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"I would have everie man write what he knowes and no more."—Montaigne

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Editorial I

Metabolic support of critically ill patients: parenteral nutrition to immunonutrition

The adaptive metabolic changes that occur during starvation were described in detail over 30 years ago and are an excellent example of an integrated physiological response that conserves body protein and maintains normoglycaemia.[1] Critically ill patients are often malnourished and then starved for several days whilst undergoing the hormonal, metabolic and inflammatory changes that are commonly referred to as the 'stress response'.[2] It seems intuitively obvious, therefore, that feeding these patients during the gross catabolic phase of their illness should be beneficial. For many years, the best route for nutritional support was not clear and it is only in the past decade that there has been general agreement that enteral feeding is the method of choice.[3] However, some patients do not tolerate enteral feeding or do not obtain sufficient intake orally or enterally to meet their nutritional needs. Total parenteral nutrition (TPN) may be used in these patients either as a supplementary feed or as the only source of nutrition. Evidence to support the beneficial effects of TPN in critically ill patients has been lacking despite studies going back to the 1970s. A meta-analysis of studies of parenteral nutrition up to 1986 found only 11 trials that were randomized or quasi-randomized, and concluded that perioperative TPN was not justified in unselected major surgery.[4] A further meta-analysis of TPN was published in 1998 by Heyland and colleagues with the objective of examining the relationship between TPN and mortality and complication rates in the critically ill.[5]

The authors initially identified 153 citations from a bibliographic search for the years 1980–1998, and a further 57 articles were found from a review of reference lists and personal files. They examined only studies that evaluated the use of supplementary TPN in patients already receiving enteral feeds or studies of TPN in patients who were otherwise receiving standard care of oral food and i.v. glucose. Studies comparing TPN with enteral feeding or other forms of TPN were excluded. Only 26 randomized trials involving 2211 patients were suitable for evaluating TPN under these conditions.

The primary outcome was perioperative mortality and the secondary outcome was the rate of major complications. The investigators carefully defined major complications and differentiated them from minor complications, such as wound infection, atelectasis, urinary tract infection and phlebitis. Data on the duration of hospital stay were not aggregated into the analysis because of the variable and infrequent reporting methods. We have previously drawn attention to the problems inherent in attempting to use length of hospital stay as a measure of outcome.[6] To try to explain the heterogeneity of the data, the authors developed several hypotheses before undertaking the statistical analysis. They looked at the nutritional status of the patients, the methodological quality of the study, the date of publication and the use of lipids, and compared surgical with critically ill patients.

The results, aggregated from 26 studies, showed no effect of TPN on the mortality:risk ratio, which was 1.03 (95% confidence interval 0.81–1.31). There was a slight decrease, which was not statistically significant, in major complications in patients receiving TPN in the 22 studies in which these were recorded (risk ratio 0.84, 95% confidence interval 0.64–1.09). When the *a priori* hypotheses were examined to try to explain these results, it was found that a significant beneficial effect of TPN on major complications was present in malnourished compared with nourished patients, in studies with a low methodological quality score, in studies published earlier than 1988, and in surgical rather than critically ill patients. The only hypothesis that did not show a significant interaction with the complication rate was the use of lipids. It is notable that there was an increased incidence of major complications in critically ill patients receiving TPN that nearly achieved statistical significance (risk ratio 2.40, 95% confidence interval 0.88–6.58). In contrast, when these hypotheses were examined using mortality as the end-point, only one remained statistically significant in favour of TPN: the surgical patient compared with the critically ill patient (P=0.03). Furthermore, the mortality rate of critically ill patients receiving TPN was significantly increased (risk ratio 1.78, 95% confidence interval 1.11–2.85). Only 14 studies reported the effects of TPN on the duration of hospital stay, and in eight studies it was shorter in the control group.

Heyland and colleagues comment that, in spite of their intention to summarize the evidence of the effect of TPN on

critically ill patients, the meta-analysis of 26 studies included only six studies of typical intensive care unit (ICU) patients. In particular, there were no studies of medical ICU patients or of patients with sepsis, and only limited assessment of trauma patients. It is common practice to aggregate studies of major surgical and ICU patients on the assumption that the physiological responses to injury and starvation are similar. But the subgroup analysis indicates that, with TPN, the complication rate and mortality rate were significantly greater in critically ill patients than surgical patients. It is no longer appropriate to apply data derived from studies of major surgery to ICU patients.

