Chapter 9
Major Infections and Sepsis

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Keywords Parenteral nutrition • Enteral nutrition • Sepsis • Trophic feeding • Early PN • Supplemental PN • Lipids • Multi-chamber bags • Immunonutrition

Key Points

- Enteral feeding may have a positive (protective) impact upon the gut by promoting both structural and functional integrity and by doing so may have an important role in the immune-competence of patients.
- Meta-analyses of elective gastrointestinal surgery and surgical critical care patients undergoing a major operation have shown that early postoperative EN had a protective effect for development of secondary infections.
- Trophic feeding may be at least equivalent to full feeding with respect to critically ill patients as a whole, but the role trophic feeding has in the septic and critically ill patient remains open to debate.
- EN is associated with fewer complications than parenteral nutrition (PN) and is more cost-effective than PN to deliver nutrition to critically ill patients.
- There is unequivocal evidence that patients receiving parenteral nutrition are at increased risk of catheter-related blood stream infections (especially fungal).
- Timing of commencement of PN has been suggested to be a significant (and modifiable) risk factor for the development of sepsis related to PN use, such that early PN may in fact be harmful.
- Supplemental PN is not to be recommended. Studies have failed to demonstrate a clinical benefit.
- Questions surrounding safety and infectious sequelae relating to intravenous lipids remain unanswered (in particular, the potentially positive benefits of omega-3 fatty acids).
- Multi-chamber bags have been shown to decrease in infections in patients.
- Immunonutrition is a term used to describe enteral feeds that have been supplemented with some combination of amino acids, omega-3 oils, and antioxidants in the belief that these components may have a beneficial impact upon immune function. Unfortunately, the evidence to date is conflicting; despite over 30 trials and at least three meta-analyses.

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- While many questions remain unanswered there is abundant evidence to suggest that starvation is to be avoided, and where possible enteral nutrition should be the first strategy that is implemented.

Introduction

Each modality of nutrition support (from none through enteral to parenteral nutrition) has its own attendant benefits and risks, particularly with respect to sepsis. In this chapter we review some basic gut immunology as it pertains to sepsis and risk of developing infection in the starved patient, and more importantly the sequence of events in patients receiving supplemental artificial nutrition. Enteral and parenteral nutrition is discussed separately regarding risk of infection, including optimal management strategies in septic patients. Lastly, immune-nutrition and other nutritional interventions purported to have beneficial impact on outcomes of septic patients are discussed and analyzed. Much of what is contained within this chapter has been discussed elsewhere in the book. For example gut immunological physiology is described in detail in Chap. 2. But the information is synthesized here as it pertains to both prevention of complications and impact of nourishment in the presence of severe infections.

Gut Immunology

The gut, as a consequence of its extensive interaction with the external environment, plays an important role in host defense, thus making the gut one of the largest components of the immune system [1]. Indeed it has been suggested that mucosal-associated lymphoid tissue (MALT), residing as non-aggregated immune cells near the basement membrane or as aggregated lymphoid tissue (i.e., Peyer's patches) comprises 50 % of total body immunity and 70 % of total antibody production [2].

The single layer of epithelial cells that makes up the functional surface area of the gut lumen (approximately 400 m^2 in area) has a dual role. It provides a semipermeable membrane for absorption of nutrients and simultaneously serves as an impermeable barrier to undesirable elements in the intestinal milieu. It achieves this not only by forming a physical barrier but also by maintaining continuous controlled inflammation through a combination of innate and adaptive immunity [3–5]. The gut is the only place in the body where activated lymphocytes are present all the time.

The innate immune system may be divided into immunologic and non-immunologic. Non-immunologic processes protecting the intestinal mucosa include physicochemical (e.g., digestive enzymes, gastric acid), antimicrobial (e.g., secretory immunoglobulin A, lactoferrin, defensins) and mechanical (peristalsis, mastication, "tight junctions" between cells). Immunologic processes are based on cells, and are the first to contact invading microorganisms [6]. These immunologic components are a non-selective (but effective) method of defense. They include the complement system, phagocytes and recruitment of natural killer cells. This arm of the immune response recognizes bacteria mainly via pathogen associated molecular patterns (PAMPs)[7]. Such recognition allows immune cells to respond to a wide array of microorganisms using a limited number of receptors. A major family of PAMP receptors is toll-like receptors (TLRs), which bind to different bacterial products and mediate pro-inflammatory signals to the cells [7, 8].

