Editorials

Coping with oxidative stress

Oxidative stress is a hot topic in the lay press, along with the proposition that taking anti-oxidants can block its ill-effects. High profile anti-oxidants include vitamins C and E, selenium, carotenoids like β-carotene and lutein (marigold extract), and flavinoids such as catechin, which is present in grape skins and most notably red wine. On the 'home shopping channel' and at innumerable web sites we are encouraged to administer anti-oxidant supplements to ourselves and our dogs and cats. The touted benefits range from immune enhancement and reduced risk of cancer, heart disease, dementia and stroke, to protection from the effects of passive smoking and smog. Claims that anti-oxidants retard aging guarantee its grip on the public imagination.

Physicians confronted with such popular cure-alls tend to dismiss them as well-marketed 'snake-oil' remedies and usually move on to more serious matters. However oxidative stress is harder to ignore, given its prominence in the mainstream medical literature in the context of many diverse conditions. These include atherosclerosis and coronary artery disease,[1,2] cancer,[3] sepsis,[4] degenerative neurological conditions,[5-7] shock and trauma,[8] anthracycline-induced cardiomyopathy,[9] schizophrenia,[10] ocular cataracts,[11] macular degeneration,[12] and cystic fibrosis.[13] In fact it has been suggested that oxidative stress is intimately involved in the molecular pathogenesis of virtually all disease.[14]

Taking these factors into account, it would seem that oxidative stress is worthy of closer attention. So how do we define this nebulous concept? To do so we must first consider the definition of 'oxidation'. Oxidation is the process in which electrons are transferred from electron donors (reducing agents) to electron recipients (oxidising agents). In such a process reducing agents are oxidised and oxidising agents are reduced.[15] Since oxidation and reciprocal reduction occur simultaneously, these are termed 'redox' reactions, and an electron donor with its corresponding oxidised form is a 'redox pair'. An example of a redox pair is the electron donor β-hydroxybutyrate and its oxidised form acetoacetate. The redox potential of a redox pair is an expression of its tendency to lose or gain electrons, and thus of its influence on the overall balance between oxidant and anti-oxidant activity.[16]

Oxidative stress is therefore a state in which cells and tissues experience an abnormal predominance of oxidant over anti-oxidant activity. Under these circumstances there is a risk of cellular and tissue injury through the generation of reactive nitrogen and oxygen species (RNOS).[17] Examples of RNOS include the superoxide anion ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), hydroxyl ions ($OH^{\cdot}$), peroxynitrite ($ONOO^-$) and hypochlorous acid (HOCl). Under certain conditions nitric oxide ($NO^{\cdot}$) itself is pro-oxidant, which is noteworthy in view of its widespread use in ARDS.

There are several metabolic pathways capable of generating RNOS. During normal oxidative phosphorylation around 2% of consumed oxygen is reduced to superoxide and hydrogen peroxide due to leakage of electrons from the electron transport chain.[18] One pathway highly relevant to critical illness is that catalysed by xanthine oxidase, an enzyme formed from xanthine dehydrogenase during hypoxia. Typical events activating this pathway are episodes of ischaemia/reperfusion such as myocardial revascularisation, free pedicle grafts and organ transplantation, or global insults such as cardiopulmonary bypass and shock/resuscitation. Oxygen suddenly made available on reperfusion is reduced to superoxide in a reaction linked to the conversion of hypoxanthine (generated from ATP hydrolysis during the anaerobic phase) to xanthine. In the presence of superoxide dismutase, superoxide is further converted to hydrogen peroxide. If iron is present, highly reactive hydroxyl ions can also be generated by the Fenton reaction.

Another pathway particularly applicable in sepsis is that catalysed by NADPH oxidase, responsible for the respiratory burst of inflammatory cells during phagocytosis. A third mechanism receiving increasing attention is the production of peroxynitrite, liberated when nitric oxide combines with superoxide. Hypochlorous acid, which appears when hydrogen peroxide interacts with neutrophilic myeloperoxidase, is also an important reactive species. Other sources of RNOS include arachidonic acid metabolism, cytochrome P_{450} and the autoxidation of ascorbic acid and other molecules.

