Jan Wernerman

Nutrition

ICU nutrition 1982

Twenty-five years ago intravenous nutrition was coming into general practice in the ICU. Many of the difficulties along the road seemed to have been solved at that time. Central venous lines were in widespread use, and nutritional products for enteral as well as parenteral use were commercially available. Devices to measure energy expenditure by indirect calorimetry were in use, and it was generally recognised that critical illness was associated with hyper-metabolism. Under the heading of "bigger is better," so-called "hyper-alimentation" was launched. This meant that patients were provided as much as 150 % of their caloric need. Hospital starvation seemed to be something from the Dark Ages, which would no longer happen anymore, at least not in the ICU. At this time, fat emulsions for intravenous use had been available in Europe for 20 years, but intravenous fat was relatively newly registered for use in North America. There was a general reluctance in North America to use fat emulsions, instead concentrated glucose solution was most often used together with amino acid solutions. At the same time, it was very popular in Europe to use a mixture of different sugars as the carbohydrate source of energy.

Naturally this over-enthusiasm mostly linked to parenteral nutrition had to sober up. It was soon demonstrated that central venous lines used for intravenous nutrition were often associated with line sepsis. It was also demonstrated that caloric over-feeding, "hyper-alimentation," was associated with a lot of problems. By the intravenous route patients were more or less force-fed, resulting in increased heat production and often an elevated body temperature [Carlsson and Burgerman 1985]. This was measured as fever and sometimes treated with antibiotics. Unfortunately, the results from indirect calorimetry were not used to administer suitable amounts of calories, but instead an extra allowance was added and patients were frequently over-fed. The levels of energy expenditure measured and reported in those days were higher compared to what is seen today [Wilmore 1977]. This was probably a reflection of the standard of patient care at that time. In particular, burn patients, trauma patients and also ARDS patients in general showed a higher energy expenditure at that time than they do today. Today, they are treated differently in many respects, better handling of burn wounds and fractures, better pain control, more adequate volume resuscitation and so on and so forth makes a big difference today compared to those days.

Approximately 25 years ago it also became obvious that micronutrients played an important role. Already at the start of hospital nutrition, today 50 years ago, enteral feeding with red rubber tubes in the stomach had proven its insufficiency. If enteral feeding was insufficient, the alternative was dextrose solutions in peripheral veins with steel needles. The time period after that provided sufficient calories and sufficient amino acids to the patients, sometimes even more than sufficient as pointed out above. Before micronutrients were given attention, case reports were published disclosing almost every shortage of vitamins or trace elements that is known. This happened when patients were kept alive for a long time by providing all the necessary macronutrients without the micronutrients. Approximately 25 years ago the necessary additives of micronutrients started to become commercially available.

The science of ICU nutrition 25 years ago was also different from today. It was common to evaluate nutrition by calculating the nitrogen balance, a technique difficult to perform and difficult to interpret in the ICU [Munro and Allison 1963]. In terms of metabolic stress, patients undergoing elective surgery or suffering from acute trauma or sepsis were not properly separated. At that time it was common to look upon the metabolic alterations associated with elective surgery as just a mild variety of the same alterations that appeared in trauma and sepsis and which later on were associated with multiple organ failure. It was approximately at this time point that patients with ARDS survived long enough to develop multiple organ failure in the sense we know it today. At that time nutritional studies in the ICU focusing on outcome were not very common. The major academic disagreements at that time were enteral versus parenteral nutrition, glucose system versus lipid system and the cost effectiveness of parenteral nutrition or nutrition as such. As we all know, these major controversies are not that much different from then as they are now.

Major achievements during 25 years

The major achievements in nutrition between 1982–2007 are: 1) better technical devices for both enteral and parenteral nutrition, 2) all-in-one formulations for parenteral nutrition, 3) Glutamine supplementation to parenteral nutrition, and 4) tight glucose control. In addition, there have been a number of other achievements with a less clear impact that will be discussed below.

