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ESPEN Guidelines on Enteral Nutrition: Intensive care ☆

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Summary Enteral nutrition (EN) via tube feeding is, today, the preferred way of feeding the critically ill patient and an important means of counteracting for the catabolic state induced by severe diseases. These guidelines are intended to give evidence-based recommendations for the use of EN in patients who have a complicated course during their ICU stay, focusing particularly on those who develop a severe inflammatory response, i.e. patients who have failure of at least one organ during their ICU stay.

These guidelines were developed by an interdisciplinary expert group in accordance with officially accepted standards and are based on all relevant publications since 1985. They were discussed and accepted in a consensus conference.

EN should be given to all ICU patients who are not expected to be taking a full oral diet within three days. It should have begun during the first 24 h using a standard

☆For further information on methodology see Schütz et al. [69] For further information on definition of terms see Lochs et al. [70]

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high-protein formula. During the acute and initial phases of critical illness an exogenous energy supply in excess of 20–25 kcal/kg BW/day should be avoided, whereas, during recovery, the aim should be to provide values of 25–30 total kcal/kg BW/day. Supplementary parenteral nutrition remains a reserve tool and should be given only to those patients who do not reach their target nutrient intake on EN alone.

There is no general indication for immune-modulating formulae in patients with severe illness or sepsis and an APACHE II Score >15. Glutamine should be supplemented in patients suffering from burns or trauma.

The full version of this article is available at www.espen.org.

Summary of statements: Intensive care

Subject	Recommendations	Grade[69]	Number
Indications	All patients who are not expected to be on a full oral diet within 3 days should receive enteral nutrition (EN).	C	1
Application	There are no data showing improvement in relevant outcome parameters using early EN in critically ill patients.		2
	Nevertheless, the expert committee recommends that haemodynamically stable critically ill patients who have a functioning gastrointestinal tract should be fed early (<24 h) using an appropriate amount of feed.	C	2
	No general amount can be recommended as EN therapy has to be adjusted to the progression/course of the disease and to gut tolerance.		3
	Exogenous energy supply:		
	• during the acute and initial phase of critical illness: in excess of 20–25 kcal/kg BW/day may be associated with a less favourable outcome.	C	3
	• during the anabolic recovery phase, the aim should be to provide 25–30 kcal/kg BW/day.	C	3
	Patients with a severe undernutrition should receive EN up 25–30 total kcal/kg BW/day. If these target values are not reached supplementary parenteral nutrition should be given.	C	9
	Consider i.v. administration of metoclopramide or erythromycin in patients with intolerance to enteral feeding (e.g. with high gastric residuals).	C	6
Route	Use EN in patients who can be fed via the enteral route.	C	7
	There is no significant difference in the efficacy of jejunal versus gastric feeding in critically ill patients.	C	4
	Avoid additional parenteral nutrition in patients who tolerate EN and can be fed approximately to the target values.	A	8

	Use supplemental parenteral nutrition in patients who cannot be fed sufficiently via the enteral route.	C	8
	Consider careful parenteral nutrition in patients intolerant to EN at a level equal to but not exceeding the nutritional needs of the patient.	C	8
Type of formula	Whole protein formulae are appropriate in most patients because no clinical advantage of peptide-based formulae could be shown.	C	5
	Immune-modulating formulae (formulae enriched with arginine, nucleotides and ω-3 fatty acids) are superior to standard enteral formulae:		
	• in elective upper GI surgical patients (see guidelines surgery).	A	10.1
	• in patients with a mild sepsis (APACHE II $<$ 15).	B	10.2
	• in patients with severe sepsis, however, immune-modulating formulae may be harmful and are therefore not recommended.	B	10.2
	• in patients with trauma (see guidelines surgery)	A	10.3
	• in patients with ARDS (formulae containing ω-3 fatty acids and antioxidants).	B	10.5
	No recommendation for immune-modulating formulae can be given for burned patients due to insufficient data.		10.4
	In burned patients trace elements (Cu, Se and Zn) should be supplemented in a higher than standard dose.	A	10.4
	ICU patients with very severe illness who do not tolerate more than 700 ml enteral formulae per day should not receive an immune-modulating formula enriched with arginine, nucleotides and ω-3 fatty acids.	B	10.6
	Glutamine should be added to standard enteral formula in		
	• burned patients	A	12.1
	• trauma patients	A	12.1
	There are not sufficient data to support glutamine supplementation in surgical or heterogenous critically ill patients.		12.2

Grade: Grade of recommendation; Number: refers to statement number within the text.

Preliminary remarks

Patients

A major methodological problem in this chapter are the terms ''ICU patients'' and ''critically ill'' as they do not refer to homogenous populations. Patients included in original trials as well as those considered in review articles vary widely in terms of diagnosis, severity of disease, metabolic derangements, therapeutic procedures, and gastrointestinal function.

Overlap with other chapters concerning patients in need of intensive care (surgery, trauma and transplant patients) is therefore inevitable.