Plasma redox status is strongly correlated with the severity of critical illness,[19] perhaps because RNOS are key players in both the generation and propagation of the inflammatory response. RNOS cause cell injury and altered cell signaling by virtue of their reactive unpaired electrons. In the presence of RNOS, cell membranes undergo lipid peroxidation, beginning with the abstraction of hydrogen atoms from unsaturated membrane lipid to form lipid alkyl radicals. On further contact with oxygen, other highly reactive lipid intermediates appear and create a positive feedback 'chain reaction' which magnifies cellular damage. Although lipid peroxidation is the best known

mechanism by which RNOS cause cell injury, RNOS can also create DNA breaks and mutations, and can activate zymogens and inactivate or hyperstimulate key cytosolic and nuclear enzymes. More recently it has become clear that oxidative stress can promote the expression of pro-inflammatory genes (for example those regulating production of TNF-α and intercellular adhesion molecules). This is achieved through activation of cytosolic nuclear transduction factors such as nuclear factor- κB.[20] There is evidence that some pro-inflammatory cytokine release in ARDS is stimulated by this mechanism.[21] Conversely, peroxynitrite can deregulate the most fundamental cell signals, such as those controlling apoptosis, by altering the activity of cytosolic nuclear transduction factors containing tyrosine.[22,23]

Endogenous anti-oxidants exist in the intracellular and extracellular environments to counteract these events. Intracellular anti-oxidants include:

1. Anti-oxidant enzymes. Examples are superoxide dismutase and various peroxidases. Superoxide dismutase is a metallo-protein existing in various isoforms, all of which convert superoxide to hydrogen peroxide. Peroxidases include catalase and glutathione peroxidase (one isoform of which is a seleno-enzyme). Peroxidases dismute hydrogen peroxide and other peroxides to water or alcohol and oxygen.
2. Non-enzymatic anti-oxidants such as reduced glutathione (GSH), ascorbate, vitamin E (α-tocopherol) and β-carotene. GSH, a sulphydryl donor, is both a substrate for glutathione peroxidase and a direct free radical scavenger. Vitamin E is fat soluble and breaks the lipid peroxidation chain reaction, and ascorbate participates in the regeneration of vitamin E. Like vitamin E, β-carotene is fat soluble. It also decreases lipid peroxidation, by means which are less clear.

Extracellular anti-oxidants include superoxide dismutase, catalase, glutathione peroxidase, albumin, lactoferrin, transferrin, haptoglobins and ceruloplasmin.

Antioxidant therapy is an attempt to bolster endogenous anti-oxidant defences. Many approaches successfully reduce oxidant injury in animal models, but proven clinical efficacy has remained elusive.[24] There are three main strategies:

1. Anti-oxidant enzyme replacement or supplementation. This can be by direct injection or inhalation of enzymes such as superoxide dismutase and catalase,[25,26] administration of synthetic molecules with activity profiles similar to native enzymes,[27] or supplementation with enzyme cofactors such as selenium (to enhance glutathione peroxidase activity).[28]
2. RNOS pathway inhibition. Examples include xanthine oxidase inhibition by allopurinol and free iron chelation using desferroxamine.
3. Administration of agents which scavenge or inactivate RNOS and reactive intermediates. Examples are vitamin E and ascorbate,[29] mannitol [30] and lazaroids.[31] Of interest, pyruvate [32] and its stable cogener ethyl pyruvate (water-solubilised by calcium in a balanced salt solution called Ringer's ethyl pyruvate)[33] provide demonstrable protection to gut mucosa from the effects of mesenteric ischaemia/reperfusion. Scavenging of RNOS is the proposed mechanism. The potential for application in designing balanced salt solutions for crystalloid resuscitation and renal replacement therapy is intriguing, with ethyl pyruvate substituted for lactate as the bicarbonate surrogate.