For parenteral nutrition, one weak point over the years has been catheter sepsis. The rate of catheter-related infections is sometimes very high, and in particular central venous lines used for intravenous nutrition are more susceptible than those not used for that type of infusion. This is, however, an issue with several dimensions. Today catheter-related infections are suggested to be a quality indicator in intensive care medicine. Proper routines for the insertions of central venous lines, hygienic routines for handling the central venous lines as well as the strict routines for the use of the line – all of them matter [Hammarskjold et al. 2006]. It is demonstrated that skill of insertion and the number of attempts needed to obtain an intravascular placement matters for the frequency of complications. Today's standard is that central venous lines are introduced under the sterile conditions of an OR, done by an appropriately trained person using an ultrasound device to identify the vessel. In that situation, intravascular placement should be achieved on the first attempt and without contamination. The hygiene standard for maintaining central venous lines should include regular changes of connecting devices under sterile conditions. All singular injections should be made through bacterial filters and connectors should not be placed in the bed of the patient. Separate lumen should be used for nutrition and for blood products only. In addition central venous lines may not be changed over guide wires unless there are special indications. In many countries today one of the major issues in the ICU round each day is whether or not the central venous line should be kept. The use of peripheral lines in the ICU is more common today that it used to be. Additionally, the procedures around peripheral lines has improved with better routines and restrictions around how many attempts may be done to introduce peripheral lines and thereby potentially destroy peripheral vessels [Berg et al. 2002]. Also for enteral feeding technical equipment has improved. The synthetic materials are softer, not causing pressure wounds in the nasal cavity or throat. The disadvantage of thin feeding catheters is that the residual volume in the stomach cannot be appropriately detected. Many centres today have good routines for inserting catheters for post-pyloric feeding. Jejunal catheters are placed with the patient in the lateral position using guide wires or by using endoscopy, or sometimes during surgical procedures as a feeding jejunostomy.

In the early days of parenteral nutrition the components were delivered individually and given separately simultaneously or mixed together in the hospital pharmacy. Today there are several commercially available all-in-one formulations. The convenience of all-in-one formulation is obvious and there are also economic advantages compared to the all-in-one formulations prepared by the hospital pharmacy, and it saves time for the nurses in the ICU. The disadvantage of all-in-one formulation is that nutritional support is less individualised. Still, the convenience associated with all-in-one probably gives more patients in the ICU an adequate nutrition.

Glutamine is not a constituent in conventional amino acid solutions for intravenous use. This is related to glutamine being unstable in aqueous solution, a problem now solved by the use of synthetic dipeptides. In intravenous nutrition studies of patients confined to intravenous nutrition, a benefit in terms of survival for glutamine supplemented nutrition is demonstrated [Griffiths et al. 1997, Goeters et al. 2002, Novak et al. 2002]. For patients for whom it is possible to feed by enteral route this advantage is less clear [Novak et al. 2002]. Some studies show effects upon infectious morbidity, other studies show no difference between groups. This is probably related to the level of glutamine depletion. It is demonstrated that low plasma glutamine, as a reflection of glutamine depletion, is associated with a higher hospital mortality, independently from the APACHE II score [Oudemans-van Straaten et al. 2001]. Identification of this subgroup of ICU patients for glutamine supplementation is probably crucial, and it is preferably done by lab tests. If lab tests are not available it is advisable to give glutamine supplementations to all patients receiving at least intravenous feeding.