In order to minimise overlap, only trials that met the following criteria were evaluated:

- The severity of disease could be deduced from the available data.
- The patients included in the study could ***not be explicitly assigned to categories discussed in other chapters*** (e.g. patients undergoing elective surgery).
- The patients were ***not routinely managed*** in ICUs for a short term.

The recommendations are thus focused on patients who develop an intense inflammatory response with failure of at least one organ or patients with an acute illness necessitating support of their organ function during their ICU stay.

The results were then classified into the following categories: surgical, medical, trauma, transplant, burns and sepsis.

Terminology

As oral intake is almost always impossible in these patients, in this chapter the term ''EN'' is confined to tube feeding exclusively without regard to any kind of oral nutritional supplement.

Outcome measures

ICU mortality, 28-day mortality and hospital mortality as well as length of stay in ICU or hospital were listed as primary outcome measures. Data on long-term survival would have been useful but were, unfortunately, not given in any of the studies. As post-ICU mortality is high, 6-month mortality was also considered a relevant outcome measure.

The rate of septic complications was listed as a secondary outcome measure. Particular emphasis was placed on identifying nutrition-related complications, e.g. infections, when such information was available.

Indications for and implementation of enteral nutrition (EN)

1. When is EN indicated in ICU patients?

All patients who are not expected to be on a full oral diet within 3 days should receive EN (C).

Comment: Studies investigating the maximum time ICU patients can survive without nutritional support would be considered unethical and are therefore not available.

Owing to increased substrate metabolism, undernutrition is more likely to develop in critical illness than in uncomplicated starvation or in less acute illness. A Scandinavian study[1] showed that patients on glucose treatment only (250–300 g) over a period of 14 days, had a 10 times higher mortality rate than patients on continuous total parenteral nutrition.

These data imply that, with an inadequate oral intake, undernutrition is likely to develop within 8–12 days following surgery. However, most of the trials studying early EN in various patient groups (see below) have compared a regimen of early EN with standard care and oral intake or with late EN after 4–6 days. As most of these studies have shown a positive effect of early EN, we have come to the conclusion that all patients who are not expected be on an full oral diet within three days should receive nutritional support.

2. Is early EN ($<$24–48 h after admission to ICU) superior to delayed EN in the critically ill?

There are no data showing improvement in relevant outcome parameters using early EN in critically ill patients. The expert committee, however favours the view that critically ill patients, who are haemodynamically stable and have a functioning gastrointestinal tract, should be fed early ($<$24 h), if possible, using an appropriate amount of feed (C).

Comment: Only one study evaluating early EN was performed specifically in critically ill patients.[2] Most studies were performed after trauma or abdominal surgery and these were summarised in 2 meta-analyses[3,4] and 2 systematic reviews.[5,6]

Meta-analyses and reviews

A meta-analysis of 15 randomised controlled trials[4] evaluated the effects of early EN in adult patients after surgery, trauma, head injury, burns or suffering from acute medical conditions. Early EN was associated with a significant reduction in infectious complications and length of stay. Owing to the heterogeneity between the studies however, the results of this meta-analysis have to be interpreted with caution.

Zaloga,[6] in a systematic review of 19 studies of early EN, found a positive effect of early EN on survival rate in one study. In 15 trials a positive impact on length of treatment, the rate of septic and other complications, and on other secondary parameters was found. They concluded that there was level 1 evidence to support the use of early EN.

The results of the Cochrane Library review by Heyland[5] however, differed in its conclusions. Heyland concluded that early EN should be recommended in the critically ill (B) whereas it should only be considered in other ICU patients (C). The problem with this review is that it included 6 trials of which only one was performed in truly critically ill patients. Zaloga[6] included this trial in his review but not the other 5.

Individual studies

After screening all the studies we have included only 6 studies in our evaluation, since the other trials on early EN did not meet our initial criteria. In contrast to the meta-analysis by Marik[4] or the review of Zaloga[6] we were only able to reach recommendation level C for early EN. This is due to some of the difficulties in interpreting some of the published data concerning critically ill patients. Furthermore, most of the trials had substantial methodological shortcomings which weakened their key findings.

The concept of early enteral versus inadequate oral or versus oral and parenteral nutrition has been best investigated in polytrauma patients. The first published trial on this topic by Moore and Jones[7] in 1986 randomised 75 patients with abdominal trauma. The control group received approximately 100 g carbohydrates for 5 days after surgery. If the patients were then not able to consume an oral diet, PN was initiated. In the study group early EN (12–24 h after trauma) was delivered via a needle catheter jejunostomy placed during emergency laparotomy. On the fourth day, the patients in the study group had a caloric intake 1.5 times higher than their energy expenditure, whereas the control group only received 1/3 of their energy expenditure. The control group developed infectious complications (intra-abdominal abscesses, pneumonia) more frequently than the study group over an unspecified period. However, the frequency of all infections as well as mortality were comparable between the groups. No data were available on length of stay. A critical issue is that total parenteral nutrition had to be provided in 30% of the control group due to insufficient oral intake. It is possible that the better outcome in the jejunostomy group had more to do with the complications associated with total parenteral nutrition in the control group than the advantages of EN in the study group.