Which brings us to N-acetylcysteine (NAC), the subject of a review article by Atkinson in the current issue of *Critical Care and Resuscitation*.[34] NAC falls into the third category of administered anti-oxidants, being both a direct scavenger of RNOS and a substrate for the replenishment of depleted GSH stores. As Atkinson points out, NAC has had a long and varied association with the care of the critically ill patient. Its original role as inhaled mucolytic is largely discredited, but the molecule has continued to crop up in our specialty in various contexts until the present day. Atkinson walks us through much of this chequered career. The popularity of NAC as an anti-oxidant is related in part to its safety profile, and also to the perceived importance of GSH in the battle against oxidative stress. Of course the major triumph has been its use in paracetamol toxicity as GSH replenisher, thanks to the landmark work of Prescott and colleagues.[35] But as Atkinson points out, early hopes of benefit in other areas have often been dashed, for example in ARDS, sepsis or hepatic failure. Even the current vogue of administering NAC to guard against renal deterioration from radio-contrast is based on limited evidence.[36]

Recently, NAC has again raised our hopes in a couple of scenarios not specifically covered by Atkinson. The first is severe trauma, where patients randomised to receive an anti-oxidant cocktail containing NAC, selenium and vitamins C and E early after presentation appeared to have a lower subsequent incidence of infection and organ dysfunction.[37] However, this study was of 18 patients only and not placebo controlled. Obviously a much larger study is required. Based on the past record of large clinical anti-oxidant trials, the likelihood of disappointment is significant. Secondly, NAC may have a role in the management of acquired pyroglutamatic (5-oxoproline)

acidosis, a raised anion gap acidosis sometimes seen as a complication of paracetamol, vigabatrin or flucloxacillin administration. Patients particularly at risk are those with sepsis, hepatic and possibly renal dysfunction.[38,39] The condition is thought to be exacerbated by GSH deficiency, and NAC administration is recommended. [38,39] This certainly seems to clear the acidosis more rapidly (unpublished personal observations), but anecdote is an unreliable basis for recommendation. Like all first impressions with NAC, closer investigation is needed.

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Supraventricular tachycardia classification: an intensivist's perspective

In this issue of *Critical Care and Resuscitation*, Durham and Worthley have reviewed bradycardias[1] and tachycardias.[2] Their classification of the various supraventricular tachycardias (SVTs), however, may lead to some confusion, for example sinus tachycardia, atrial flutter and atrial fibrillation are classified under *atrial tachycardias* and AV nodal re-entry tachycardia, AV re-entry tachycardia, sinus node re-entry tachycardia, "intra-atrial re-entry", non-paroxysmal junctional tachycardia and multifocal atrial tachycardia are classified under *supraventricular tachycardias*. This confusion in classification and nomenclature is understandable because, as yet, there is no concise, comprehensive or universally accepted system for classifying the SVTs that can be used by intensivists at the bedside. Outdated terms, such as "paroxysmal atrial tachycardias", which in the past was synonymous with *all* SVTs are still used occasionally and at times are even used to refer to unifocal atrial tachycardias due to an automatic focus in the atrium, which is non-paroxysmal. Other terms such as paroxysmal supraventricular tachcyardia or paroxysmal junctional tachycardia, both of which refer to AV nodal re-entry tachycardia or AV re-entry tachcyardia are still in common use and may mislead the uninitiated. Complex algorithms are available for SVTs with a normal QRS,[3] but may be of little use in managing a critically ill patient in a busy intensive care unit.

Before attempting to classify SVTs, it is necessary to agree on some definitions. A supraventricular tachycardia (SVT) is any tachycardia that requires atrial or AV nodal (junctional) tissue for its initiation and maintenance.[4] The term "the supraventricular tachycardias" refers to *all* SVTs and "supraventricular tachycardia" refers to *any* SVT, for example AV nodal re-entry tachycardia, atrial fibrillation, etc. All narrow complex tachycardias are virtually by definition supraventricular in origin. Wide complex tachycardias are usually ventricular although some may be supraventricular in origin, (e.g. SVT with bundle branch block, pre-excitation, etc).

For arrhythmia analysis, the surface ECG remains the single most important non-invasive test, but even when reviewed by experts, the ECG will provide a correct rhythm diagnosis only about 80% of the time.[4] Recognition and timing of P waves (atrial activity) relative to the QRS complex (ventricular activity) will assist greatly in rhythm diagnosis.[5]

We believe a simpler and more clinically useful system classifies the SVTs into AV node (junction) dependent or AV node (junction) independent.[6,7] Atrioventricular node and AV junction are terms that are used interchangeably.