The singular most influential intensive care medicine study during the last 25 years is the demonstration by Prof. Greet van den Berghe that tight glucose control gives better survival [van den Berghe et al. 2001]. This was done in a single unit study but appropriately powered to demonstrate the survival benefit. The initial publication was in surgical patients, preferably patients undergoing open heart surgery. The benefits in terms of survival were also associated with a benefit in morbidity in terms of less infections, less need for renal replacement therapy, less days on a ventilator and less critical illness myopathy/neuropathy. Five years later, still in a single centre study, Prof. van den Berghe demonstrated that the same was true for long-stay ICU patients with medical diagnoses [van den Berghe et al. 2006]. However, in that study the patients with a short ICU stay did not show any benefit. Although insufficient in number for a conclusive statement there was a tendency that these patients may even be at a disadvantage. Among the ICU patients with medical diagnoses, the incidence of hypoglycaemia was considerably higher as compared to the surgical patients. Furthermore, two other multi-centre studies in Europe were prematurely stopped for safety concerns because of the high incidence of hypoglycaemia (www.clinicaltrials.gov VISEP-trial and Glucontrol study). None of these other two studies demonstrated any benefit of tight glucose control as reported in preliminary data at recent congresses. Although there was a high incidence of hypoglycaemia in these studies also, this was not directly related to mortality. The patients included in Prof. van den Berghe's study were properly fed during insulin treatment, something less well-documented in the other two studies. Another possible difference is whether or not the patients in the treatment group actually were subjected to normoglycemia. Among the reasons to prematurely stop one of the studies, beside the frequency of hypoglycaemia, was also the protocol violation of not separating the intervention group from the control group properly. Thus, today there is still confusion on this matter. Nevertheless Prof. van den Bergh's studies clearly show that metabolic care makes a difference. Normoglycemia has been shown earlier to be beneficial in acute myocardial infarction on insulin dependent diabetics and in women giving birth. It is clearly difficult to obtain a strict normoglycemia in ICU patients, which is the challenge for the future.

Experiences on the way during 25 years

Already from the very start synthetic fat emulsions, aiming to imitate the endogenous chylomicrons, were subject to problems. In Europe the development of Intralipid® into a commercial product used in clinical settings was not accompanied by a similar development in North America. The fat emulsions tested for clinical introduction in North America failed to show sufficient safety. Patients had severe allergic reactions and these products never made it to the market. The negative attitude towards fat emulsions as unsafe has therefore stayed on. In addition Intralipid®, with a high content of omega-6 fatty acids is claimed to have immune-compromising effects. There is a large literature of experimental evidence demonstrating negative effects of long chained omega-6 fatty acids on various aspects of immune function. There are also published cases in clinical practice where this might have been the case. Unfortunately, there are no prospective randomised clinical trials which demonstrate this negative effect in clinical practice.

In order to improve immunological function several enteral formulas have been launched under the heading of immuno-nutrition or immune-enhancing nutrition. These formulas are enriched in their content of arginine, omega-3 fatty acids, nucleotides, antioxidants and sometimes glutamine. A number of clinical studies have been performed in patients undergoing elective surgery and in ICU patients. For the surgical patients, out of the scope of this chapter, there seems to be a general beneficial effect [Heyland and Samis 2003]. However in the ICU patients the results of these studies have been very disappointing. Several studies even point out the possibility that such formulas may cause harm in subgroups of ICU patients [Bower et al. 1995, Bertolini et al. 2003, Dent et al. 2003]. The studies have several inherent problems including the difficulty of adequate feeding by the enteral route. Overall, the results can be summarised as that these formulas have no place in the intensive care unit.

For omega-3 fatty acids, there is a lot of experimental evidence demonstrating an antiinflammatory effect. This may be attributed to omega-3 fatty acids having a beneficial effect upon prostaglandin and thromboxane systems. Furthermore, omega-3 fatty acids incorporated into biological membranes in the body may have antiinflammatory properties. Clinical studies give evidence for extra supplementation of omega-3 fatty acids by the enteral route. In ARDS patients, the number of ventilator days as well as oxygenation index is shown to decrease, and in a recent study of sepsis patients the mortality is shown to decrease [Gadek et al. 1999, Pontes-Arruda et al. 2006, Singer et al. 2006]. The latter study shows a remarkable effect on outcome with the numbers needed to treat to be 6, which is an extraordinary clinical effect that needs to be confirmed in future studies.

