

## Editorials

# Vasopressin - an old warhorse on a new campaign

From the earliest days of critical care medicine, arginine-vasopressin has been part of our therapeutic armamentarium, the time-honoured indications being diabetes insipidus and bleeding oesophageal varices. By administering pharmacological doses of this non-peptide pituitary hormone we have been able to control variceal haemorrhage in 80% of cases, albeit with a high rebleed rate. The mechanism of action is splanchnic vasoconstriction, by stimulation of mesenteric V<sub>1a</sub> receptors.<sup>1</sup> However the cost has been a 10% incidence of myocardial ischaemia, some risk of hyponatraemia, and the possibilities of splanchnic dysoxia and worsening coagulopathy.<sup>2</sup> Consequently the somatostatin analogue octreotide<sup>3</sup> and the vasopressin analogue terlipressin<sup>4,5</sup> have largely supplanted vasopressin in the management of oesophageal varices. Both have better side-effect profiles and more selective splanchnic vasoconstrictor activity.

Desmopressin (DDAVP) is a long acting vasopressin analogue.<sup>6</sup> Its main action is on V<sub>2</sub> receptors controlling water permeability in the renal collecting ducts, and it has little V<sub>1</sub> activity. It also stimulates endothelial release of von Willebrand's factor. DDAVP has largely displaced arginine-vasopressin preparations as first line treatment for the other classic indication, central diabetes insipidus. Thus until recently it looked as though the era of arginine-vasopressin was on the wane. In particular, any new ideas of administering vasopressin when splanchnic perfusion is a high priority seemed incongruous. Yet, it is in precisely this area that vasopressin is making a come back.

In the current edition of *Critical Care and Resuscitation*, Drs Russell and Glover provide a comprehensive review of the physiology and clinical applications of vasopressin in critical illness.<sup>7</sup> Others have gone about the same task in recent times.<sup>1,8</sup> This flurry of interest stems from the realisation that after more than fifty years, vasopressin might have something new to offer. Reports of successes are now appearing in septic shock,<sup>9</sup> some other forms of distributive shock,<sup>10,11</sup> and even in cardiac arrest.<sup>12</sup>

The role of vasopressin in cardiac arrest is under careful consideration by resuscitation councils around the world. Adrenaline is certainly not the perfect

resuscitation agent. To give an extreme example of its deficiencies, one study of 194 in-hospital cardiac arrests from Brisbane showed no differences in immediate survival or hospital discharge rates when low and high dose adrenaline were compared with placebo.<sup>13</sup> It is thus logical to look for an alternative agent. Vasopressin in pharmacological doses seems to be at least as effective as adrenaline in redirecting blood flow to heart and brain, while lacking its adverse metabolic consequences and dysrhythmogenic potential.<sup>8</sup> It is also readily administered via the endotracheal and intra-osseous routes. After evaluating the evidence, the International Liaison Committee on Resuscitation (ILCOR) has already included one 40U dose of vasopressin as an alternative to adrenaline in shock-refractory ventricular fibrillation.<sup>14</sup> However it is fair to say that the place of vasopressin in the cardiac arrest resuscitation sequence remains to be established. Accordingly, the European, British and Australian Resuscitation Councils are yet to adopt the ILCOR recommendation. Drs Russell and Glover take us through the limited current evidence for and against the use of vasopressin in this context.<sup>7</sup>

Perhaps a more engaging area of interest is that of distributive shock, and in particular therapy-resistant septic shock with its high mortality. How can we justify the use of a potent splanchnic vasoconstrictor such as vasopressin in septic shock, when splanchnic dysoxia may actually be part of the problem?<sup>15</sup> The essential point is that although patients with vasodilatory shock generate very high plasma concentrations of vasopressin initially, these fall rapidly to quite low levels.<sup>1</sup> One plausible reason for this biphasic pattern is that overstimulation is followed by simple depletion of neurohypophyseal stores.<sup>16</sup> Other possibilities include baroreceptor failure,<sup>17</sup> and inhibition of vasopressin production and release by high noradrenaline<sup>18</sup> and NO concentrations.<sup>1</sup>