The results of the meta-analysis do not support the continuing use of TPN in critically ill patients. Indeed, the authors suggest that the only possible use for TPN may be in patients who cannot tolerate enteral nutrition. Since this view was based on a single study of surgical patients, in which TPN was no better than i.v. glucose, its relevance to critically ill patients must be doubtful.[7] Proponents of the continuing use of TPN in the ICU must provide evidence of benefit in the face of the unambiguous conclusions of the recent meta-analysis. In our view, TPN in the critically ill patient is of historical interest only, and this form of nutritional support should be confined to the malnourished, surgical patient.

With the popularization of the enteral route for feeding has come the realization that the incorporation of other compounds in the standard enteral feed may have beneficial effects on the metabolic, inflammatory and even immune response to injury. Novel substrates, such as medium-chain and short-chain fatty acids, glutamine and branched-chain amino acids, have been investigated.[8] More recently, attention has turned to the use of arginine, glutamine, nucleotides and omega-3 fatty acids as immunomodulators. The notion is simple and attractive: enhance immune function in the critically ill by the use of key nutrients in the enteral feed and the incidence of infectious complications and even the mortality rate should be improved. Immunonutrition was reviewed last in this journal in 1996.[9]

The most commonly used commercial preparation, Impact, contains the basic amino acid arginine, omega-3 fatty acids and RNA. The evidence to support the immune-enhancing properties of these three compounds is of varying quality. There is a considerable literature on the immunological effects of arginine and also of glutamine, which is incorporated in another commercial preparation, Immun-Aid. These amino acids enhance cellular immunity, modulate tumour cell metabolism, augment lymphocyte and macrophage proliferation (particularly glutamine), improve wound healing and decrease nitrogen loss post-operatively.[10–13] The ability of glutamine to maintain intestinal barrier function and prevent the translocation of bacteria and endotoxins from the gut lumen to the circulation may be particularly important in critically ill patients.[14] There are other properties of arginine that may also be important in modifying the physiological responses to injury. Arginine stimulates the secretion of several hormones, including the anabolic hormone insulin, and prolactin and growth hormone.[15] It may also be involved in the local regulation of tissue blood flow as it is a precursor of nitric oxide.[16]

The omega-3 fatty acids were thought initially to enhance immune defences through increased production of prostaglandin E_3 (PGE_3), which is less immunosuppressive than PGE_2, which is usually released in the inflammatory response. PGE_3 down-regulates the production of the proinflammatory cytokines tumour necrosis factor-α and interleukin-Iβ (IL-Iβ), and the major cytokine IL-6. The omega-3 fatty acids also have effects on the release of thromboxane A_2 and PGI_2 (prostacyclin), and inhibit a variety of cellular and humoral immunological mechanisms. The effects of these compounds on immune function have been reviewed in detail, but the literature pertains mainly to surgical oncology patients.[17 18]

The administration of RNA or synthetic polynucleotides to enhance immune function is less convincing. Dietary nucleotides are essential for cell-mediated immunity and T-lymphocyte function.[19 20] However, most experimental work has been undertaken in animals using nucleotide-free diets over several weeks, and the relevance of much of these data to critically ill patients is obscure. In 1995, Heyland and colleagues reviewed the available studies and concluded that there was little evidence to support the use of dietary RNA supplementation in patients.[21] We suggest that this opinion is still valid.

Cerra and colleagues published a preliminary study in 1990 that showed the effects of a combination of nutrients in enhancing immune function in ICU patients.[22] This seminal work has stimulated further clinical studies in the past decade to examine not only immune function but also the potential clinical benefits in patients receiving immunonutrition. In 1999, Heys and colleagues reported a meta-analysis of randomized controlled trials of enteral immunonutrition in patients with critical illness and cancer.[23] The authors conducted a search for articles published between 1990 and 1998 and identified 11 randomized controlled trials evaluating the use of enteral nutritional support supplemented with combinations of key nutrients (immunonutrition) versus standard enteral nutrition. They evaluated only the clinical outcome: major infectious complications, nosocomial pneumonia alone (as a possible indicator of changes in immune function) and mortality. The duration of stay in the ICU and hospital were analysed when the information was documented. In eight studies, Impact (L-arginine, *n*-3 essential fatty acids and RNA) was used, Immun-Aid (L-arginine, L-glutamine, branched-chain amino acids, *n*-3 essential fatty acids and RNA) was used in two studies, and in one study the experimental diet was enriched with L-arginine and L-glutamine.