The controversy of the route of administration for ICU nutrition unfortunately persists. Part of the controversy is which evidence is relied upon. There are two major meta-analyses that come to opposite conclusions [Heyland et al. 2003, Simpson and Doig 2005]. The two meta-analyses basically reviewed the same studies (fig. 1). The difference is how they interpret the evidence from the reviewed studies, and what significance they give to the different pieces of evidence. In Dr Heyland's meta-analysis the result is that there is no difference in mortality combined with a benefit for enteral nutrition in terms of morbidity. Drs Simson and Doig come to the conclusion that there is an advantage in terms of mortality for parenteral nutrition. This is of course frustrating, but this difference is clearly attributable to which patients are discussed. Several studies in the literature include patients who were possible to feed by the enteral route, and who should have been fed accordingly, but who were randomised to receive parenteral nutrition. Several studies also report an unacceptably high level of catheter-related infections. In one study, where the function of the gastrointestinal tract was used as criterion for inclusion to randomisation, the result is in a way remarkable. [Woodcock et al. 2001]. It both points out how difficult it is to assess the function of the gastrointestinal tract, and it also points out that ability to feed by the enteral route might be the best criterion for a functioning gastrointestinal tract. Nevertheless, when patients with an uncertain function of the gastrointestinal tract were randomised the number of complications, the morbidity, was lower for the group receiving enteral nutrition. However, at the same time, mortality showed a strong tendency to become higher. In that study, as well as in many more studies, it is obvious that the longer the patient stays in the ICU, the larger the number of complications, regardless of the route of feeding. This particular study is small in terms of the number of patients, which were randomised, and it is therefore inconclusive. However, in all other studies where patients have been randomised have not had this particular criterion addressed. This gives a back-

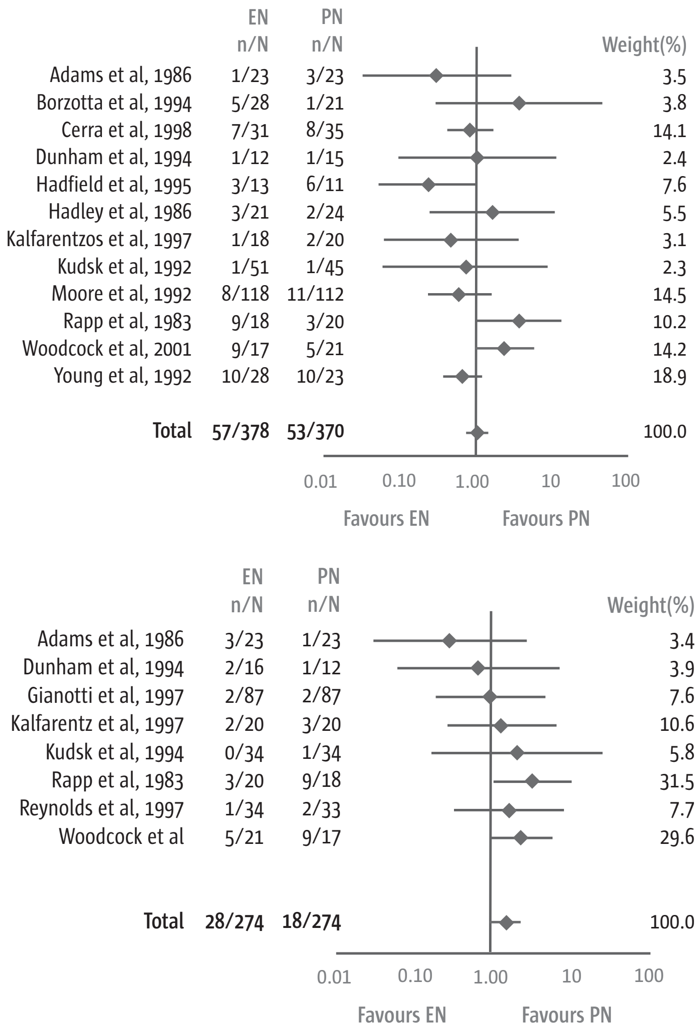

Fig. 1 Results of two recent meta-analyses over studies comparing the effect upon mortality of enteral or parenteral nutrition to ICU patients [Heyland et al. 2003, Simpson and Doig 2005]. As can be seen, the overlap in reviewed studies is considerable. The difference in selection of studies causes the difference in results [Woodcock et al. 2001, Adams et al. 1986, Borzotta et al. 1994, Cerra et al. 1988, Dunham et al. 1994, Gianotti et al. 1997, Hadfield et al. 1995, Kalfarentzos et al. 1997, Kudsk et al. 1992, Moore et al. 1992, Rapp et al. 1983, Reynolds et al. 1997, Young et al. 1987]. Heyland et al (upper panel) find no difference, while Simpson and Doig (lower panel) find a lower mortality for patients on parenteral nutrition.

ground, and a further dimension to the difficulties in evaluating the existing evidence of parenteral versus enteral nutrition in the ICU.

