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Current State of Knowledge

Enteral and parenteral nutrition

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1. INTRODUCTION

In recent years the field of nutritional support in critically ill patients was been changed by several factors concurring together. These include a better knowledge of the body´s metabolic response to critical illness and exciting new technological developments that improve the way we can provide support to the patients. The different metabolic response to illness accordingly to the nature of the disease process and even to the species level began to be clarified. The role of the gastrointestinal tract for the maintenance of a normal local and general immune response, and the acknowledgement that its failure can lead to bacterial translocation and become a motor to Multi-Organ dysfunction Syndrome (MODS) became more established. This was one of the factors that increased the renewed interest in enteral nutrition.

Large multi centers trial in People provided essential knowledge that permitted, within certain limitation, to guide veterinarians for treating their own patients. And finally the role of specific nutrients and its potential therapeutical role in critical illness begin to be studied (e.g.: glutamine). In the following sections, by asking and answering specific questions, the author will describe briefly the new developments associated with this fascinating field of Critical care Medicine.

2. WHY SHOULD WE GIVE NUTRITIONAL SUPPORT?

The answer to this question reflects the paradigm shift that this field has witnessed. Classically nutritional support in Critical Care Medicine was considered an adjuvant therapy to support the stress response, by providing enough nutrients to reduce the drain of endogenous stores and the body mass´s depletion and prevent malnutrition. (McClave & Heyland, 2005).

Nowadays, especially through enteral nutrition, nutritional support is being increasingly used as a therapeutic tool to modulate immune response (pharmarconutrition), prevent complications, reduce disease morbidity and produce a positive impact in the outcome, by changing the disease´s clinical course.

3. THE METABOLIC RESPONSE TO CRITICAL ILLNESS AND ROLE OF THE GASTROINTESTINAL TRACT

The body response to stress is characterized by e elevation of growth hormone, cortisol, endogenous catecholamines and glucagon levels. At the same time a state of insulin resistance occurs, possibly induced by decreased phosphorylation of the insulin receptor and decreased intra-cellular second messenger signaling. The net effect of these hormonal changes is an increase in neoglucogenenesis, lipolysis and glycogenolysis to produce energetic substrates for the body to fight the “stressor”. Catabolism of the body proteins also increases not only to increase subtracts availability for energy production but also to increase aminoacids availability for liver production of acute phase proteins. This metabolic response makes that critically ill patients frequently become hyperglycemic, hyperlipidemic and with a negative nitrogen balance. The result of this negative nitrogen balance can be a depression of T and B lymphocyte function, decreased phagocytosis, chemotaxis and bacterial killing, decreased wound healing and the decreased recovery of immune competence. Hyperglycemia by itself can have its own negative consequences (see later). Compared to normal starvation, the metabolic response to critically illness has significant more severe peripheral protein degradation, ureagenesis, gluconeogenesis, poor hormone counter regulatory capacity, and faster body store´s depletion. In “simple” starvation, the principal fuel is fat as, in critical illness, amino acids, glucose and triglycerides are used as fuel.

Many critically ill patients are also anorectic and as consequence do no use the GI tract. Gut disuse can lead to deterioration of the functional and structural integrity of the gut. A reduction in villous height, cellular proliferation, and mucosal mass and brush border enzymes occurs. Other consequences of gut disuse include reduced production of bile salts and IgA, villus atrophy and decreased peristaltism, which can all contribute to bacterial luminal overgrowth. GI adaptive immune responses are also affected. Without enteral feeding, a shift from aTh2 to Th1 response occurs associated to a decreased production of IL-4, IL5, IL-6, Il-10 and IL-14. In essence the absence of enteral nutrition increases the pro-inflammatory response seen in critical ill patients. Gut disuse also leads to increase intestinal permeability and

decrease infiltration of lymphocytes in the Gut-lymphocyte associated tissue. This can increase the translocation of bacteria and /or if its products from the gut to the rest of the body, thus amplifying the pro-inflammatory response. The latter is also a consequence of the increased production of gut derived factors as a reaction to the bacteria and its products presence which reach the systemic circulation predominantly by the lymphatic system. The question of which of the factors, the bacteria and /its products or the gut derived factors that are produced, are the main responsible for the pro-inflammatory state is not clear at the moment.

4. WHICH PATIENT NEEDS NUTRITIONAL SUPPORT?

We now know that no single clinical or laboratory information is pathognomonic to diagnose acute protein malnutrition although a complete history and the evidence a poor body condition are useful guides in particular circumstances. Classically it is assumed that every critically ill patient has been going without nutrition for 3 days (1 day in neonates) should have nutritional support instituted. The expected level of stress, expected time of anorexia, need for surgery or anesthesia and patient characteristics should also guide the decision of providing nutritional support. An example of this statement is the case of a young, healthy animal that goes into surgery for pyometra and is expected to stay in the ICU for just one night. Most probably this animal will not need any particular or aggressive type of nutritional support besides intravenous fluid and electrolyte therapy. The situation is different if the animal has sepsis, trauma, burns or other type of severe critical illness. In this case the nutritional support should be started as soon as possible and once the electrolyte, hemodynamic, metabolic and acid-base disorders are controlled, which for most patients means the first 24 hours of hospitalization.