Graham and coworkers[8] randomised 32 polytrauma patients with head injury to receive either early jejunal feeding or delayed gastric feeding. With the early jejunal feedings, daily caloric intake improved (2102 versus 1100 kcal/day) and the incidence of bacterial infections and length of stay in ICU was significantly reduced. There were no data on mortality.

Chiarelli et al.[9] randomised 20 patients with burns ranging between 25% and 75% total body surface area. EN was initiated within 4 h after injury in the study group and 57 h after injury in the control group who had received no nutrition up to that time.

Early EN did not reduce length of stay but was associated with a significantly reduced incidence of positive blood cultures as well as with a normalisation of endocrine status. Precise data on morbidity as well as on the total caloric intake during the immediate days after injury are lacking.

Eyer et al.[10] randomised 52 patients with blunt trauma to receive either early or late feeding. The early EN group received nutritional therapy within 24 h, whereas the control group only received nutritional therapy after 3 days. In total, 14 of the 52 patients had to be excluded from the study, because they either died within 48 h or because the target protein intake of 1.5 g/kg BW/day was not achieved. The authors concluded that early EN had no positive effect on ICU length of stay, ventilator days, organ system failure or mortality. The group receiving early EN even suffered a greater number of total infections (pneumonia, infections of the urinary tract).

These negative results were met with massive criticism by the advocates of early EN,[11,12] who suggested that nutritional therapy had been initiated too late in the study group (>24 h) and had not been administered via a jejunostomy, which would have allowed an earlier initiation of feeding. The study was also criticised because significantly more patients with severe thoracic trauma and significantly reduced lung function (lower Horowitz quotient) had been entered in the study group and this was suggested as a possible cause for the higher infection rate (esp. pneumonia) in this group.

Hasse et al.[13] investigated the impact of early EN on the outcome of 50 liver transplant patients. The patients were randomised to receive either EN within 12 h after transplantation or maintenance i.v. fluid until oral intake was initiated on day 2. Caloric intake was 3–4 times higher in the group receiving early EN during 3–4 days after transplantation and 80–110% of the actual energy expenditure was therefore met early.

Despite the higher caloric intake in the early EN group, no significant effect was found on length of time on ventilatory support, length of stay in ICU and hospital, number of readmissions, infections, or rejection during the first 21 post-transplant

days. However, viral infections occurred less frequently in the early EN group.

Singh et al.[14] compared the effect of early postoperative EN with spontaneous oral intake in patients with nontraumatic intestinal perforation and peritonitis. Early EN was delivered, via an intra-operatively placed jejunostomy, within 12 h of surgery. In total, 42 patients were included (21 in the study group, 22 in the control group). On day 1 the EN group received a higher intake (800 versus 400 kcal) and by day 4 this had increased further to >2000 kcal, while the control group still had a very low oral intake. With the early EN, a significant decrease of infectious complication rates was observed, although mortality did not differ between the groups.

None of the above trials met the current standards for a controlled trial (prospective, randomised and double blind) with power calculations and error estimation for the anticipated effects.

Because of the small number of patients studied, the data on mortality are difficult to interpret and a classification of observed effects according to the underlying diseases does not make sense.

In contrast to animal models, it remains unclear whether early EN—even in small amounts, might prevent alterations of intestinal permeability in man.

A newer study,[2] published after the two meta-analyses cited above, evaluated early versus late (day 1 versus day 5) EN in mechanically ventilated patients. Patients in the early feeding group had statistically greater incidences of ventilator-associated pneumonia (49.3% versus 30.7%; $P = 0.020$) as well as a longer intensive care unit (13.6 ± 14.2 days versus 9.8 ± 7.4 days; $P = 0.043$) and hospital lengths of stay (22.9 ± 19.7 days versus 16.7 ± 12.5 days; $P = 0.023$). It should be noted, that patients randomised to late EN also received 20% of their estimated daily nutritional requirements during the first 4 days. This study therefore, actually compared early aggressive versus less aggressive feeding rather than early versus late feeding. Unfortunately, the study was also not randomised, since group assignment was based on the day of enrolment (odd-versus even-numbered days).

In summary, the evidence in favour of early EN in critical illness is not as strong as suggested by Zaloga[6] We conclude however—based more on current data and our own experience than on conclusive scientific data—that early EN in an appropriate amount (see statement 3) and with the aim of avoiding gut failure can be recommended at level C.

3. How much EN should critically ill patients receive?

No general amount can be recommended as EN therapy has to be adjusted according to the progression/course of the disease and to gut tolerance. During the acute and initial phase of critical illness an exogenous energy supply in excess of 20–25 kcal/kg BW/day may be associated with a less favourable outcome (C).