1. *AV node dependent* sometimes referred to as "the junctional tachycardias" require a re-entrance circuit or ectopic focus that must include the AV node. Blocking the AV node, for example with adenosine, will terminate these tachycardias.
   i. *AV nodal re-entry tachycardia (AVNRT)* is a regular tachycardia in which there are dual pathways in, or close to, the AV node. The re-entry circuit consists of an anterograde limb and a retrograde limb. In most instances, simultaneous or near simultaneous depolarisation of both atria and ventricles occur, resulting in P waves occurring at the same time as the QRS, so that they are hidden within the QRS or occur in the terminal part of the QRS (pseudo-S wave in leads II, III, aVL - atrial activation takes place in a caudocranial direction).

ii. *AV re-entry tachycardia (AVRT).* This is a regular re-entry tachycardia using an accessory pathway which bypasses the AV node. This tachycardia is often referred to as a reciprocating tachycardia. In Wolff-Parkinson-White (WPW), there is anterograde conduction through the accessory pathway during sinus rhythm resulting in ventricular pre-excitation (short PR interval, delta wave, widening of the QRS). About 25% of accessory pathways are concealed (i.e. no pre-excitation during sinus rhythm) as conduction is only possible retrogradely from ventricle to atrium. The most common regular SVT in patients with an accessory pathway is an orthodromic AVRT with impulses passing anterogradely through the AV node and retrogradely over the accessory pathway, resulting in inverted P waves in leads II, III and aVF which are visible shortly after each QRS.

iii. *Accelerated idionodal rhythm*. This is caused by enhanced automaticity within the AV node. This rhythm is commonly referred to as "non-paroxysmal nodal (junctional) tachycardia" which is somewhat misleading, especially considering that the heart rate is often less than 100/minute and rarely faster than 130/minute. The ECG features of this arrhythmia include a regular narrow complex QRS, sometimes with AV dissociation. Treatment of this rhythm per se is rarely required.

2. *AV node independent tachycardias*. The AV node is not necessary to sustain the tachycardia (i.e. the AV node is an "innocent bystander". This group of supraventricular tachycardias is often referred to as "the atrial tachycardias", as only atrial tissue is integral to the initiation and maintenance of the tachycardia.[6] AV node independent tachycardias include:

   i. *Unifocal atrial tachycardia (UAT)*. This term remains somewhat unclear as UAT may be due to atrial re-entry (i.e. paroxysmal) or due to a rapidly discharging automatic focus within the atrium (i.e. automatic and, therefore, non-paroxysmal). The rhythm may be incessant and often very difficult to manage. There is usually a single abnormal P wave visible on the surface ECG with the RP greater than PR interval. Occasionally, there may be AV block (unifocal atrial tachycardia with block), especially in patients with digitalis intoxication.

   ii. *Multifocal atrial tachycardia (MAT)*. This rhythm is distinguished by three or more morphologically different P waves and an irregular atrial rate, usually about 100 - 130/minute with varying PR intervals and AV block. The atrial rate and isoelectric periods between adjacent P waves help differentiate this rhythm from atrial fibrillation. This is a common rhythm in the critically ill, occurring mainly in patients with chronic pulmonary disease and hypoxia or cardiac disease and is associated with a high mortality, presumably secondary to underlying disease. Digitalis is ineffective.

   iii. *Atrial flutter*. This rhythm is usually due to a single re-entry circuit lying within the right atrium. Rhythm diagnosis is usually not a problem. Atrial flutter waves (characteristic saw tooth appearance with no isoelectric line) at or close to 300/minute. AV conduction block (2:1) is usually present unless treatment has been commenced with drugs, such as beta blockers or digoxin, that block AV node conduction. Such drugs may lead to higher degree block, which may be variable.