As shock proceeds and endogenous vasopressin levels fall, patients often become exquisitely responsive to exogenous vasopressin, but in physiological rather than pharmacological doses. In fact, effective infusion rates (for example 0.01 - 0.04 U/min) merely achieve plasma concentrations little different from those generated spontaneously in simple cardiogenic or hypovolaemic shock. At these concentrations the perfusion of gut or myocardium is unlikely to be under threat. Vasopressin administration in septic shock is thus more akin to 'hormone replacement therapy',<sup>1</sup> and part of an emerging trend towards better endocrine support of the critically ill.<sup>19</sup>

The mechanism of the exquisite vascular sensitivity is intriguing. The low systemic vascular resistance of septic shock and associated reduced responsiveness to noradrenaline are linked to activation of ATP-sensitive K<sup>+</sup> channels.<sup>20</sup> These channels are blocked by vaso-

pressin,<sup>21</sup> providing a unique avenue of attack in the high mortality noradrenaline-resistant subgroup. This is not to say that we should now use vasopressin in every instance of septic shock. There are still many unknowns, as Drs Russell and Glover point out,<sup>7</sup> which mitigate against adoption of this agent across the board. But in the high mortality groups in which vasodilatory shock shows little or no response to therapy, it seems reasonable to restore 'physiological' levels of the hormone. In their review, Russell and Glover also explore other vasodilatory states in which vasopressin is showing promise, such as the hypotensive brain-dead organ donor and the patient with distributive shock post cardiopulmonary bypass.

There is a twist to all of this of course. Australian intensivists who weigh up the evidence and decide to bring out the vasopressin in severe septic shock face an unexpected hurdle. Fresh batches of the drug are currently unavailable. Unexpired stocks of arginine-vasopressin are a rapidly diminishing resource. Presumably the market forces which govern all our lives have brought this about. (As others have noted,<sup>12</sup> it is over fifty years since the patent on vasopressin expired.) Luckily there is one possible work-around in the form of terlipressin. Terlipressin (triglycyl-lysine-vasopressin) is a long acting vasopressin analogue ( $t_{1/2} = 6$  hours) with a good track record in the early control of variceal bleeding.<sup>4,5,22</sup> It is a lysine-vasopressin prodrug. In one small case series, terlipressin 1-2 mg intravenously in therapy-resistant septic shock reduced noradrenaline requirements for at least the next 5 hours.<sup>23</sup> Ischaemia of myocardium, gut or digits did not become a problem in the seven patients treated. Three of the seven survived to hospital discharge.

My own single experience with terlipressin has also been positive. However two things should be emphasised here. First, the evidence for its efficacy in septic shock is closer to the realms of anecdote. Second, we are back in pharmacological rather than physiological territory. Nevertheless terlipressin is a drug with a better safety profile than vasopressin at these doses, particularly when it comes to myocardial ischaemia and plasminogen activation.<sup>4,5,22,24</sup> This is coupled with the convenience of single dose administration. Most importantly, it is available.

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## What cardiovascular parameters should we aim for in the management of septic shock? (or are catecholamines being used to excess?)

During a friendly banter, one of my cardiological colleagues once stated that all ICU therapy can be explained by the three A's: an 'art line', adrenaline and amiodarone, with the implication that what we measure we try to change rather than understand and treat the underlying disease.

There is no doubt that some ICU treatments, particularly those that are governed by protocols, may give this false impression of our practice. However, in the example of a patient with a ruptured gastric ulcer and septic shock: 'disease specific treatment' (e.g. corrective surgery to repair the perforated viscus, surgical drainage and antibiotics) without multiorgan support can be just as lethal as multiorgan support without 'disease specific treatment'. This has been demonstrated in an experimental model of septic shock where appropriate antibiotics and cardiovascular support when used separately had only a small effect in reducing mortality, yet when used together had a marked synergistic effect in reducing mortality (although it is interesting to note that the effect of cardiovascular support was due largely to the intravenous fluid administered rather than the inotropic agent).<sup>1</sup>

Nonetheless, while our focus is on both resuscitation and getting the diagnosis and treatment for the disorder right, in shock there is little understanding as to what cardiovascular parameters (e.g. mean arterial pressure,

cardiac output, oxygen delivery) we should aim for, to reduce mortality.