The best strategy for the future is definitely to watch for good routines in the unit, in this particular case to minimise the complications associated with parenteral as well as enteral administration of nutrients. Secondly, assuring that patients are fed properly from the start of their ICU stay.

ICU nutrition 2007

Overall, the position of nutrition in the ICU today is an established treatment that many colleagues in intensive care medicine do not give very much emphasis. Still, it is highly likely that the outcome in the group of long-term patients in the ICU is highly dependent upon adequate nutrition. Results are emerging demonstrating that an accumulated energy deficit is to the clear disadvantage of the patient [Villet et al. 2005, Dvir et al. 2005, Reid and Campbell 2004]. Of course such results must be interpreted carefully, but also when multiple regression analysis compensates the differences in underlying pathology and risk stratification, the results pointing out a connection between underfeeding and complications and increased mortality remain. Studies of the cumulative energy deficit show that a large portion of it is created during the first week of ICU stay. Of course a short-term patient that will leave the ICU within a few days and commence eating ordinary food is not a big problem. On the other hand, if a malnutriated patient comes to the unit and stays for several weeks, no feeding during the initial period may be detrimental. In the literature there is very little evidence that a circulatorily unstable patient will not utilise nutrition. In particular when such a patient is measured by indirect calorimetry, it is clearly demonstrated that oxygen is consumed and carbon dioxide produced, *ergo* macronutrients are being combusted. The route of nutrient administration may be discussed. A circulatorily compromised patient may not be a suitable candidate for enteral nutrition. Overall over-enthusiastic enteral supply may be to the harm of the patient. It has been clearly demonstrated that doctors frequently overestimate gut function [Woodcock et al. 2001]. So, parenteral nutrition in the initial phase of ICU stay may be necessary in many patients. Such a combination of enteral and parenteral nutrition, with today's knowledge, is probably the best way to avoid an accumulated energy deficit. To obtain this target it is necessary to keep a nutritional record, where daily balances are recorded and action is taken on