During recovery (anabolic flow phase), the aim should be to provide 25–30 total kcal/kg BW/day (C).

Comment: There is general agreement that hyperalimentation (provision of more energy than actually expended) should be avoided in the critically ill, although this has not yet been confirmed by randomised controlled trials. Even generally reported target values of 25–30 total kcal/kg BW/day for men and 20–25 total kcal/kg BW/day for women may be too much during the first 72–96 h of critical illness.

A prospective observational cohort study[15] on patients with an ICU length of stay of at least 96 h showed that patients who received only 33–66% of the target energy intake had a significantly greater likelihood of being discharged from hospital alive (odds ratio 1.22, 95% confidence interval 1.15–1.29) than those who received 66–100% of the target intake (odds ratio 0.71, 95% confidence interval 0.66–0.75). The results are difficult to interpret as the severity of illness, the incidence of undernutrition, and the length of stay in relation to the level of caloric feeding were not reported.

Although this was not a randomised clinical trial, the results raise the same concern as those reported by Ibrahim et al.[2] and support the idea that, during the acute phase of critical illness, the provision of higher amounts of nutrients is associated with a less advantageous outcome. However, this is an area which is in particular need of prospective studies, since hypocaloric feeding in the initial phase of ICU-stay may or may not be a disadvantage for the patient. In particular, caution is warranted in patients with prior undernutrition.

A recent trial has put emphasis on the relation between growing energy deficit and the number of complications[16] There seems to be a cut off of cumulated energy deficit (10,000 kcal) beyond which the complications increase (infections, wound healing).

During stabilisation and recovery (anabolic flow phase) larger amounts of energy (25–30 total kcal/kg) are required to support the anabolic reconstitution.

4. Which route is preferable for EN?

There is no significant difference in the efficacy of jejunal versus gastric feeding in critically ill patients (C).

Comment: When jejunal feeding can be easily carried out (post abdominal trauma or elective abdominal surgery), it is likely to be the best option. Other critically ill patients may be fed via a jejunal tube only after they have shown intolerance to gastric feeding. In these patients jejunal feeding should be initiated under strict clinical observation.

Jejunal feeding was compared with gastric feeding in 11 randomised trials.[17–26] Five of these studies reported the amount of nutrition received by each method.[17,18,23–25] It was found to be equal in three studies, better with gastric in one, and better with jejunal feeding in another.

Although the rate of development of pneumonia was less with jejunal feeding in three studies,[21,23,26] there was no difference between the two methods of feeding with respect to mortality or length of stay.

We conclude that these results do not justify a general recommendation for jejunal feeding in critically ill patients (A). Otherwise, as most of the studies reporting positive effects of early postoperative enteral feeding were performed with jejunal feeding via a needle catheter jejunostomy, we recommend that, when jejunal feeding can be carried out easily, it should be given (C). In other patients it should be performed only after they prove intolerant to gastric feeding (C).

5. Is a peptide-based formula preferable to a whole protein formula?

No clinical advantage could be shown for such a formula in critically ill patients (Ia). Therefore, whole protein formulae are appropriate in most patients (C).

Comment: The observation that exocrine pancreatic function is reduced in sepsis[27] gave rise to concerns about the digestion and absorption of whole protein formulae in critical illness.

Peptide-based (low molecular) formulae have therefore been evaluated in four randomised trials[27–30] with contradictory results. While two of them[28,30] described a reduction in the incidence and/or frequency of diarrhoea using a peptide-based formula, another study[29] found a higher frequency of diarrhoea with such a formula and the fourth one[27] found no difference.

As no clear cut advantage of peptide-based formulae has been demonstrated in these studies and taking into account the higher price, we concluded that the use of peptide-based formulas should not be recommended (C).

6. When should motility agents be used in critically ill patients?

IV administration of metoclopramide or erythromycin should be considered in patients with intolerance to enteral feeding e.g. with high gastric residuals (C).

Comment: Eighteen randomised studies evaluating the use of motility agents in critically ill patients that were published before 2002 have been summarised in a meta-analysis by Booth et al.[31] Six of these studies evaluated the use of motility agents for the placement of jejunal feeding tubes, 11 examined the gastrointestinal function and one study tested the use of metoclopramide for the prevention of pneumonia. Eight of ten studies that evaluated the effect of motility agents on measures of gastrointestinal transit demonstrated positive effects. However, the study reported by Yavagal et al.[32] found that the incidence of pneumonia was not influenced by metoclopramide. On the contrary, there was even a non-significant trend towards a higher incidence of pneumonia (16.8% versus 13.7%) in patients that received the drug.

The results of this meta-analysis are further supported by three studies published subsequently.[33–35] One study[34] found no advantage from the use of erythromycin in terms of the time taken to achieve full EN in children after primary repair of uncomplicated gastrochisis. The second study[35] reported no positive effect of metoclopramide on gastric emptying in patients with severe head injury. The third[33] found a significant difference in the amount of feed tolerated at 48 h (58% versus 44%, $P = 0.001$) using erythromycin versus placebo. There was no effect on the amount of feed tolerated throughout the entire duration of the study.