In septic shock if the haemodynamic variables reveal a low systemic vascular resistance then agents with a peripheral vasoconstricting effect (e.g. adrenaline,<sup>2</sup> noradrenaline<sup>3</sup>) are often used to maintain the mean arterial pressure (MAP) between 70 - 90 mmHg. However, are these values too high? In one study of septic pigs (after fluid loading) a noradrenaline infusion to increase the MAP from 52 to 65 mmHg increased splanchnic oxygen delivery, jejunal microvascular blood flow and renal blood flow with no further increase when the MAP was increased to 77 mmHg.<sup>4</sup> In another study in patients with septic shock, increasing the MAP from 65 mmHg up to 85 mmHg with noradrenaline was not associated with any significant improvement in systemic oxygen metabolism, skin microcirculatory flow, urine output or splanchnic perfusion.<sup>5</sup>

Other vasoactive agents that have been used in septic shock include vasopressin,<sup>6</sup> nitric oxide synthase inhibitors<sup>7</sup> and bradykinin antagonists.<sup>8</sup> However, vasopressin in doses > 0.04 U/min may be associated with deleterious effects on renal, pulmonary, cardiac and cerebral circulations,<sup>9</sup> and a recent large multicenter randomised, placebo controlled trial in patients with septic shock was terminated as the non-selective nitric oxide synthase inhibitor L- NG-methylarginine hydrochloride was associated with a significant increase in mortality.<sup>10,11</sup> Also in a recent randomised double-blind placebo controlled trial of the bradykinin antagonist, CP-0127, in patients with the systemic inflammatory response syndrome with either hypotension or dysfunction of two organ systems, resulted in no significant effect on survival at 28 days.<sup>12</sup>

Following early studies, particularly those by Shoemaker, *et al*, reporting a higher mortality in patients who were unable to increase cardiac output in response to surgical stress compared with those who could,<sup>13,14</sup> clinicians focused their attention on oxygen delivery rather than blood pressure maintenance in septic shock. This led to the use of 'goal-directed' hyperdynamic states (e.g. oxygen delivery > 600 mL/min/m<sup>2</sup>, in association with a cardiac index > 4.5 L/min/m<sup>2</sup> and an oxygen uptake > 170 mL/min/m<sup>2</sup>) in an attempt to improve mortality in septic shock.<sup>15</sup> However, as thoughtfully discussed by Morgan,<sup>16</sup> the case for 'goal-directed' therapy is by no means established, with at least five studies failing to show any survival benefit attributable to supranormal 'goal-directed' therapy<sup>17-21</sup> and one study showing that the mortality actually increased.<sup>20</sup>

When little evidence exists for the ideal cardiovascular parameters in acute cardiovascular failure, sometimes it is useful to review studies in patients with chronic cardiovascular failure.

In chronic heart failure, inhibiting the innate sympathetic activity and reducing blood pressure or cardiac output has been beneficial. For example, vasodilator therapy with hydralazine and isosorbide dinitrate added to digoxin and diuretics has been demonstrated to reduce mortality in chronic heart failure from 38% to 25% at 2 years.<sup>22</sup> Also, angiotensin converting enzyme (ACE) inhibitors produce both short- and long-term clinical improvements in patients with chronic heart failure,<sup>23-25</sup> although as these are usually superior to other vasodilator drugs, the reported beneficial outcomes may be due to additional effects such as a reduction in the growth factor effect of angiotensin II on cardiac 'remodelling',<sup>26</sup> bradykinin induced regression of vascular hypertrophy<sup>27</sup> and preconditioning myocardium against ischaemia.<sup>28</sup>

A meta-analysis of 22 trials involving 10,135 patients with largely mild to moderate heart failure found a benefit with beta adrenergic receptor blockade in patients with chronic heart failure<sup>29</sup> that translated into a reduction in mortality of 3 and a reduction in hospital admissions of 4 for ever 100 patients treated per year.<sup>30</sup>