When the data were aggregated for the meta-analysis, there was a significant decrease in the risk of developing

major infectious complications in the immunonutrition group (odds ratio 0.47, 95% confidence interval 0.32–0.70). However, there was no significant improvement in the incidence of nosocomial pneumonia (odds ratio 0.91, 95% confidence interval 0.53–1.56). Supplemented enteral nutrition was associated with a significant decrease in the duration of hospital stay of 2.5 days (95% confidence interval 1.0–4.0), although the duration of stay in the ICU did not change in the four studies in which this variable was noted.

At first sight, the results of the meta-analysis are impressive, with a lower risk of developing a major infectious complication and a shorter duration of hospital stay in the patients given immunonutrition. In contrast, however, there was an increased risk of death in the immunonutrition group (odds ratio 1.77, 95% confidence interval 1.00–3.12) that just failed to reach statistical significance. It is possible that the lower incidence of major infections and shorter hospital stay in the supplemented group may simply have been a consequence of the increased early mortality. There is no mention in most of the studies analysed of the bias of death on these variables and the need to 'censor' this effect. Indeed, there is an uncanny parallel between the findings of the meta-analysis and a study of immunonutrition in critically ill patients that was published in 1998 after the literature search.[24] In this recent investigation of 101 patients, the use of Impact was found to have no effect on mortality (48% in the Impact group, 44% in the control group), but was associated with a significant reduction in the need for pulmonary ventilation (6.0 *vs* 10.5 days, $P = 0.007$) and a decrease in the duration of hospital stay (15.5 *vs* 20 days, $P = 0.03$). When the duration of hospital stay of patients who died was removed from the results, the difference was no longer statistically significant (P=0.08).

It is important to note that, in the meta-analysis of immunonutrition, the majority of studies (six out of 11) examined surgical patients usually with an upper gastrointestinal malignancy. In four of the surgical studies no patients died. Only five studies investigated critically ill patients, and these were predominantly patients with major trauma. As in the TPN meta-analysis,[5] results from typical ICU patients were not available to assess the effects of immunonutrition.

Obviously, there is a need for further randomized controlled studies of immunonutrition in critically ill patients. Future studies must have adequate statistical power, well-described patient groups, precisely defined nutritional regimens, an appropriate control nutritional group and accurate outcome measures. The results of the meta-analysis of immunonutrition hint at beneficial effects: decreases in the incidence of major infectious complications and in the length of hospital stay. It is imperative that appropriate studies of immunonutrition are undertaken to avoid the confusion and uncertainty that has accrued after 25 years of research into TPN. At present, the value of immunonutrition in critically ill patients is not proven.

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Editorial II

Safe placement of central venous catheters: where should the tip of the catheter lie?

Central venous catheters are ubiquitous in modern hospital and ambulatory medicine, with up to 6 million insertions per year in the USA[1] and 200 000 per year in the UK.[2] Despite this, there is still considerable doubt as to what constitutes optimal practice in terms of catheter composition, route of placement and the minimization of complications such as catheter-related sepsis, thrombosis and vessel perforation.

In this issue of the journal, Schuster and colleagues describe an elegant post-mortem, radiological study of pericardial anatomy.[3] This work is based on the premise that, in order to prevent atrial or ventricular perforation and subsequent cardiac tamponade, the central venous catheter tip should not lie within the boundaries of the pericardial sac. In seeking to prevent this dramatic but rare complication are we exposing the patient to other equally serious but more insidious complications? The answer is probably yes. These issues are explored in this editorial.

Catheters will generally function equally well for pressure measurement and fluid infusion if the tip is situated in any major vein, above or below the heart. For dialysis or the infusion of irritant/hypertonic fluids, a high rate of blood flow past the catheter tip is desirable and this requires the placement of the luminal opening in as large a vessel as possible. However, the package inserts of many central venous catheters give very strong warnings about the absolute requirement for catheter tips to lie outside the heart to avoid perforation and subsequent pericardial tamponade.[4] In the USA, the Food and Drug Administration has issued advice emphasizing this point. This advice is based on numerous case series reporting the association between intracardiac placement of the catheter tip and (usually fatal) tamponade.[1 5–7] Authors of recent case series have acted as expert witnesses in cases of litigation related to fatal tamponade.[1 5] These experts may have been chosen for their polarized opinions. The outcome of such litigation has dictated the response of regulatory authorities and manufacturers. Despite this, the level of awareness of the issue amongst physicians, anaesthetists and radiologists was reported in 1995 to be low.[5]

Cardiac tamponade related to central venous catheterization follows a predictable pattern. Most cases occur in the first week after insertion.[5 6] Chest pain, nausea, dyspnoea, cyanosis, tachycardia, hypotension, engorged neck veins and pulsus paradoxus may occur hours before decompensation. The correct clinical diagnosis is rarely made and cardiac arrest usually ensues, with a mortality exceeding 70%. In most cases, review of the chest radiograph taken before tamponade reveals the catheter to be inside the cardiac silhouette.[5] At post-mortem, the fluid removed from the pericardium may be serous or serosanguinous, or may resemble the fluid being infused before tamponade. Interestingly, in a small proportion of patients it is not possible to find a definite track through the myocardium.

