we are concerned about here is the recurrent debate on the implications of heterogeneity[13] at the patient,[14,15] institutional,[16] or analytic level.[17,18] That is, will "dissimilar" patient and site characteristics and numbers vitiate the results of a trial which reports an overall treatment effect. However, the problems of multi-institutional trials are not uniquely different from those of the single institution, although the preponderance of multi-institutional trials may force us, rather, to seek solutions to these problems and not ignore them. In particular, we note recent recommendations for individualisation of patient therapy[19,20] and debates on the appropriate form of site-weighting and site-treatment interactions (the so-called type II vs type III model),[21-23] the use of random-effects approaches to model site-effects[24,25] and Bayesian methods as an alternative to traditional ANOVA analysis.[26] These questions are, of course, pertinent to another paradigm, that of meta-analysis and the close comparisons, at least at the analytic level, between meta-analysis and multi-centred trials has been commented upon.[27,28] This close relation has seen changes in clinical trials mandated by meta-analysis,[29] and the meta-analysis of individual patient data has been suggested as being at the top of the hierarchy of strength of evidence concerning efficacy of treatment.[30]

Two other aspects of trial methodology deserve further attention:

i) the problem of "optimal" cut points in the evaluation of (and implementation in subsequent trials) prognostic factors. There has been extensive discussion of the problems of this approach in the cancer[31-33] and statistical literature.[34,35] The problems are those of increased Type I error, inflated estimates of effect and increased variance of these estimates and decrease in the efficiency of analysis. Appropriate adjustment of p-values may be made for this form of exploratory analysis.[32,36] That this may effect the outcome of trials may be indicated by recent research into the effect of anti-tumor necrosis antibodies (MAK 195F) in sepsis and septic shock. In a preliminary assessment of safety and efficacy of MAK 195F,[37] the prognostic value of IL-6 concentrations of greater than 1000 pg/mL was established by retrospective cut-point analysis with no adjustment of the p-value. Although in the subsequent randomised placebo-controlled RAMSES[38] study of MAK 195F, a difference in mortality rates was observed between patient groups with IL-6 levels above and below 1000 pg/mL (40% vs 50%, $p < 0.001$), this did not translate into a mortality difference between treatment and placebo groups with IL-6 levels > 1000 pg/mL ($p = 0.36$). The recently completed MONARCS trial[39] is reported to have demonstrated a mortality difference based upon the same criteria, but this study has yet to be published. Similar prognostic cut-point classification occurred in the recent investigation of cortisol levels and cortisol response to corticotrophin in septic shock.[40] Subsequent reports of improved mortality[41] based upon this rationale will, again, await review of the published trial.

(ii) the problem of "responsiveness" in assessing therapeutic interventions: this rather subtle problem was first given prominence in the cancer literature. It involves the responsiveness of patients to chemotherapy in terms of a "remission" or rate of favourable response, being interpreted as evidence

that the effect of treatment was to prolong overall survival. At the most, this is trivially true (patients who survive longer have a better outcome), but when differences in survival time (responders vs non-responders) are subjected to formal test (for example log rank test), bias in favour of responders may occur because these patients are being counted at risk of failure (death) before the time of response. As response to treatment and survival are both outcome variables, the use of testing to compare responder and non-responder survival distributions merely serves to confirm or deny the association between response and survival; it does not necessarily invoke a causal pathway.[42-44] We may think of a number of reasons why this scenario may occur: early deaths are counted as non-responders, by definition response involves a "guarantee time" before the response occurs, "response" may be a surrogate for the selection a particular patient subset not previously identified at initial randomisation (that is the distribution of frailties[45,46] [an "unobservable" prognostic index] between responders and non-responders, differs) and the failure to appropriately operationalise the notion of response.

The translation of these analytic principles to the critically-ill context may not be straight forward, given the obvious different time scales and problems of definition of response. For instance, in the observational studies and trials looking at the effectiveness of increases in oxygen delivery in septic patients,[47] responsiveness was usually defined as an increase in cardiac output, but this may be an insensitive criteria. Such responsiveness was located in particular patient subsets in the trials addressing the question of goal-oriented therapy.[48,49] This may not be surprising, but it serves to caution us in our interpretations of what a response actually means (did it select out a group of patients with "better" (or worse) prognosis) and how it should be appropriately analysed. We may also speculate that where no improvement in mortality has been observed, but there are improvements in other end-points (rates of infection, length of stay), the same mechanisms may be operative.[50]

Dr J. L. Moran
Dr. S. L. Peake
Intensive Care Unit
Queen Elizabeth Hospital
SOUTH AUSTRALIA 5011