Concerning the use of positive inotropic agents in the management of heart failure, there has been only one agent that enhances myocardial contractility that has not increased mortality compared with placebo. This is digoxin.<sup>31</sup> While amrinone, milrinone, vesnarinone, pimobendan, flosequinan, xamoterol, pirbuterol, ibopamine and prolonged infusions of dopamine and dobutamine have all had isolated reports of improved outcome, their use in larger prospective, randomised controlled trials usually reveal an increase in mortality.<sup>32,33</sup> In the recent multicentre, prospective, randomised study of levosimendan (a calcium sensitiser) in hospital inpatients with severe low-output heart failure that reported a lower mortality in the levosimendan group in the first 180 days, levosimendan was compared with dobutamine, not placebo.<sup>34</sup>

Intensivists use inotropic agents with impunity. Yet where is the evidence? Even adrenaline which is commonly used during cardiac arrest (which some may believe reflects more the state of acute cardiovascular failure than chronic heart failure) has never been shown to be more beneficial than placebo for cardiac resuscitation in human beings.<sup>35</sup>

In this issue of Critical Care and Resuscitation, Brown *et al*, report nine critically ill patients with catecholamine resistant hypotension caused by dynamic left ventricular outflow tract obstruction in the absence of asymmetric septal hypertrophy<sup>36</sup> (a characteristic of hypertrophic cardiomyopathy), and raise the issue once again of the beneficial and adverse effects of vasopressor agents in the management of shock.

Left ventricular outflow tract pressure gradients change with preload, contractility and afterload; increasing with a reduction in preload, increase in contractility and reduction in afterload (a not uncommon triad in patients with septic shock), all of which act by decreasing the left ventricular volume, accelerating blood flow through a reduced outflow tract and accentuating the apposition of the anterior mitral valve leaflet against the septum. Treatment requires maintenance of sinus rhythm, intravascular fluid (without causing or accentuating pulmonary oedema), reduction in positive inotropic agents and judicious use of vasopressors with the acceptance of a lower cardiac output and MAP. Perhaps this is a reasonable formulae for the management of all patients with septic shock?

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## Drug overdose: a disorder that is now rarely managed in the tertiary hospital intensive care unit?

In this issue of the journal, Deshpande describes an interesting case of fluvoxamine overdose.<sup>1</sup> Fluvoxamine is a serotonin reuptake inhibitor which has reduced risk of toxicity in overdose compared with older generation antidepressants. This patient experienced a drug related seizure, remained hyper-reflexic, required conventional symptomatic supports, and recovered well. In two accompanying reviews: Clinical Toxicology Parts I and II,<sup>2,3</sup> Worthley provides an in-depth and highly current review of drug overdose and poisoning.

It seems that an intensive care doctor must now come to terms with (and learn to spell) a whole lexicon of new words including "fluoxetine, sertraline, moclobemide, selegiline, nefazodone, venlafaxine, reboxetine, viloxazine, and others." Clearly what one really needs is an up to date, accessible, ready reference guide to these

drugs. These reviews provide such a reference - and enable one to heave a sigh of relief. These are an outstanding reference tool, and admirably bridge my gap from the 1990's to current toxicology. The toxicology reviews are in reality a textbook in evolution, and as such provide a substantive update on those in Worthley LIG – Synopsis of Intensive Care Medicine 1994.<sup>4</sup>

Luckily for me the “treatment (of overdose) is generally symptomatic” and “only 20% of patients who have taken an overdose are in any danger”.<sup>2</sup> This is because as a senior intensivist I rarely get to treat patients with an overdose of any sort any more. At the downsized “large” central metropolitan university teaching hospital and major trauma centre where I work, three factors have combined to decrease my workload of overdose and poisoning patients to a trickle. Decreasing intensive care unit bed availability due to a chronic nurse shortage, an acute, near complete, loss of backup agency nursing staff following the health department intervention to reduce ballooning expenditure and increasing triage to our hospital of severely injured major trauma patients. These factors have meant that we either cease elective cardiac surgery altogether to create some bed space, or choose instead not to admit critically ill patients who are the most stable to transfer out. Nearly all overdose patients are suitably stable. So these have become our number one patient group for immediate transfer.