   iv. *Atrial fibrillation (AF*). This is the most common sustained rhythm seen in critically ill patients, especially after heart surgery. With the exception perhaps of patients with WPW and pre-excitation, the ECG rhythm diagnosis is usually straightforward. Atrial activity is chaotic and if seen on the surface ECG consists of rapid (350-600/minute) irregular depolarisations varying in amplitude and morphology (fibrillation waves). The ventricular response is irregularly irregular. Most atrial impulses are not conducted to the ventricles resulting in an untreated ventricular rate of 100 - 180 beats/min.

   v. Other AV node independent tachycardias include *sinus node re-entry tachycardia (SNRT)* which incorporates a re-entry circuit within the sino-atrial node. As the tachycardia originates in the sinus node, the P waves will be identical to sinus P waves. SNRT, unlike sinus tachycardia, begins and ends abruptly (i.e. it is paroxysmal). Review of the heart rate trend monitor is useful in critically ill patients when this rhythm (or any paroxysmal tachycardia) is suspected.

Despite our best efforts, the rhythm diagnosis of a tachycardia may still elude us. Under these circumstances, a description of the ECG characteristics and a differential diagnosis of the rhythm is warranted. For example, 'regular narrow complex tachycardia at 160/minute' with a list of possibilities in order of probability, for example "AVNRT or AVRT or atrial flutter with 2:1 AV block". Vagal manoeuvres or drugs (e.g. adenosine) which block AV nodal conduction may improve diagnostic accuracy. SVTs that continue in the presence of AV block are unmasked as AV nodal independent (i.e. atrial tachycardias), for example unifocal

atrial tachycardia or atrial flutter. An SVT that terminates with a non-conducted P wave is likely to be AVRT or AVNRT.[4]

The classification used by Durham and Worthley[2] is historical and we believe may be confusing to an intensivist dealing with a supraventricular tachycardia in a critically ill patient. Hopefully, these brief comments will shed some light on a complex issue and assist in arrhythmia management.

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Consent for the critically ill patient

Doctors have a legal duty not to treat patients without their consent (or the consent of someone authorised to consent on their behalf) or without some other lawful justification. A patient treated without such consent or lawful justification may bring a claim against the doctor in trespass. The tort of trespass protects a person's right to bodily inviolability and if breached, then a claim may be successful even if the doctor is found not to have acted negligently. The patient is not required to show that he or she suffered any actual physical injury or damage as a result. The touching without consent is sufficient to bring a claim. Clearly being aware of this duty is a very important element in good medical practice. It is especially important in the intensive care setting as most critically ill patients are not competent to provide consent.

Freebairn *et al*, are to be commended for their careful and accurate review of this difficult area in this issue of *Critical Care and Resuscitation*.[1] However, it is important to note that this paper refers to New Zealand law, and to emphasise the authors' point that "the legal intricacies of informed consent vary from one country to another". Statute law applies only in its own jurisdiction and in Australia it varies from state to state. Even the common law is problematic as whilst a court may be influenced by findings of other jurisdictions, those judgments may not be binding.

The legal duties of doctors are rooted in many branches of the law including civil and criminal law, regulatory or public law, human rights and administrative law.[2] In Australia, the Federal system of government empowers both the Commonwealth and the State and Territory governments to legislate in relation to health and medical matters. Therefore, in Australia, legislation and the common law may vary significantly between states and territories so that doctors must be aware of the law applicable in the jurisdiction in which they practice. This variability in the law is well demonstrated by the issue of consent.

Freebairn *et al*, correctly state that proxy consent from next of kin for incompetent patients is without legal basis in New Zealand. According to common law, next of kin have no lawful authority to make medical decisions on behalf of adult patients.[2] The New Zealand Health and Disability Commissioner Act 1994 does not provide for proxy consent except for minors, those with an appointed guardian and those who have established an enduring power of attorney.[3] A similar situation exists in most states and territories of Australia, except New South Wales, South Australia and Tasmania which have legislation to support proxy consent.