The incidence of tamponade is impossible to know precisely. Since the introduction of central venous catheterization in the 1950s, hundreds of millions of catheters have been inserted. Over the same period, the number of reported cases of associated tamponade is in the hundreds. Thus, even allowing for unrecognized and unreported cases, the scale of the problem is put into perspective. Experience with transvenous cardiac pacing is also instructive: the deliberate placement of transvenous pacing wires into the right atrial or ventricular wall very rarely results in tamponade.[8] To prevent tamponade, it would appear reasonable to avoid placement of the catheter tip within the right ventricle or deep into the right atrium (RA). However, there is increasing

recognition that placing the tip in positions above the RA is also associated with significant complications.

Perforation

Catheter perforation of the central veins has been widely reported and may result in pleural effusion, hydrothorax, haemothorax, hydromediastinum, pneumothorax and pneumomediastinum.[9–11] Although the effects are less dramatic than for perforation of the heart, there is appreciable morbidity and finite mortality.[10] Hydromediastinum resulting in cardiac tamponade has been reported,[7] and perforation of the medial wall of the superior vena cava (SVC) can produce tamponade directly.[6] This is explained by the finding by Schuster and colleagues that the pericardium may ascend alongside the medial wall of the SVC by up to 5 cm (mean 3 cm).[3] Thus, placement just proximal to the atrium does not obviate the risk of tamponade.

Perforation is thought to occur as a result of mechanical trauma from the catheter tip or chemical damage from infused solutions.[12] This results in two warning signs: visceral-type chest pain on infusion of drugs or parenteral nutrition solutions[13] and a curved appearance of the distal catheter seen on chest x-ray.[9]

Factors affecting the risk of perforation by catheters (both venous and cardiac) are numerous. Stiffer catheters are more likely to perforate.[14] Stiffness is a function of the composition of the catheter (Silastic probably being safest) and the number of the lumen (a function of the greater diameter and presence of 'septa' within the catheter). The angle that the catheter tip makes with the wall of the vein or heart is crucial; both *in vitro*[14] and clinical evidence indicates that the more perpendicular the catheter to the wall, the greater the risk of perforation.[11 15] Left-sided catheters pose a particular problem because the left innominate (brachiocephalic) vein forms a near right angle to the SVC. Catheters entering the SVC from the left therefore have a tendency to impinge on the lateral wall of the SVC. The resulting increased risk of perforation is well documented.[9 11 15]

A sharp, inflexible catheter tip increases the risk of perforation, as does excessive mobility of the tip (seen with brachial catheters upon movement of the arm). Fluid infused under high pressure or at a high flow rate may increase the risk of perforation; this may occur with the use of side ports as well as end ports. When myocardial perforation does occur in this situation, the risk of tamponade is greatly increased. Finally, it is likely that some perforations are due to trauma from the guidewire or dilator, particularly when tamponade occurs early after insertion.

Thrombosis and catheter-related sepsis

The overall thrombosis rate from central venous catheterization is between 30 and 70%.[16–18] Thrombosis occurs where there has been repeated trauma to the endothelium from the catheter tip.[19] There is increasing evidence of a relationship between high placement of the catheter tip (upper SVC or above) and thrombosis.[19 20] Although most thrombosis is either asymptomatic or results in catheter blockage alone, life-threatening sequelae are probably under-recognized. The incidence of pulmonary embolism from catheter-related thrombosis may be up to 60% for both short- and long-term catheterization;[16 21 22] one study reported a mortality of 12%.[22] In addition, thrombosis of the axillary or subclavian veins can lead to significant morbidity and requires anticoagulation; SVC obstruction is possible and may be fatal.[19]

Catheter-related sepsis (CRS) is a major problem, with a direct mortality rate of 25%.[23] A clear relationship has been established between CRS and thrombosis,[16 17] and when the two combine to produce septic thrombophlebitis the result is devastating. Although it is not clear whether infection predisposes to thrombosis or *vice versa*, the morbidity and mortality that potentially originate from thrombosis due to a high-lying catheter tip (with or without infection) is enormous, and in quantitative terms may far exceed that related to cardiac tamponade.