In fact a recent study in people suggests that most important of the type of nutritional support, the timing of initiating it is of uttermost importance. In a Era where the mantra is to give enteral support, the authors were able to demonstrate that even parenteral nutrition, if imitated early, had a better outcome in mortality than late enteral nutrition (Simpson & Doig, 2005).

5. ROUTE OF NUTRITION: ENTERAL VERSUS PARENTERAL

Based in what has been said before about pathophysiology associated to gut disuse, in theory enteral nutrition should be more beneficial to the outcome of critically ill patients. This seems to be the case, with a recent meta-analysis in people (Doig *et al*, 2009) showing a reduction in mortality associated to the use of enteral nutrition. The proposed benefits of enteral nutrition are many and include the maintenance of the mucosal mass and stimulation of the mucosal cell proliferation and intestinal blood flow, production of brush border enzymes, maintenance of villus height, maintenance of epithelial cells tight junctions and of intestinal epithelial protective role against bacterial translocation. It also stimulates the secretion of colecistiquinine, gastrin, bombesin and bile salts, which have trophic effects in the epithelium and for some of them (bile salts, lactoferrin and mucosal IgA) antibacterial activity. The existence of enteral nutrients also aids for the persistence of the normal intestinal flora, which function as a barrier to pathogenic bacteria.

Enteral nutrition has beneficial immune effects as well. It stimulates the activation of CD4Th2 cells and the production of IL-4, IL5 and IL10 (anti-inflammatory phenotype) and of regulatory T cells (Th3 and Tr1), which increases immunotolerance (McClave& Heyland, 2005). These effects can help in decreasing the pro-inflammatory state that characterizes the systemic inflammatory response syndrome (SIRS).

The complications associated to EN are mainly mechanical (e.g. tube kinking or obstruction), food intolerance (manifested by diarreia and gas accumulation) and vomiting. In cases of overfeeding, metabolic abnormalities can also become apparent, including hyperglycemia, electrolytes disturbances hepatic dysfunction and respiratory distress.

Parenteral nutrition (PN) has been associated to more complications, especially of mechanical, infectious and metabolic nature, although most of them are not life-threatening (Queau *et al* 2011). PN is also much more cumbersome and expensive than EN. In people recent guidelines state that PN should not be used if the oral route is available (Kreymann *et al* 2009). Nevertheless PN can be used in some circumstances, including when the GI tract cannot be used, (e.g. severe gastrointestinal íleus or when the vomiting and regurgitation is not controlled), when there is an increased risk of aspiration (e.g. patient with coma) and in pancreatitis. In fact the in the retrospective study of Queau *et al*, 2011, the major reason to institute PN was pancreatitis, in both dogs and cats. Although PN still remains the gold standard treatment for nutritional support in animal with pancreatitis, in people the current tendency is to gradually move to EN, as EN has been shown to be associated to lower mortality, rate of complications, decreased organ failure and number of surgical interventions (Yi *et* al, 2012). In animals the same approach should be tried. The latter recommendation is particularly important in cats, due to the risk of hepatic lipidosis. A recent study addressed the question of nutritional support in dogs with pancreatitis and the authors found that EN was well tolerated by the patients and that it was associated to fewer complications (Mansfield *et al* 2011).

PN can be used in two ways: total parenteral nutrition (TPN) and Partial Parenteral nutrition (PPN), if we opt to give by parenteral route all or just a portion of the energy and amino acid requirements respectively. The former needs to be given by a central route because of the high hypertonicity of the final solutions. TPN is associated to higher incidence of metabolic changes, namely hyperglycemia and hyperlipidemia. TPN solutions can be homemade, although the commercial "All in one" bags, available from some manufacturers greatly facilitates the mixing of these solutions, with at the same time minimizing bacterial contamination. PPN is cheaper and can be safely administered through a

peripheral vein. PPN has been used safely in small animal patients. In a retrospective study performed by Chan *et al*, 2002, PPN was found to be safe. In fact observed complications did not have any impact in the duration of hospitalization or outcome. However the use of PPN was not associated to a better outcome when used exclusively and when compared with early feeding. PN can also be associated with EN in selected cases although there are no studies that demonstrate a benefit for this approach in veterinary medicine. By contrary a recent study found that this approach has not been beneficial in an experimental model of pancreatitis (Alhan *et al*, 2004).