In New South Wales, the Guardianship Act 1987 permits the person responsible for the incompetent patient to consent to major and minor medical treatment on their behalf. A hierarchy of "persons responsible" is set out in Section 33a of the Act and includes the spouse, carer, relative and close friend.[4,5] In South Australia, the Guardianship and Administration Act 1993 authorises a relative of an incompetent patient to consent to medical treatment on the patient's behalf if there is no legally appointed guardian.[6] In Tasmania, the

Guardianship and Administration Act 1995 allows the person responsible for the patient to provide consent, and Section 4 of the Act sets out a hierarchy.

In other Australian states and territories, relatives and carers have no lawful authority to consent to treatment for incompetent patients. Consent via an application for guardianship could be sought but this is a lengthy process. If doctors were required to seek authorisation for every medical procedure via an application to the Guardianship Board, the system would be placed under enormous pressure and the health care for incompetent patients would inevitably suffer. In practice, most decisions on behalf of incompetent patients are made informally following discussion with, and agreement by, the patient's family or carer. Clearly such an approach does not conform strictly with the law and could result in a claim for trespass, as discussed above. In such a case the defences of necessity and emergency treatment may apply, but these are largely untested in the Australian judicial system. As suggested by Skene,[2] this is an area where the "strict requirements of the law and its actual operation may diverge" as occurs in many areas of medical practice.

In conclusion, the review of Freebairn *et al* should be essential reading for intensivists in New Zealand. However intensivists on the other side of the Tasman should read it with interest, but then refer to local legislation and common law.

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L-lactic acidosis: not just an hypoxic disorder

During glycolysis, glucose is converted to pyruvate in the cytosol and the oxidised form of nicotinamide adenine dinucleotide (i.e. NAD^+) is reduced (i.e. NADH). Within the mitochondria and in the presence of oxygen, pyruvate is converted to acetyl coenzyme A (CoA) by the enzyme pyruvate dehydrogenase (PD) and NADH is oxidised by oxidative phosphorylation to generate ATP.

Pyruvate dehydrogenase is an important regulatory step, as it is inhibited by ATP, acetyl CoA and NADH (which increases in an anaerobic environment), and is activated by insulin, AMP and NAD^+. If energy is required (i.e. ATP is needed) and PD is inhibited (e.g. anaerobic conditions) glycolysis can only proceed with the reoxidation of NADH. This occurs during the conversion of pyruvate to lactate by lactate dehydrogenase providing the NAD^+ needed to allow the earlier glycolytic compound of glyceraldehyde-3-phosphate to be converted to 1,3-biphosphoglycerate, generating 2 mmol ATP per 1 mmol glucose.

With inadequate tissue oxygenation lactate accumulates, although conversely the assessment of cellular hypoxia (i.e. the cellular redox state) by measuring blood lactate, is often of limited value because the lactate level may also be raised when there is an increase in the rate of glycolysis without hypoxia (e.g. respiratory alkalosis). Measurement of the lactate /pyruvate (L:P or $NADH/NAD^+$) ratio has been used to distinguish an increase in glycolysis (where the L:P ratio is normal, i.e. 10:1) from hypoxia (where the L:P ratio is increased, i.e. greater than 10:1). However, this assumes that the cytoplasmic redox potential (measured by the L:P ratio) reflects the mitochondrial redox potential, which may not be so.[1] The cytosolic and mitochondrial redox states may even be reversed.[2] A normal beta-hydroxybutyrate/acetoacetate ratio may indicate a normal hepatic mitochondrial redox state, which may exist with an abnormal lactate/pyruvate ratio to indicate an abnormal redox state of organs other than the liver.[3] However, in the critically ill patient these metabolites are often not in equilibrium.[4] Moreover, specimen artifacts (e.g. non-arterial specimens, specimens not transported 'on-ice' or a delay in measurement)[5] may falsely elevate the L:P ratio.[6]

The normal post absorptive basal production of lactate in the human ranges between 1000 - 1500 mmol /70kg/day,[7,8] with 25 - 50% arising from red blood cells. Normal arterial blood lactate levels are usually less than 2 mmol/L and levels between 2 - 4 mmol/L are abnormal but of uncertain clinical significance.[9] Lactic

acidosis is defined as a metabolic acidosis associated with an arterial blood concentration of lactate > 5.0 mmol/L, although in most cases of lactic acidosis the levels are between 10 and 30 mmol/L.