We concluded that the results of these studies do not support the routine use of motility agents in critically ill patients (A). Metoclopramide (doses, regimen) or erythromycin (idem) can be used for the symptomatic treatment of patients who do not tolerate sufficient enteral feed (C). Cisapride is no longer approved and should not be used in these patients.

EN versus PN

7. Should EN be preferred to PN?

Patients who can be fed via the enteral route should receive EN (C).

Comment (Meta-analyses and reviews): One meta-analysis[36] and one systematic review[37] investigated this issue. The meta-analysis[36] of 27 trials including 1829 patients evaluated 20 trials comparing EN by tube with PN and 7 trials comparing oral nutrition with PN. Most of these trials, however, were not performed on critically ill "ICU" patients but on elective surgical patients and whether the results can be extrapolated to the critically ill remains uncertain.

The aggregated results showed no significant difference in mortality rate with tube feeding [RR 0.96; 95% CI 0.55–1.65] nor with oral feeding [RR 1.14; 95% CI 0.69–1.88] versus parenteral nutrition. Clinically, the most relevant finding was a significantly lower cumulative risk of infections with either enteral or oral nutrition than with parenteral nutrition (EN versus parenteral nutrition RR 0.66; 95% CI 0.56–0.79, oral nutrition versus parenteral nutrition RR 0.77; 95% CI 0.65–0.91). ICU or hospital length of stay was not evaluated.

In a systematic review, Lipman[37] considered decreased costs to be the only relevant difference between EN and parenteral nutrition. He concluded that there was no reduction in complications with tube feeding, no reduced rate of infections, no functional or morphological improvement of the intestinal tract, no reduced rate of bacterial translocation, no benefit on relevant outcome measures such as survival, length of stay or rate of infections; nor did he consider EN to be more "physiological". Only in patients with abdominal trauma, was EN found to decrease septic morbidity (see below).

Individual studies

We found only 7 studies which met our criteria for ICU patients.[11,38–43] All of these trials compared EN with PN.

No significant difference in mortality was found between those receiving EN or PN. There was also no significant difference between length of stay in ICU or hospital between the two regimens. Only 2 studies[11,42] showed a significant reduction in the rate of septic complications. The study by Kudsk et al.[11] comparing EN versus PN in 89 patients after blunt or penetrating trauma, showed that there were significantly fewer infections with EN in patients with an injury severity score >20 and abdominal trauma index >24 (15% versus 67%).

The study by Moore et al.[42] assessed 75 patients with abdominal trauma. Infections developed in 17% of the enterally and 37% of the parenterally fed patients ($P = 0.03$).

The clinical relevance of these results is lessened by the fact that there was no improvement in length of stay or mortality in the studies that reported a significant decrease in septic complications. In addition, these studies were undertaken when blood sugar control was not on the agenda, and it is well known that PN is more commonly associated with hyperglycemia than EN.

In summary we conclude that the available studies do not show a definite advantage of EN over PN except for cost reduction. However, we support the expert opinion that, although over aggressive EN may cause harm, patients who can be fed enterally should receive it, but that care must be taken to avoid overfeeding.

8. Under what conditions should PN be added to EN?

In patients who tolerate EN and can be fed approximately to the target values no additional PN should be given (A).

In patients who cannot be fed sufficient enterally the deficit should be supplemented parenterally (C). In patients intolerant to EN, careful parenteral nutrition may be proposed at a level equal to but not exceeding the nutritional needs of the patient (C). Overfeeding should be avoided.

Comment: Five studies comparing EN alone with EN plus PN were analysed in a meta-analysis published by Dhaliwal et al.[44] The analysis revealed that the addition of PN to EN had no significant effect on mortality. Also, there was no difference between the two groups in the rate of infectious complications, length of hospital stay, or days on the ventilator.

The majority of the trials were carried out before the era of glucose control which started after the Louvain trial in 2001.[68] The ancient parenteral trials are likely to have been associated with major hyperglycemia—their poor outcomes are therefore not to be considered as being due to PN alone.

In most of the studies, patients who were on EN alone already met the lower target values of caloric intake cited above. As the provision of more energy can be associated with a worse outcome, adding PN is unlikely to improve outcome under these circumstances. For this reason additional PN should

not be given to those who are already meeting EN targets for intake (A).

We conclude, however, that patients who fail to reach even the lower target for intake using EN should receive additional PN (C).

9. Should vulnerable patients (i.e. undernourished, chronic catabolic disease) be treated in a different way?

Patients with a severe undernutrition should receive EN up 25–30 total kcal/kg BW/day. If these target values are not reached, supplementary PN should be given (C).