6. HOW MUCH, HOW AND WHAT TO GIVE?

Once the decision about using EN or PN has been made, an estimation of the energy needs of the patient should be undertaken. In the past it was commonly assumed that critically ill patients would have increased energy requirements. As a consequence, the calculated Resting Energy Requirement (RER) was normally multiplied by an illness factor, characteristic of each disease.

This practice is being abandoned because the existing formulas designated to estimate energy requirements are not accurate, potentially leading to over and under feeding. Because instruments that could accurately estimate RER, like indirect calorimetry are not readily available to the veterinary emergency clinician, and because over feeding can increase the risk of complications, especially in the acute phase of the disease, it is now recommend *to not use any type of illness factors* and to begin nutritional support with the RER. A recent study of critically ill patients showed that adopting a conservative approach in calculating energy requirements led to a better rate of hospital discharge (Brunetto *et al* 2010). Energy requirements are not static however and the clinician should be ready top change the energy support if the clinical condition of the patient dictates those changes.

The proposed formula that can be used to obtain RER is the following:

Resting Energy Requirements (RER)=

70 x BW $^{0.75}$ where BW is body weight in Kg

Obese patients should have their RER based on their lean weight. Although some disease states such as sepsis, head trauma and burns are expected to have energy requirements higher than RER, it is still advised to begin with lower levels in these cases. To avoid complications associated to overfeeding (mainly from the gastrointestinal tract but also metabolic), the RER should be achieved in the course of 1 to 3 days. Typically on day 1 one gives 30% of the RER, on day 2, 60% and one day 3 the total calculated RER.

Once the RER is calculated, next is the calculation of protein needs and how to supply the estimate the RER in terms of protein and non-protein obtained calories. Classically the amount of protein to be fed should be 4 to 6 gr of protein for each 100Kcal of energy for dogs and 6 gr for 100 Kcal for cats. Some veterinarians prefer to calculate the amount of calories needed from a non-protein origin (lipids and carbohydrates) and then add the proteins. However because the metabolic response in the critically ill is designed to induce protein catabolism and to use amino acid precursors as a source of calories, this approach frequently leads to an excessive caloric supply and hyperglicemia and hyperlipidemia. A more reasonable approach is to subtract the amount of calories provided by the proteins to the total RER.

Using this approach, the amount of protein derived calories will be roughly 15-25% for dogs and 25 to 35% for cats, as protein provides 4 kcal /gr. Depending of the disease condition one can opt to choose the lower or the higher end of this range to supply protein requirements. For example in azotemic patients or in hepatic failure the lower value should be chosen. The remaining RER will be provided by non-protein calories, namely in lipids and carbohydrates.

In EN, once the energy and protein requirements are chosen, the clinician can then choose from the several available diets which will be used. Factors that can help in this decision include the caloric and protein content of the diet but also the type of EN support. For example if we use jejunostomy tubes we will need to give nutrition in a liquid form. In PN the next step is to choose which amount of lipids and carbohydrates we will need to add to the final PN solution.

Lipids are a useful form of calorie provision and traditionally they were used to provide 50 to 70% of RER with the remaining calories being supplemented in the form of carbohydrates (mainly dextrose). In people there is a huge debate now about the amount of and type of lipid supplementation in critically ill patients because lipid infusions can have immune modulating properties (Hamawy *et al* 1985). In fact the decision to include lipids in PN formulations has grade C (expert opinion) level of evidence ((Kreymann *et al*, 2009).. Nevertheless most investigators advise to use lipids to provide up until 50% and 20- to 30% of non –protein calories in adults and in children respectively (McClave& Heyland, 2005).. It is also now evident that soybean oil should be avoided as a sole lipid source, as this type of lipid has been associated to a state of proinflammation. Alternatives include the use of a mixture of soybean oil, middle chain triglycerides (MCT) and fish oil (Kreymann *et al*, 2009). In small animal nutrition the amount of lipids should be restricted to no more than 2gr/kg/day (Freeman & Chan, 2006). In face of these findings the author adopts a more conservative approach and does not increase the level of lipid as non-protein source for more the 50% of energy requirements.

Once the amount of lipids and carbohydrates have been defined, the last step before initiating PN is to add vitamins, specific aminoacids (e.g. glutamine) and trace elements to the final PN solution.