Lactic acidosis is often classified as either type A, in which an inadequate delivery of oxygen for tissue requirements generates lactate faster than it can be removed, or type B, where overt tissue hypoxia does not appear to play a major role. However, both types often share mechanisms of over production and underutilisation.

In the acutely ill patient, lactic acidosis is often assumed to be due to an inadequate delivery of oxygen to the peripheral tissues, which may not be so. For example, lactic acidosis associated with an excessive β_2 adrenergic effect (e.g. excessive adrenaline, salbutamol or isoproterenol infusions, or the adrenaline 'surge' during injury and sepsis)[10] is caused by an increase in glycogenolysis (by activating muscle and hepatic glycogen phosphorylase) which increases both pyruvate and lactate production. However, a β_3 adrenergic effect may also be present, increasing lipolysis (by activating hormone-sensitive lipoprotein lipase) and acetyl CoA and NADH production, which in turn inhibit pyruvate oxidation and cause an increase in the lactate/pyruvate ratio in the absence of tissue hypoxia.[11] Furthermore, an acute fulminating form of beri-beri (i.e. thiamine deficiency) known as acute pernicious beri beri (or known to the Japanese as shoshin beri beri; sho = acute damage and shin = heart[12]) presents clinically with shock (absent arm pulses but moderately strong femoral pulses),[13] cyanosis, dyspnoea, lactic acidosis, high cardiac output, depressed left ventricular function, low systemic vascular resistance, high circulating catecholamine levels (increasing lactate production) and high mixed venous oxygen saturation.[14-18] The lactic acidosis is not caused by an inadequate oxygen delivery to peripheral tissues; it is due to a block in mitochondrial pyruvate metabolism, as both pyruvate dehydrogenase and alpha ketoglutarate dehydrogenase require thiamine pyrophosphate as a cofactor. Lactic acidosis has also been described in association with parenteral nutrition, caused not only by thiamine deficiency (provoked by the infused glucose),[19,20] but also by fructose, sorbitol and xylitol toxicity.[21]

In this issue of the journal, Corcoran *et al,*[22] describe a case of shoshin beri beri precipitated by intravenous glucose, and highlight once again this non-hypoxic cause of lactic acidosis. They conclude that patients with an altered conciousness in emergency or intensive care departments, should be given thiamine within the first 5 minutes of management. However, one could probably extended this recommendation to include all critically ill patients.

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Early enteral nutrition support improves outcome: hypothesis or fact?

A recent editorial that reviewed the evidence for improved outcome following early enteral nutrition[1] would seem to reflect current critical care preference for the enteral route of nutrition and to be in accord with an evidence-based approach to the assessment of interventions in clinical practice.[2] The conclusion from the editorial was unequivocal: "Using an evidence based approach, the recommendation for early enteral feeding in critically ill patients is a Level I recommendation". The studies [n = 19] spanned nearly 20 years from 1979 to 1998 and involved disparate patient ages (e.g. paediatric, adult, elderly), groups (e.g. burns, trauma and elective and emergency surgery) and primary study outcomes (e.g. discrete physiologic changes, patient outcomes). Only four of the studies[3-6] reported formal intensive care patients and only three of the studies[5,7,8] reported costs. Thus, any attempt at an overall assessment, as a gestalt of "Improved outcome, yes/no" is confounded by study heterogeneity. The relevance of some of the studies to critical care medicine also appears doubtful, as reflected in the successive nomination of the patients as "critically ill", "seriously ill" and/or "injured". Furthermore, improvements in physiologic data or the occurrence of infection and/or complications, however defined, should be interpreted in the light of their effects on hospital stay, cost or mortality. Given these cautions, we sought to extend the qualitative editorial analysis by meta-analytic techniques,[9] in an attempt to quantify certain outcomes (e.g. mortality, infection, complications and hospital length of stay) with respect to the early and delayed enteral feeding groups.