Comment: There are no studies addressing this question explicitly in critically ill patients. A subgroup analysis in review by Braunschweig et al.[36] showed that patients with severe undernutrition had a significantly higher mortality risk (RR 3.0; 95% CI 1.0–8.56) with an oral diet or standard care than with PN.

Another subgroup analysis in the same paper[36] compared EN with PN in patients with severe undernutrition (3 trials) and found a 2.5 times higher risk of death among patients receiving EN compared with those treated by PN.

In these studies however, the amount of energy supplied by EN is not given. We surmise that the differences in outcome in these studies depend more on the amount given rather than the route of delivery. Based on this assumption, it was agreed that in patients with severe undernutrition—or in patients with a chronic catabolic disease—target values should be met fully using supplementary PN if necessary (C).

Immune-modulating nutrition

Three methodological ***problems*** arise when evaluating published studies on immune-modulating nutrition:

- selection of patients,
- type of enteral formula used,
- how to handle conclusions from prospective data compared with post hoc analyses.

Selection of patients

Numerous studies of immune-modulating nutrition have been carried out in patients with different diseases. The meta-analysis published by Heyland[45] has shown that the results of these studies depend significantly on the patient group involved.

Most of the studies of immune-modulating nutrition focus on post- and perioperative feeding in elective surgical patients. These patients will not be discussed in depth in this chapter since they are discussed in the surgery and oncology chapters of these guidelines.

Type of enteral formula

Enteral immune-modulating nutrition implies a formula enriched with several "functional" substrates. The observed effects cannot, therefore be ascribed to one single substrate. As the various commercial formulae used in published studies differ in their composition, which may exert a significant influence on the results, no overall synthesis of the results is possible. However, since many of the studies have used a particular formula, enriched with arginine, nucleotides and ω-3 fatty acids, these can be summarised together, while those employing different formulae will be considered separately.

Post hoc analyses

Some of the larger studies employing immune-modulating nutrition in ICU patients present post hoc analyses as the main result of the study. Furthermore, the mortality is often not identical in the groups, which make conclusions regarding morbidity very difficult.

10. Is a immune-modulating formula enriched with arginine, nucleotides and ω-3 fatty acids superior to a standard enteral formula in any group of critically ill patients?

10.1 ***In elective upper GI surgical patients: yes (A) See guidelines on surgery.***

10.2 ***Patients with a mild sepsis (APACHE II$<$15) should receive immune modulating EN with such a formula (B). No benefit could be established in patients with severe sepsis, in whom a immune-modulating formula may be harmful and is therefore not recommended (B).***

Comment: This issue was investigated by Galbán et al.[46] in medical and surgical patients with sepsis in a trial that employed the same formula as the two former trials.[47,48] A significant reduction in mortality could be shown ($P<0.05$) for the whole study population. Yet, in a subgroup analysis based on the severity of illness, the difference in mortality was only significant in the group of patients with an APACHE II score between 10 and 15 ($P = 0.02$) In the

group of patients with an APACHE II score of 15–26, no significant reduction in mortality was observed. Patients with an APACHE II score >25 even had a trend towards a higher mortality. (A serious problem with this study is the unexpectedly high mortality rate of the control patients in the APACHE II 10–15 stratum 30%.) However, mortality was reduced in the treatment group, even compared with that predicted by the APACHE II score.

No significant difference was found regarding length of stay in ICU (16.6 ± 12.9 days, $P = 0.41$) and information about length of stay in hospital was not available. A trend towards a reduced incidence of nosocomial infections was noted in the group receiving immune-modulating nutrition (46 versus 68 incidences, $P = 0.24$). The rate of bacteraemia was significantly lower in this group (8% versus 22%, $P = 0.01$).

A subgroup analysis in the trial reported by Bower et al.[48] revealed a significantly higher mortality in septic patients receiving immune-modulating nutrition (11/44 versus 4/45 patients, 25% versus 8.9%, $P = 0.021$, significance calculated by the author).

Later, the idea that some immuno-modulating fomulae are doing more harm than good in severely ill patients, has also been raised in the study reported by Bertolini et al.[49] This study compared a formula containing extra L-arginine, ω-3 fatty acids, vitamin E, beta carotene, zinc, and selenium with a standard formula. After recruitment of 237 patients, the study was stopped for patients with severe sepsis because an interim subgroup analysis of 39 of such patients revealed that the immune-modulating formula was associated with a significant higher ICU mortality compared with the standard formula (44.4% versus 14.3%; $P = 0.039$).

We conclude that immune-modulating nutrition of the kind employed in these trials, improves outcome only in less severe sepsis (APACHE <15), whereas this effect is no longer significant in patients with severe sepsis and even tends to be of harm in severely ill patients. Given the possible association with an increased mortality in patients with severe sepsis, we conclude that these formulae should not be used in patients with severe sepsis.