So drug overdose has become, in my part of the world, a disease managed by emergency medicine physicians and by intensivists who work in intermediate level metropolitan public and private hospital intensive care units. In these units, beds may have been vacated by the major trauma patients who have now been relocated into the major trauma centres.

Some overdoses are clearly not “stable”, even at my centre. One example is a patient with severe cardiac depression after tricyclic antidepressant or antiarrhythmic overdose. Such a situation may initiate an appropriate call for the extracorporeal membrane oxygenation (ECMO) team. Similarly difficult is the tragically late recognition of paraquat as the overdose agent, and the recognition that ECMO does not prevent the inexorable pulmonary deterioration characteristic of this poison. The controversial question of hyperbaric oxygen therapy (or not) for carbon monoxide poisoning is nicely handled in the Part II review,<sup>3</sup> with the most recent randomised trial data correctly noted to strongly support the case against.<sup>5</sup>

Finally, I haven't encountered either Hemlock or Spanish Fly overdose recently, but I was amused to note that the author of Clinical Toxicology Part II, found that the aphrodisiac reputation of the latter agent to be somewhat “dubious”.<sup>3</sup>

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## Nutrition as therapy: let's look at the evidence

Much has been written about the impact of nutrition, both enteral and parenteral, on various outcomes in hospitalised patients, including the critically ill.<sup>1-3</sup> Perhaps since the definitive large scale trial,<sup>4</sup> which helped define its role some 24 years after the initial description,<sup>5</sup> the star of parenteral nutrition (TPN) is waning<sup>6,7</sup> and enteral nutrition (EN) has displaced parenteral as the preferred form of nutrition in the critically ill.<sup>8</sup> However, recent reviews have questioned the role and value of nutrition itself<sup>1,9</sup> and it is perhaps now apposite to consider the effect of nutrition as a form of ‘treatment’.

To review the effect of nutrition, as a form of ‘treatment’ for various disorders, involves either a search for evidence of improvement in certain patient variables, measured before and/or after nutrition (e.g. biochemical variables, indices of immune function, changes in nitrogen balance or increase in patient muscle strength)<sup>10-12</sup> or, alternatively, evidence for improvement in key outcome variables, such as mortality, complications, length of stay and cost.

Currently it is the latter set of outcomes that we believe demonstrate efficacy of therapy, with the former list of variables being considered surrogate end-points for the latter.<sup>13,14</sup> Nevertheless, even a valid surrogate must not be merely correlated with a true clinical outcome; rather, the effect of the intervention on the

surrogate end-point must *predict* the effect on the clinical outcome.<sup>15</sup>

The classic statistical definition of a surrogate end-point was provided by Prentice:<sup>16</sup> "...a response variable for which a test of the null hypothesis of no relationship to the treatment groups under comparison is also a valid test of the corresponding null hypothesis based upon the true endpoint". This is a restrictive definition and, paradoxically, may be not be able to be "meaningfully tested".<sup>17</sup> Freedman *et al*,<sup>18</sup> provided alternative criteria in the form of the proportion explained; the ratio of the treatment effects on the primary end-point, with and without adjustment of the surrogate. A high proportion equated with a useful surrogate. However, this measure has been shown to have considerable variability<sup>19,20</sup> and (with the realisation that any proper demonstration of the efficacy of a surrogate requires large patient numbers and strong treatment effects) recent attention has been directed to meta-analytic methods for establishing criteria.<sup>21</sup> The current position is one of uncertainty about the establishment of exclusively statistical criteria for pure surrogate studies<sup>14</sup> and cautions have been expressed regarding such attempts.<sup>15,22</sup> That the recent clinical review of surrogate end-points by Bucher *et al*,<sup>23</sup> offered no precisely quantifiable criteria for the "resolution of ...(this)... scenario" and concluded that "treatment recommendations based on surrogate outcome effects can never be strong", is illustrative of the above concerns. Therefore, further use of such surrogate end-points with respect to "nutrition as therapy" will be for illustrative purposes only.