Initially, a fixed effects meta-analytic model was chosen. For binary data, Mantel-Haenszel methods were used to estimate risk ratios. For continuous data, weighted mean differences were computed.[10] Study heterogeneity was estimated (chi-square statistic) and, if present ($p < 0.1$, the low power of this test is noted), a corresponding random effects model (DerSimonian and Laird method) was used.[9] Only prospective randomised trials were considered and no attempt was made to source other references as the purpose was to assess the evidence cited in the editorial.

The estimates for mortality, infection, complications and hospital length of stay between the early and delayed groups are shown in Table 1 (data set up such that relative risk (RR) < 1 favours the early enteral group).

No significant cost difference between early and delayed groups was found in studies reporting costs. Study calendar time and country currency differences precluded meaningful pooled analysis. What is also apparent is the variable incidence of outcome reporting which is missing in 33% - 50% of studies and variably

Table 1. Summary of outcome measures across studies comparing early and late enteral nutrition (total n=18)

Study	*Studies*	*Study*	*Fixed effects estimator*				*Heterogeneity*	*Random effects estimator*		
Effect	*(n)*	*size (median, range)*	*RR*	*Mean diff*	*CI (95%)*	*p*	*p*	*RR*	*CI(95%)*	*p*
Mortality	12	(60,15-195)	1.08	NA	0.67 to 1.73	0.78	0.76	NA		
Infection	12	(46,20-195)	0.60	NA	0.44 to 0.80	0.001	0.09	0.57	0.37-0.89	0.01
Complication	9	(61,28-195)	0.78	NA	0.63 to 0.97	0.03	0.005	0.69	0.47-0.99	0.05
Hospital Length of stay (days)	10	(30,15-122)	NA	-0.89	-1.47 to -0.31	0.003	0.69	NA		

RR = relative risk, Mean diff = weighted mean difference, CI = confidence interval, NA = not applicable, p = p value

missing across study effects (Table 1, column 2) and the modest study size. No mortality effect was apparent using fixed effects methods, but both infection, which was recorded as all infectious complications (e.g. wound infections, pneumonia etc), and non-infective complications were reduced in the early group (risk ratio significantly < 1). The random effects model broadened the confidence intervals, but point estimates were still significant.[11]

Publication bias[12] was not demonstrated using the adjusted rank correlation (Begg and Mazumdar), the regression asymmetry (Egger *et al*) and "trim and fill" tests,[13,14] ($p > 0.1$), although funnel plots of study size versus relative risk were asymmetric for both infection and complication. Using a cumulative meta-analytic approach,[15] which provides cumulative pooled estimates from earliest to most recent trial, no longitudinal change in mortality estimate (studies spanning 1980 to 1998) was noted (p always > 0.1). However, the beneficial effects (RR estimate significantly < 1) of early enteral nutrition on incidence of both infection (studies spanning 1979 to 1997) and complication (studies spanning 1986 to 1997) were not established until after the third trial for both infection (1989) and complication (1991).

We also sought multivariable predictors of between-study heterogeneity by meta-analytic regression,[16,17] using a restricted maximum likelihood estimator.[18] For infection, year of study publication ($p = 0.04$), patient age ($p = 0.008$) and gender ($p = 0.001$) explained all of the between study variance (τ^2) of the null model ($\tau^2 = 0.545$). For complication, gender ($p = 0.06$) reduced τ^2 of the null model from 0.517 to 0.246. Such explorations are essentially data-driven and depend upon appropriate recording of covariates. However, they serve to remind us that the salutatory effects of early enteral nutrition (e.g. reduction of infection and complication) may not be consistent across studies or patient sub-groups.[19] Hospital length of stay was reduced in the early enteral group, but the mean effect was small at -0.9 of a day (mean length of stay across all studies, 30 days). Given the vagaries of hospital discharge policies,[20] the clinical impact of such a reduction is not immediately apparent.

Both qualitative and quantitative analysis would appear to have identified some benefits from early enteral nutrition, although these are not translated into reductions in either mortality or hospital stay. Firm efficacy recommendations flowing from either analysis are vitiated by the presence of substantial missing data and the implications of study heterogeneity. We suggest that the proposition: "Early enteral nutrition support improves outcome (in critically ill patients)" is not yet a "fact" nor a Level 1 recommendation.

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