7. WHAT´S NEW IN SMALL ANIMAL NUTRITION?

7.1.Tight glycemic control

One of the main concerns about excess caloric intake is the induction of hyperglycemia. This is common in the acute phase of the disease because the metabolic response increases

endogenous glucose production. If we provide excessive amounts of exogenous glucose, directly or through an indirect way (such excess of lipids) than the obtained hyperglycemia will be more severe. Since Van der Berghe and collaborators, in 2001, shown that tight glucose control was associated to a better outcome in critically ill patients that the approach to hyperglycemia in critically ill patients have changed. Before that study, the existence of hyperglycemia was tolerated to certain levels, as this was believed to be part of a normal response to critical illness. We now know that hyperglycemia leads to impaired neutrophil phagocytosis and chemotaxis, glycosylation of immunoglobulins, impaired wound healing, exacerbation of inflammation and alterations of the complement cascade (McClave & Heyland, 2005). The Van der Berghe group demonstrated that placing patients with glucose levels at 4.4 to 6.1 mmol/L, instead of the classical levels of 10 to 11 mml/L, led to a lower incidence of sepsis, reduction in ventilator days, ICU stay and decreased hospital mortality. If this was associated to just the normoglycemia or due to the anti-inflammatory actions of insulin remains speculative. Since then the tight glucose control hypothesis has been shown to lead to better outcomes in other settings as well although the ideal glucose range in ICU patients remains to be defined (Mesotten *et al* 2009). In Human Medicine is recommended that if adequate devices for blood-glucose measurement and insulin administration are available, together with an extensive experience of the nursing staff, the tight glucose approach should be implemented. There are no studies about tight glucose control in veterinary medicine. Nevertheless in light of these findings, efforts should be done to avoid hyperglycemia in small animal critically ill patients.

7.2. New ways of providing enteral nutrition

The ways of providing enteral nutritional support can be numerous: nasogastric and nasoesophageal, gastric, oesophagostomy and jejunostomy tubes, each one with its specific indications and contra-indications and whose discussion is outside the scope of this article. However recently a new development has been made concerning jejunostomy tubes. These have been advised to be used whenever we prefer to use enteral nutrition but in patients who cannot tolerate food placed above the pylorus. J tubes have normally been placed through a surgical approach. However this constitutes a disadvantage as some of the patients that may benefit from its placement are poor surgical candidates. Recently two new approaches for the placement of nasojejunostomy tubes have been published, one endoscopically assisted (Campbell & Daley, 2011) and other fluoroscopically assisted (Beal & Brown, 2011). These new approaches are revolutionary because they provide the means to support enteral nutrition in patients that otherwise would have to be placed with PN thus potentially leading to better outcomes associated to EN.

7.3. Pharmarconutrition

In recent years several nutrients have emerged as potentially therapeutic in critically ill patients. These include arginine, glutamine, omega 3 fatty acids, carnitin and anti-oxidants, minerals and vitamins. Most of the available trials in people have evaluated the benefits of this nutrients isolated. In Human Medicine the results of several trials have shown that glutamine supplementation is beneficial, reducing mortality, hospital stay and infectious complications especially if applied by parenteral route (McCleve & Heyland, 2005). Current recommendations suggest glutamine to be added to PN solutions. However evidence that supports enteral diets supplemented with glutamine is only available for patients with major burns and trauma (McCleve & Heyland, 2005). The dose of glutamine that have been suggested to dogs with parvoviral hemorrhagic gastroenteritis is 0,5 g/kg/day divided twice a day in drinking water (Hackett, 2011). The situation is different for arginine, being now established that its supplementation can worse prognosis in patients with sepsis (McCleve & Heyland, 2005). The rationale for using minerals such as zinc, selenium, manganese or copper (especially in burns) and vitamins such vitamin E and C is that these nutrients are essential cofactors for body´s enzymatic defense mechanisms against oxidant injury. In critically ill patients, these systems tend to become overwhelmed due to increase free radical production. In burned patients it is demonstrated the presence of a copper deficit as well. There is now evidence that supplementation with these micronutrients in trauma and burn patients, especially of selenium and zinc and by parenteral use improves recovery, (Berger, 2006). There are not published studies which describe the benefits of supplementing minerals and vitamins in veterinary clinical critically ill patients. However the evidence from Human data and experimental studies suggest that they should be considered, especially by the IV route.

8. CONCLUSION

The field of veterinary nutrition is evolving at a fast pace. Following similar trends in Human Medicine, the role of nutritional support in critically ill veterinary patients is moving from just being supportive to actually influence the clinical course of the disease. It is not difficult to envisage a nearby future where an animal arriving into the small animal critical care unit will have his own individual nutritional plan accordinglyto the new paradigms. In the beginning more emphasis will be placed in pharmarconutrition, by administration of key nutrients that can modulate the inflammatory response (such as essential omega 3 fatty acids, trace minerals, vitamins and glutamine) and to preserve gut integrity and function at all costs. Later on the course of the disease, as patient metabolism and energy needs change, the maintenance of caloric and protein needs will be the main goal although pharmarconutrition will continue. Finally more close to discharge, the role of nutritional support will be to give nutrients that promote recovery and the cessation of the inflammatory process. Existent nutritional deficiencies associated to the duration of hospitalization will also be corrected. This developments will certain be accompanied by new methods of identifying the nutritional status of the patient and new ways of delivering effective nutrition.

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