A number of recent reviews have highlighted particular problem areas within the nutrition paradigm; the discourse has been either at the level of the individual study,<sup>24-27</sup> or at a qualitative overview of the same.<sup>28,29</sup> Our review focuses on the assessment of the efficacy of nutrition at the meta-analytic level, looking at the aggregate results of randomised controlled trials (RCTs).<sup>30</sup> That such a strategy may obfuscate differences between patient subsets must be acknowledged; however, subset or sensitivity analysis, even when protocol specified, is at best hypothesis generating. Moreover, the reduced size of such subsets with respect to the overall meta-analysis introduces further uncertainty into treatment estimates, although this is rarely commented upon, and sub-analyses defined a priori are implicitly given the same status as more powerful aggregated estimates. For instance, in the meta-analysis of early EN in gastrointestinal surgery,<sup>31</sup> anastomotic dehiscence rates were the main outcome measure. These rates were reported in only 8 of the 11 studies; in 2 studies where the anastomosis was proximal to the site of enteral feeding and in 6 where

the anastomosis was distal to the feeding site. Yet the conclusion of the meta-analysts was that there was "little evidence" that the site of anastomosis relative to the EN feeding site was important. Thus, in the context of paucity of data, observed risks may not adequately reflect the true underlying risk and estimates may be inefficient or biased. This is especially important when considering the significance (p value) of the treatment effect in meta-analyses and patient subsets. The usual variance estimator in meta-analyses is biased<sup>32</sup> and the "standard" test procedure, model choice between fixed and random effects dependent upon diagnosis of heterogeneity, is anti-conservative (type I error rates of nearly 10% if heterogeneity is present).<sup>33</sup> Estimation techniques which may offer advantage in this context are restricted maximum likelihood estimation,<sup>34,35</sup> which produces conservative standard errors (that is type I error rates close to nominal levels) and full Bayesian analysis,<sup>36</sup> where in the process of producing posterior estimates of parameters, "strength is borrowed" from larger studies to inform smaller.

Table 1 shows nutritional effect estimates in 11 meta-analyses.<sup>6,30,31,37-44</sup> The later meta-analysis of immunonutrition by Heyland *et al*,<sup>40</sup> is used in preference to a consideration, separately, of the similar theme meta-analyses of Beale *et al*<sup>45</sup> and Heys *et al*.<sup>46</sup> With respect to nutritional intervention in "general" patients (Table 1, meta-analyses number 1-3), there was no effect on mortality, or a treatment effect of EN on remission in Crohn's disease, or on various outcomes in stable COPD and elderly patients with hip fracture. In the "acutely/critically ill" patient (Table 1, meta-analyses 4-11), no mortality effect was demonstrable from specific nutritional intervention (EN, immunonutrition EN or TPN), timed delivery of EN (early vs late) or EN compared with TPN. Infectious complications were reduced with early delivery of EN and immunonutrition EN versus TPN, but significant heterogeneity was also demonstrated. No statistically significant advantage of nutritional modality was evident with respect to non-infectious complications, but both early EN (versus late) and immunonutrition were associated with a significant reduction of length of stay (LOS), albeit there was again, heterogeneity of effect. Two other pertinent meta-analyses, reported in abstract form only, may be summarised:

- a) early (initiation within 72 hr of index event) EN vs early TPN;<sup>47</sup> 26 studies, with a reduction in LOS, infections and complications with EN, but an increased incidence of diarrhoea with EN and,
- b) glutamine supplementation in critically ill adults,<sup>48</sup> 14 RCT, showing a lower complication rate (RR 0.81; 95% CI 0.67-0.99) and shorter LOS.