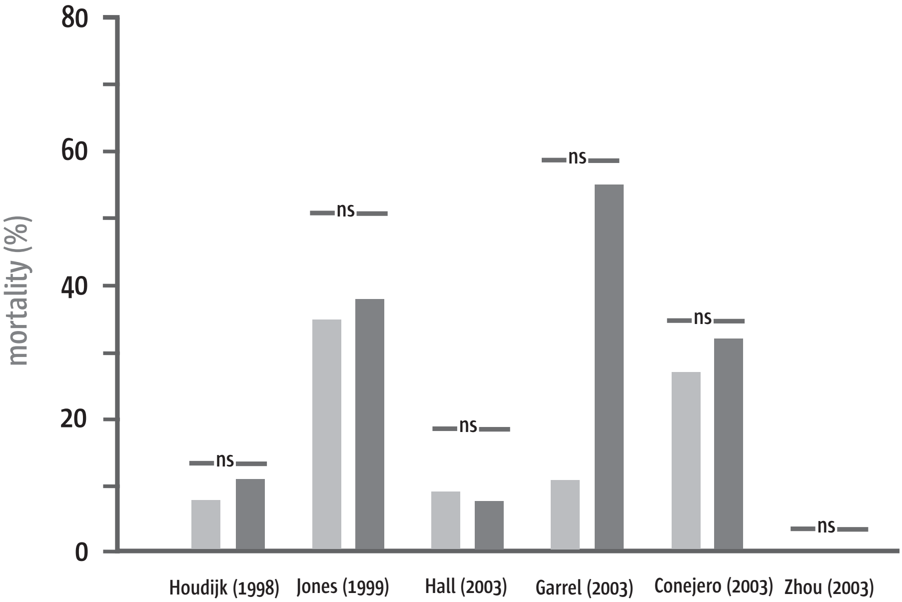

Fig. 2 Mortality rates in studies over ICU patients randomised to be given enteral nutrition supplemented with glutamine or not [Conejero et al. 2002, Garrel et al. 2003, Hall et al. 2003, Houdijk and van Leeuwen 2000, Jones et al. 1999, Zhou et al. 2003]. The diagram depicts the wide range of mortality rates reflecting the heterogeneity of patient populations included in the different studies. Taken together the studies over enteral nutrition supplemented with glutamine are therefore not conclusive.

the rounds to prevent under-nutrition. Ideally nurses should make these calculations each shift and the nutrition given should be adjusted accordingly.

For special nutrients the addition of intravenous glutamine has sufficient evidence. So far this evidence is confined to patients on parenteral nutrition [Novak et al. 2002]. There are different interpretations of whether this effect is a treatment of a shortage or whether there is a specific effect linked to an extra supply of glutamine, a pharmaco-nutritional effect. In contrast to the results from studies of intravenously supplied glutamine, studies with enterally supplied glutamine are so far not conclusive. Some studies show a beneficial effect upon morbidity while others show no effect at all. In general these studies include patients with a good prognosis in terms of mortality (fig. 2), and it is not clear to what extent they actually represents subjects which are depleted in glutamine or have an elevated need for glutamine. So far, however, there are no studies demonstrating adverse effects related to glutamine supplementation. So, the safety issue is not a problem. The issue is rather whether or not a relatively expensive supplementation can be encouraged.

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R. Michael Grounds and Richard M. Venn

Sedation and analgesia in ICU

Introduction

Many patients in the intensive care unit (ICU) will require some form of sedation or analgesia, particularly those who require mechanical ventilation or those who have just undergone surgery. Sedation comes from the Latin word *sedare* meaning to sooth to calm or to allay fear. Thus the principal aims of sedation are, where appropriate, to improve patient comfort, reduce patient stress, facilitate interventions, allow effective mechanical ventilation, encourage sleep and possibly help to prevent post-ICU psychological problems

The many influences in the ICU affecting the well-being of the patient and the various non-pharmacological and pharmacological measures utilised to minimise their impact are demonstrated in figure 1.

Indications and need for sedation/analgesia

Patient comfort and psychology/anxiolysis

It is essential to provide some sort of anxiolysis for the patient who is now no longer in control of their own breathing and is fearful of the disease and the frequently busy and noisy ICU environment. Survivors of intensive care have reported distressing memories and anxiety, fear, pain and the presence of various catheters and procedures such as physiotherapy and airway suction [Jones et al. 1979, Stein-Parbury and Mckinley 2000].

Analgesia

Patients in intensive care frequently experience pain or discomfort. Failure by carers to recognise that the patient may be experiencing pain, may result in the patient receiving unnecessary sedatives, since pain may show as agitation or anxiety. Usually the source of pain is self evident: post-operative, procedural (e.g. physiotherapy, dressing change, bronchoscopy) or premorbid disease (e.g. rheumatoid arthritis). However prolonged immobility, urinary catheters, surgical drains, non-invasive ventilation, and airway suctioning, may also cause discomfort [Novaes et al. 1999, Desbiens et al. 1996, Stein-Parbury and Mckinley 2000]. Pain is usually associated with sympathetic hyperactivity with increases in heart rate, arterial pressure, and myocardial oxygen consumption and may lead to myocardial ischaemia in those already at risk [Epstein and Breslow 1999, Mangano et al. 1992]. Pain may also be the cause of post operative atelectasis due to guarding and reduced or restricted chest wall and diaphragmatic movement [Desai 1999, Gust et al. 1999].