10.3 ***Trauma: Yes (A) See guidelines on surgery.***

10.4 ***Burns: No recommendation regarding supplementation with ω-3 fatty acids, arginine, glutamine or nucleotides can be given for burned patients due to insufficient data. Trace elements (Cu, Se and Zn) should be supplemented in a higher than standard dose (A).***

Comment: There are 2 studies investigating the effects of immunonutrition on burned patients that obtained very different results.

In the double blind trial reported by Gottschlich,[50] 50 patients were prospectively randomised into three groups to compare an experimental low-fat formula enriched with arginine, histidine and cysteine with two enteral formulae, a standard one and a high-fat one (45%). Mortality was 2/17 in the experimental group, 1/14 in the standard and 7/19 in the high fat group ($P = 0.06$). Time spent on ventilator support was shortest in the experimental group (9 days), followed by the group with standard formula (10 days) and was longest in the high-fat group (14 days).

There was a significant difference in the length of stay in hospital when corrected for burned surface area. 0.83 in the experimental group versus 1.21 days per % BSA ($P<0.02$) in the two other groups. Wound infections were significantly reduced ($P<0.03$), while incidence of other septic complications was similar ($P = 0.07$). In summary, this study merely shows a significantly shorter length of stay in hospital in the experimental group, with no difference in mortality compared with the group receiving a standard formula.

The second study[51] randomised 49 patients to receive either an immune-modulating formula (the same as described in[48]) or a standard high protein formula. There was a trend towards a higher mortality (20% versus 12.5%) using the immune-modulating formula but no difference in the length of stay in ICU or hospital. A slightly higher incidence of septic complications (2.38 per patient versus 1.71) was also observed.

We conclude that the available data and not sufficiently convincing to form a valid opinion. The results however suggest that immune-modulating formulae should not be administered uncritically to these patients.

However, a randomised controlled study[52] showed that the supplementation of trace elements with a daily dose of 40.4 μmol Cu, 2.9 μmol Se and 406 μmol Zn for 30 days after burn injury reduced the number of bronchopneumonic infections and also reduced the length of hospital stay:

10.5 ***ARDS:*****Patients with ARDS should receive EN enriched with ω-3 fatty acids and antioxidants (B).**

Comment: The influence of this specific nutritional formula on patients with ARDS has only been investigated in one prospective, randomised double blind controlled trial.[53] In this study a special high-fat formula containing eicosapentaenoic acid (EPA), γ-linolenic acid and antioxidants but no glutamine, arginine, or nucleotides was used.

In total, 146 patients were enrolled, of which 98 patients were evaluated. Multiple broncho-alveolar lavages revealed significant decreases in the number of total cells and neutrophils/ml of recovered lavage fluid with EPA compared with a standard high-fat formula). A significant reduction of days on ventilator support (11 versus 16.3 days, $P = 0.016$), of length of stay in ICU (12.8 versus 17.5 days) and a reduced incidence of organ failure was reported in the compliant patients. However, no difference was evidenced in the ITT analysis. For this reason, the recommendation can only be issued on a B level.

10.6 *ICU patients with very severe illness and who do not tolerate more than 700 ml EN/day should not receive a formula enriched with arginine, nucleotides and ω-3 fatty acids (B).*

Comment: In patients who are unable to tolerate an adequate amount of nutrients ($<$ 2500 ml/72 h) enterally, a negative effect of immune-modulating nutrition has been reported. As it is impossible to predict the amount of feed that will be tolerated, such a formula should not be administered routinely in severely ill patients.

Meta-analyses and reviews

Studies of immune-modulating nutrition have been submitted to 3 meta-analyses[45,54,55] and 3 systematic reviews.[56–58] Of these, only the meta-analysis by Heyland et al.[45] and the reviews by Montejo and Nitenberg differentiated between elective surgical and critically ill patients. For this reason, the meta-analysis by Beale and Heys together with the systematic review by Zaloga have only limited value in terms of critically ill patients. Heyland et al.'s[45] analysis suggested no effect on mortality in elective surgical patients although the incidence of infections and length of stay were significantly reduced. A reduced length of stay was also shown in critically ill patients, but there was no effect on the rate of infectious complications. Because a trend towards increased mortality was found in the critically ill, Heyland concluded that immune-modulating nutrition could not be recommended generally for the critically ill.

The meta-analysis by Heys et al.[55] showed a non significant decrease in septic complications (wound infections, intra-abdominal abscesses, pneumonia and septicaemia) and nosocomial infections. No subgroup analysis of the critically ill was performed.

The potentially inverse correlation between the variables "length of stay", "rate of infectious complications" and "mortality" represents a methodological problem. Mean length of stay and infectious complications are reduced when more patients die early. A significant difference in mortality might, therefore, also influence these variables.

This problem was discussed by Nitenberg et al. in their systematic review and by Beale et al.[54] in their meta-analysis. Beale et al. concluded that immune-modulating nutrition was associated with a significant reduction of length of stay in hospital (-2.9 days, $P = 0.0002$). This was confirmed in a subgroup analysis of surgical and medical patients whose length of hospital stay was also significantly reduced (-2.3 days, $P = 0.007$ resp. -9.7 days, $P = 0.01$). To exclude the influence of mortality on these parameters, only surviving patients were compared in a second analysis. In the group of surgical patients, the differences in length of hospital stay and rate of infectious complications remained significant but in the group of medical patients the difference was no longer significant (-11 days, $P = 0.07$).