**Table 1. A summary of 11 meta-analyses that consider the effects of nutrition**

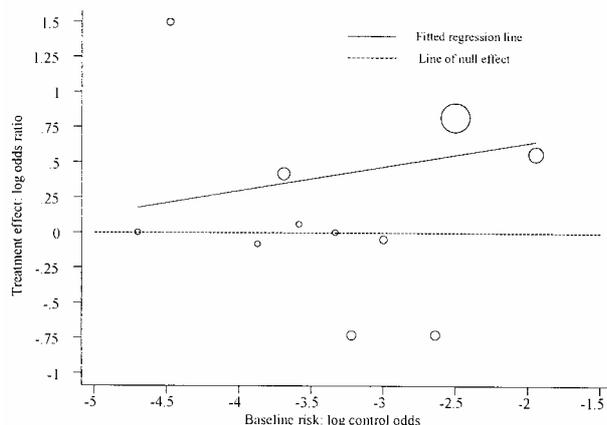
Metan no	Meta-analysis: specific	Ref no	Year	RCT	Patient no	Mortality effect (study no)	Infections effect (study no)	Complications effect (study no)	LOS (days) effect (study no)
1	EN in Crohn's disease remission (a) elemental vs non-elemental diets  (b) EN vs steroids	38	2002	9	298	no difference: OR 1.15(0.64-2.08) EN less effective OR 0.3(0.17-0.52)			
2	Nutritional supplements in stable COPD	37	2002	9	277	no effect on lung function, exercise tolerance, anthropometric measurements			
3	Nutritional supplements in hip fracture in elderly	35	2002	15	1054	no strong evidence of effect over multiple nutrient supplement types			
4	TPN vs EN: (a) tube feeding          (b) standard care	36	2001	27	1829	no effect (9) RR 0.96(0.55-1.66)	decreased (15) RR 0.6(0.56-0.79)	nutritional no effect (10)* RR 1.36(0.96-1.83) other no effect (9) RR 0.92(0.55-1.65) other no effect (7) RR 0.87(0.74-1.03)	NA          NA
5	EN: early vs late acutely-ill patients	43	2001	15	753	no effect (6) RR 0.74(0.37-1.48)	decreased (12)* RR 0.45(0.3-0.66)	no effect RR 0.82(0.56-1.19)	decreased (12) 2.2(0.81-3.63)
6	EN: early vs late post GIS surgery	42	2001	11	837	no effect (6) RR 0.48(0.18-1.29)	decreased (8) RR 0.72(0.53-0.98)	no effect RR 0.53(0.26-1.08)	decreased (11)* 0.84(0.36-1.33)
7	Immuno-nutrition	40	2001	22	2419	no effect (22) RR 1.10(0.93-1.31)	decreased (18)* RR 0.66(0.54-0.80)	NA	decreased (17)* 3.3(1.025-5.63)
8	TPN vs standard therapy in critically-ill	6	1998	26	2211	no effect (26) RR 1.03(0.81-1.31)	NA	no effect (22)* RR 0.84(0.64-1.09)	no effect (9)* 1.55 (-1.25 to 4.36)
9	TPN vs standard therapy in surgical patients	41	2000	27	2907	no effect (27) RR 0.97(0.76-1.24)	NA	no effect (2)* RR 0.81(0.65-1.01)	no effect (8) 0.65 (-1.82 to 3.11)
10	TPN vs EN: head injury (a) early vs late          (b) parenteral vs enteral	44	2002	6	257	no effect (6) RR 0.71(0.43-1.17)	NA	NA	NA
				5	207	no effect (5) RR 0.66(0.41-1.07)	NA	NA	NA
11	EN vs TPN in pancreatitis	39	2002	2	70	no effect RR 0.56 (0.05-5.62)	NA	NA	NA

Ref no = reference number, Year = year of publication of meta-analysis, RCT = number of randomised controlled trials considered in meta-analysis, Patient no = total patient number in meta-analysis, Mortality = effect of nutritional intervention on mortality, Infections = infection rate recorded in meta-analysis, Complications = complications (non-infective) recorded in meta-analysis analysis; (i) nutritional = complications specific to provision of nutrition, (ii) other = complications not specific to provision of nutrition, effect (study no) = effect of nutritional intervention (number of RCT upon which estimate is based), LOS = length of stay (hospital) in days, RR = risk ratio (point estimate(95% CI)), \* = significant heterogeneity recorded in meta-analysis, EN = enteral nutrition, TPN = total parenteral nutrition, COPD = chronic obstructive pulmonary disease, GIS = gastro-intestinal, NA = not available.