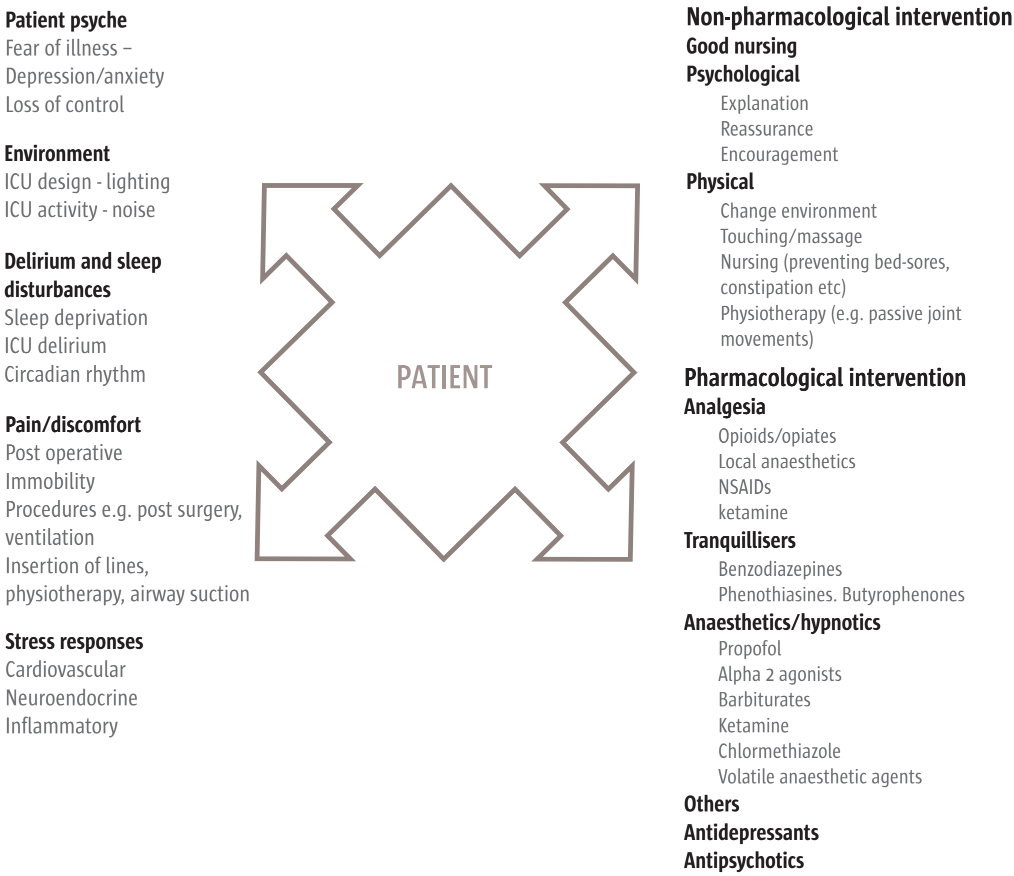

Fig. 1 Diagrammatic representation of factors affecting patients in ICU and the possible intervention to improve their comfort.

Sleep deprivation

All critically ill patients suffer from severe sleep deprivation, averaging approximately only two of every 24 hours, with only 6 % of sleep time in REM sleep (normal 25 %) [Cooper et al. 2000, Freedman et al. 2001]. The aetiology of sleep disruption is not entirely understood but is clearly related to the environment (excessive noise, lighting, procedures and mechanical ventilation), metabolic consequences of critical illness and, disturbingly, the sedative and analgesic agents utilised [Bently et al. 1977, Freedman et al. 1999, Gabor et al. 2003, Pandharipande and Ely 2006]. Although sedatives are extremely important for patient comfort, it is very important that the prescriber achieves the correct balance since unnecessary sedation may contribute to sleep deprivation.

Attenuation of the stress response

The benefits of effective analgesia on the cardiovascular stress responses have been discussed. The extubation period, when the patient is weaned from mechanical ventilation to spontaneous respiration and the endotracheal tube is removed, is a prime example of a situation where continuing sedation can attenuate the cardiovascular stress response that presents as tachycardia and hypertension, with potential myocardial ischaemia. Conti et al have shown that these haemodynamic disturbances and ischaemic events are attenuated