Individual studies

Most of the studies included in the subgroup analysis of critically ill patients in Heyland's study[45] do refer not to a mixed population of intensive care patients but specifically to those suffering from trauma, sepsis or burns. We therefore began by analysing two trials[47,48] involving a mixed study population. Both studies employed the same formula (enriched with arginine, nucleotides and $\omega-3$ fatty acids as described by Bower et al.[48]), and the following statements are, therefore only valid for this product.

No positive effects on mortality could be demonstrated in these two major prospective trials. The study by Bower et al.[48] even showed a higher mortality in the group receiving immune-modulating nutrition (23/147 versus 10/132 patients, 15.6% versus 7.6%, respectively, $P = 0.049$). This finding was confirmed by the results of the subgroup analysis of septic patients (11/44 versus 4/45 patients, 25% versus 8.9%, $P = 0.021$) and critically ill (12/103 versus 6/87 patients 11.6 versus 6.9%, $P = 0.26$) (significance calculated by the authors).

However, the difference in mortality was mainly due to patients who could not be fed "successfully" (i.e. $>$ 2.5 l/72 h). In this subgroup (of unsuccessfully fed) mortality was 13/47 (28%) in those receiving an immune-modulating formula versus 3/32 (9%) in the control group receiving a standard formula ($P = 0.028$, significance calculated by the authors). (Whether patients who received

immune-modulating nutrition were more severely ill cannot be deduced since APACHE II values were only reported for deceased patients. Patients able to be fed successfully did not have a significant difference in mortality (10% or 7%, respectively), but such a low mortality implies that these patients were not severely ill in the first place

Atkinson et al.[47] also found mortality was slightly, but not significantly, higher in patients receiving immune-modulating nutrition (48% versus 44%), In contrast to the study of Bower et al.,[48] this was observed primarily in the subgroup of patients who had reached a certain level of feed intake after 72 h (42% versus 37% n.s.). Patients who could not be fed successfully had a mortality of 42% whether they received an immune-modulating or a standard formula. This study[47] did not investigate the rate of infectious complications.

Bower et al.[48] reported a non significant reduction in days spent in hospital (21 versus 26 days) for all patients. Only in the retrospectively defined subgroup of patients who tolerated more than 5750 ml of feed within 7 days was there a significant reduction of days spent in hospital (21 versus 29 days, $P<0.05$). No information on length of stay in ICU was provided.

Atkinson et al.[47] found no difference regarding length of stay in ICU and hospital between the two groups. In the subgroup analysis of patients who received more than 2500 ml within 72 h, a significant reduction in length of stay in ICU or hospital (7.5 versus 12 days, $P = 0.02$, 15. 5 versus 20 days, $P = 0.03$) was shown, as well as a reduced occurrence of SIRS.

Both trials, however reported a significant effect on length of stay but only in a subgroup of patients successfully fed and not in an intention-to-treat analysis. This may be simply a reflection of the fact that the most severely ill patients not only tolerate less feed due to impaired gastrointestinal function but also have an inherently higher risk of dying. These data may suggest that the positive effect of this particular immune-modulating formula exists only in less ill patients, as in patients after elective surgery.

According to these data, immune-modulating nutrition with a composition as described in[48] can reduce length of stay in ICU or hospital in patients who ingest >2500 ml/72 h or at least 5750 ml within 7 days (the evidence of this has been rated as level II only because the result was only shown in a *retrospective* subgroup analysis.) However, the complementary subgroup analysis of patients who tolerated <2500 ml/72 h or <5750 ml within 7 days also showed a negative effect on mortality. As these patients cannot be identified in advance, we concluded that such a formula should not be used routinely in severely ill patients.

12. Should EN nutrition be supplemented with glutamine?

12.1 *Glutamine should be added to a standard enteral formula in burned patients (A) and trauma patients (A)*

12.2 *There are not sufficient data to support enteral glutamine supplementation in surgical or heterogenous critically ill patients.*

Comment: The supplementation of a standard formula was studied in burned patients in four published trials.[59–62] Two of them[60–62] showed a significant improvement in wound healing and a reduction in length of hospital stay. Garrel et al.[60] reported significantly reduced mortality (54.5% versus 10.5%, $P<0.05$). The fourth study[59] found an improvement in intestinal permeability and a reduction in plasma endotoxin levels.

One published study[63] examined the addition of glutamine to a standard enteral formula in 72 trauma patients. There were significantly lower rates of bacteraemia, pneumonia and sepsis in the treatment group.

Four studies in heterogenous groups of critically ill patients[64–67] did not find any significant difference in infectious complications, length of stay or mortality.

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