Therefore, in nearly 10 000 patients and over 100 randomised controlled trials, the only consistent aggregate effect was a decrease in infectious complications and length of stay with the provision of enteral nutrition, but even then only in a minority of trials. Although these two benefits are analytically consistent, what was obvious was a systematic under-reporting of non-mortality outcomes across all meta-analyses (see Table 1, "effect (study no)"). That this has not been commented upon by the meta-analysts is cause for concern, as the implications of missing data<sup>49</sup> are those of bias and inefficiency in estimation. This problem has been termed "within-study selective reporting of subgroups".<sup>50,51</sup> As with publication bias, the most likely explanation of this selective reporting is that of non-significance. When the "missingness" has been addressed by appropriate imputation techniques,<sup>50</sup> the initial estimate of effect was seen to be exaggerated. In the absence of covariates, an alternative strategy could be meta-regression of treatment effect against baseline risk, as a surrogate for patient severity of illness. However, the uncritical use of weighted linear regression,<sup>52</sup> by ignoring regression to the mean, is associated with biased estimates and full Bayesian analysis, producing empirical estimates of the true

posterior parameters, is recommended.<sup>53</sup> Using such a Bayesian approach,<sup>54</sup> with an uninformative (uniform) prior, a significant relationship was demonstrated (on the log odds scale) between treatment effect and control arm mortality in the Heys *et al* meta-analysis of immunonutrient supplements,<sup>46</sup> as demonstrated in Figure 1. The fitted regression line shows an increase (> 0) in log odds ratio from low to high baseline risk; that is, as baseline risk (and presumably patient severity of illness) increases the adverse effect on outcome (i.e. mortality) produced by immunonutrient supplements also increases.

Nutritional efficacy was demonstrated in some patient subsets. Major complications were significantly lower in malnourished patients with TPN versus standard therapy,<sup>6</sup> in studies with lower methods scores and when TPN was initiated pre-operatively.<sup>41</sup> Early versus late EN was associated with a substantive reduction in LOS in trauma/head injured/burn patients;<sup>42</sup> immunonutrition formulas with high versus low arginine content appeared to be of advantage with respect to infectious complications and LOS;<sup>40</sup> immunonutrition reduced infectious complications and LOS in elective surgery versus critically ill patients. In the latter group, LOS was reduced by immunonutrition,



**Figure 1.** Treatment effect (log odds ratio) versus baseline risk (log control odds) for immuno-nutrient supplements using full Bayesian regression analysis. Vertical axis, log odds ratio; +ve log odds, adverse effect; -ve log odds, beneficial effect. Horizontal axis, log control odds; increase in risk as log control odds becomes less negative. Horizontal dotted line, line of null effect (log of odds ratio of 1). Solid line, regression fit. Circles, individual studies; size of circles inversely proportional to inverse of log odds ratio (large circles correspond to large studies).

but, in the absence of a reduction in infections, this was thought to be dependent upon the trend to increased mortality in studies using low arginine EN.<sup>40</sup> The status of these sub-analyses has been commented on above and a more consistent approach would be to use multivariate meta-regression.<sup>55,56</sup> Calendar time dependence of treatment effect, such as produced by dichotomising the trial time span within a meta-analysis,<sup>6,30,41</sup> may also be better understood using cumulative meta-analysis.<sup>57</sup> Similarly, the frequent use of trial quality scales<sup>6,30,40,41</sup> to interpret effect estimates ("poorer" quality associated with inflated estimates) presupposes a linear and additive notion of "quality", which notion may be inconsistent.<sup>58,59</sup> Finally, given the frequently noted low power of tests for heterogeneity,<sup>60</sup> the persistent use of a strict 0.05 level of p value (instead of 0.1) for the diagnosis of heterogeneity<sup>42</sup> will increase the type I error rate and is unjustifiable.

The above cautions on the overinterpretation of meta-analytic reviews of nutrition and has resonance with the 1995 critique of Koretz on nutrition in the intensive care unit.<sup>25</sup> What can be said at this juncture is that:

- i) there is no evidence that mortality is affected by specific nutritional intervention other than the obvious intervention to prevent actual starvation,
- ii) early EN, compared with delayed EN or TPN, is associated with a decrease in the incidence of infectious complications and LOS, but this advantage is substantially confounded by heterogeneity of effect and the consequences of missing data and,

- iii) enthusiasm for the aggressive provision of EN or TPN as therapeutic modality is misplaced.

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