Extravasation

Extravasation of fluid or drugs from proximal side-holes is a potentially serious complication of catheters inserted to an inadequate depth.[24]

Positioning

A major problem in correctly siting central venous catheters is the lack of reliable surface landmarks. Although some authors recommend points such as the sternal angle as being at the level of the junction of the SVC and right atrium,[11] most recommend a chest x-ray as the only practical, reliable test. Schuster and colleagues identify the carina as a radiological landmark below which the tip is likely to be within the pericardial sac.[3] However, given that the SVC is only 6 cm long and the carina is roughly 3.5 cm higher than the SVC/atrial junction, placing the tip above the carina is likely to put it in a risk area for thrombosis or, particularly for left-sided catheters, into a position at higher risk of perforation. In addition, a frontal chest radiograph does not exclude a catheter position in smaller vessels (e.g. azygos vein) or an extravascular site adjacent to the correct site.

The use of right atrial electrocardiography during insertion of central venous catheters has been claimed to be of value.[26] However, such a technique can tell the operator only whether the tip is within the atrium, not where it is within the venous system. The use of an image intensifier permits visualization of the tip position but is not available routinely. Ultrasound, although very useful for aiding insertion, is of limited value in confirming tip placement. It will show misplacement in the subclavian, axillary or

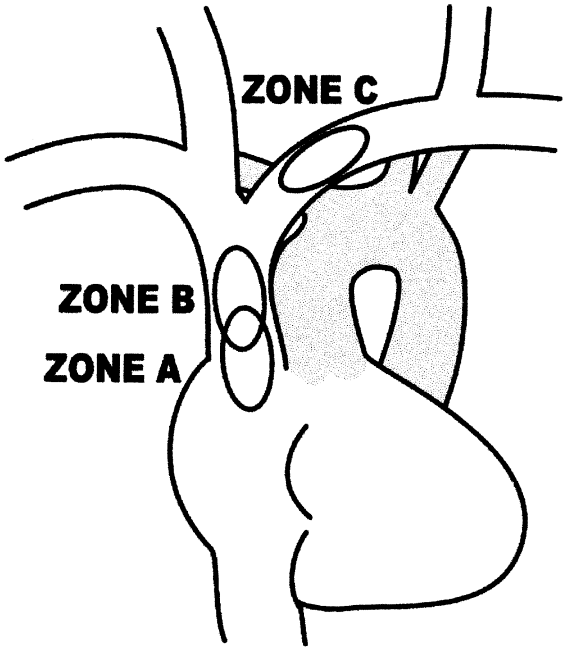

Fig 1 Stylized diagram of heart and great veins. Angles may be more acute *in vivo*.

internal jugular veins but is not suitable for imaging the SVC. Venography and even computed tomography are of value in situations where the line position is in doubt and reinsertion is undesirable.

Current guidelines on tip position focus only on the risk of tamponade. We believe that an unsatisfactory tip position above the heart should not be accepted purely to satisfy these guidelines. Whenever the catheter negotiates a sharp bend, the catheter must be passed a reasonable distance beyond the bend such that the axes of the catheter and vein are aligned. In the case of insertion from the left side, this may be achievable only by siting the tip in the right atrium. Reference to a stylized diagram of the heart and great veins may provide some guidance (Fig. 1).

Zone A (low SVC/upper right atrium). This is a suitable tip site from any access point in the upper body. We believe catheter tips can be sited safely within the upper right atrium provided they do not abut the atrial wall end-on or pass through the tricuspid valve or into the coronary sinus.[6 13 20 25 26]

Zone B (upper SVC). This is a suitable site for tips of catheters placed via the right internal jugular route.[9 10]

Zone C (mid-point, left innominate vein). This is a suitable site for the tip when the catheter is introduced from the left internal jugular or subclavian vein, and reduces the risk of SVC perforation.[11]

Conclusions

The catheter tip should be placed in as large a vein as possible, ideally outside the heart and parallel with the long axis of the vein such that the tip does not abut the vein or heart wall end-on.

There are complications associated with all tip positions and a lack of good evidence on which to base practice. There is no evidence that the complications of short-term versus long-term catheterization are qualitatively different, but the event rate per patient is likely to be higher with the latter, requiring meticulous attention to detail.

Individual clinical factors must dictate the choice of access point and site of the catheter tip. Ultimately, the risks of central venous catheterization will be minimized only by clinicians having a detailed knowledge of the complications of catheterization, a high index of suspicion that clinical deterioration may be due to the catheter, and a readiness to take action. Clinicians should audit their results and be prepared to justify individual practice.

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