REFERENCES

1. Moran JL, Peake SL, Solomon P. Reporting of clinical trials using group sequential methods. Critical Care and Resuscitation 2001;3:146-147.
2. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359-1367.
3. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344:699-709.
4. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Eng J Med 2000;342:1301-1308.
5. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368-1377.
6. EaSt 2000 software. http://www.cytel.com/new.pages/EAST.2.html. 2001. Cytel Software Corporation.
7 . S+SeqTrial @ http://www.cmis.csiro.au/S-PLUS/.
8. Evans TW. Hemodynamic and metabolic therapy in critically ill patients. N Engl J Med 2001;345:1417-1418.
9. Colditz GA, Miller JN, Mosteller F. How study design affects outcomes in comparisons of therapy. I: Medical. Stat in Med 1989;8:441-454.
10. Colditz GA, Miller JN, Mosteller F. Measuring gain in the evaluation of medical technology. Int J Technol Assess Health Care 1988;4:637-642.
11. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998;338:347-354.
12. Burns LR, Wholey DR. The effects of patient, hospital, and physician characteristics on length of stay and mortality. Medical Care 1991;29:251-271.
13. Louis TA. Assessing, accommodating, and interpreting the influences of heterogeneity. Environ Health Perspect 1991;90:215-222.
14. Rothwell PM. Can overall results of clinical trials be applied to all patients? Lancet. 1995;345:1616-1619.
15. Ioannidis JP, Lau J. The impact of high-risk patients on the results of clinical trials. J Clin Epidemiol 1997;50:1089-1098.
16. Horwitz RI, Singer BH, Makuch RW, Viscoli CM. Can treatment that is helpful on average be harmful to some patients? A study of the conflicting information needs of clinical inquiry and drug regulation. J Clin Epidemiol 1996;49:395-400.
17. Simon R. Patient heterogeneity in clinical trials. Cancer Treat Rep 1980;64:405-410.
18. Britton A, McKee M, Black N, McPherson K, Sanderson C, Bain C. Threats to applicability of randomised trials: exclusions and selective participation. J Health Serv Res Policy 1999;4:112-121.
19. Dans AL, Dans LF, Guyatt GH, Richardson S. Users' guides to the medical literature: XIV. How to decide on the applicability of clinical trial results to your patient. Evidence-Based Medicine Working Group. JAMA 1998;279:545-549.
20. Glasziou PP, Irwig LM. An evidence based approach to individualising treatment. BMJ 1995;311:1356-1359.

21. Gallo PP. Center-weighting issues in multicenter clinical trials. J Biopharm Stat 2000;10:145-163.
22. Schwemer G. General linear models for multicenter clinical trials. Control Clin Trials 2000;21:21-29.
23. Kallen A. Treatment-by-center interaction: what is the isuue? Drug Information Journal 1997;31:927-936.
24. Senn S. Some controversies in planning and analysing multi-centre trials. Stat Med 1998;17:1753-1765.
25. Fleiss JL. Analysis of data from multiclinic trials. Control Clin Trials. 1986;7:267-275.
26. Gould AL. Multi-centre trial analysis revisited. Stat Med 1998;17:1779-1797.
27. DeMets DL. Methods for combining randomized clinical trials: strengths and limitations. Stat Med 1987;6:341-350.
28. Senn, S. The many modes of meta. Drug Information Journal 2000;34:535-549.
29. Chalmers TC, Lau J. Changes in clinical trials mandated by the advent of meta-analysis. Stat Med 1996;15:1263-1268.
30. Olkin I. Meta-analysis: reconciling the results of independent studies. Stat Med 1995;14:457-472.
31. Altman DG. Categorising continuous variables. Br J Cancer 1991;64:975.
32. Altman DG, Lausen B, Sauerbrei W, Schumacher M. Dangers of using "optimal" cutpoints in the evaluation of prognostic factors. J Natl Cancer Inst 1994;86:829-835.
33. Hilsenbeck SG, Clark GM, McGuire WL. Why do so many prognostic factors fail to pan out? Breast Cancer Res Treat 1992;22:197-206.
34. Lausen B, Schumacher M. Evaluating the effect of otimized cutoff values in the assessment of prognostic factors. Computational statistics & Data Analysis. 1996;21:307-326.
35. Morgan TM, Elashoff RM. Effect of categorizing a continuous covariate on the comparison of survival time. J Am Stat Soc 1986;81:917-921.
36. Hilsenbeck SG, Clark GM. Practical p-value adjustment for optimally selected cutpoints. Stat Med 1996;15:103-112.
37. Reinhart K, Wiegand-Lohnert C, Grimminger F, et al. Assessment of the safety and efficacy of the monoclonal anti-tumor necrosis factor antibody-fragment, MAK 195F, in patients with sepsis and septic shock: a multicenter, randomized, placebo-controlled, dose-ranging study. Crit Care Med 1996;24:733-742.
38. Reinhart K, Menges T, Gardlund B, et al. Randomized, placebo-controlled trial of the anti-tumor necrosis factor antibody fragment afelimomab in hyperinflammatory response during severe sepsis: The RAMSES Study. Crit Care Med 2001;29:765-769.
39. Presented at 21st International Symposium on Intensive Care and Emergency Medicine, Brussels March 20-23, 2001.
40. Annane D, Sebille V, Troche G, et al. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA. 2000;283:1038-1045.
41. Annane D. Corticosteroids for septic shock. Crit Care Med 2001;29:Suppl-20.
42. Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response. J Clin Oncol 1983;1:710-719.
43. Morgan TM. Analysis of duration of response: a problem of oncology trials. Control Clin Trials 1988;9:11-18.
44. Weiss GB, Bunce H, III, Hokanson JA. Comparing survival of responders and nonresponders after treatment: a potential source of confusion in interpreting cancer clinical trials. Control Clin Trials 1983;4:43-52.
45. Yashin AI, Iachine IA. How frailty models can be used for evaluating longevity limits: taking advantage of an interdisciplinary approach. Demography 1997;34:31-48.
46. Vaupel JW, Yashin AI. Heterogeneity's Ruses: Some surprising effects of selection on population dynamics. The American Statistician 1985;39:176-185.
47. Heyland DK, Cook DJ, King D, Kernerman P, Brun-Buisson C. Maximizing oxygen delivery in critically ill patients: a methodologic appraisal of the evidence. Crit Care Med 1996;24:517-524.
48. Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group. N Engl J Med 1995;333:1025-1032.
49. Yu M, Burchell S, Hasaniya NW, Takanishi DM, Myers SA, Takiguchi SA. Relationship of mortality to increasing oxygen delivery in patients > or = 50 years of age: a prospective, randomized trial. Crit Care Med 1998;26:1011-1019.
50. Bower RH, Cerra FB, Bershadsky B, et al. Early enteral administration of a formula (Impact) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: results of a multicenter, prospective, randomized, clinical trial. Crit Care Med 1995;23:436-449.