Adaptive immunity is mediated through humoral immunity (B cells) and cellular immunity (T cells). Humoral immunity leads to appropriate production of antibodies, while cellular immunity protects against harmful intracellular events that are not amenable to the effects of antibodies. Following activation of the innate immune system, antigen presenting cells (APCs), which belong to the innate immune system, activate T cells that are part of the adaptive immune system [9]. T-cells may then differentiate into three types of so-called effector cells (Th1, Th2, and Th3) depending on

the antigen presented. Each subtype produces its own cytokine milieu, and may be involved in positive or negative feedback. Th1 cells release IFN-γ, TNF-α and IL-2, up-regulating the inflammatory response. Th2 cells secrete IL-4, IL-5, IL-6, IL-10, and IL-13, which act to down-regulate the immune response [10, 11]. Th2 cells also activate B cells to differentiate into plasma cells. These are responsible for most of the total immunoglobulin production, in particular secretory IgA (sIgA). sIgA serves to prevent bacterial attachment to the mucosa and to inhibit immune system activation. The adaptive immune system can respond to specific antigens and is capable of immune memory.

Another important aspect of controlled intestinal inflammation in MALT/GALT is the migration of immune cells into the inflamed mucosa. Peyer's patches do not have lymphatic vessels, so alternative methods of recruitment are required. This process involves a sequence of rolling, activation, arrest and transmigration of the inflammatory cells. In the final steps of this process the cells are tightly linked to the tissue, mediated by cell-surface-expressed integrins (particularly L-selectin and α4β7-integrin) and tissue expressed adhesion molecules (particularly ICAM-1 and MAdCAM-1) [12–14]. Following antigenic exposure, activated lymphocytes (i.e., B and T cells) migrate to regional mesenteric lymph nodes. Once in the lymph nodes the cells undergo a process of maturation and proliferation. They then migrate out through the thoracic duct into the systemic circulation, and return to their tissue of origin.

Starvation may have a negative impact upon the gut by disturbing both structural and functional integrity. It is known for instance that starvation may induce villous atrophy. A decrease in mucosal mass of up to 15 % in humans has been observed. This decreases absorptive capacity and more importantly digestive (protective) brush border enzymes and antimicrobial secretions (pancreatic enzymes, proteases, etc.). Further, there is loss of tight junctions between enterocytes. There is diminished blood flow [15, 16], which leads to a reduction in the production and release of a variety of agents including cholecystokinin, gastrin, bombesin, and bile salts. All of these may have a trophic effect on the intestinal epithelium [17]. These changes further affect gut permeability and so predispose to significant bacterial translocation. Some studies have documented presence of microbial DNA from presumed trans-located bacteria, or components of bacteria, in septic patients who have negative blood cultures [18].

Not only can these changes impair the ability to respond to new infectious challenges, they may also lead to loss of established antiviral and antibacterial defenses and impair the ability to respond to new infectious challenges. For instance, in mice exclusively fed parenterally, as little as 5 days of gut disuse resulted in the loss of protection to a respiratory virus and a reduced clearance of that virus [19]. However, once the mice were refed enterally immunologic memory returned.

Similarly, absence of enteral nutrition (albeit while being parenterally fed) has been shown to decrease MAdCAM-1 expression in Peyer's patches in animal models within hours [20]. This leads to a 50–60 % reduction in cell counts, with subsequent alteration to CD4/CD8 counts (from a normal of 2:1–1:1) with associated reductions in IL-4 and IL-10 [21–23]. The consequences of these observed changes are activation of the adaptive immune system by inhibition of counter-regulation (i.e., a shift from Th2 to Th1 phenotype). Thus allowing primed or activated neutrophils to pass out of the gut and into the systemic circulation thereby (potentially) leading to a heightened and prolonged systemic inflammatory response and all of its negative consequences.

Enteral feeding may have a positive (protective) impact upon the gut by promoting both structural and functional integrity and by doing so may have an important role in the immune-competence of patients. This is discussed in more detail later.

Enteral Nutrition

Early enteral nutrition is recognized as an important adjunct in the management of the critically ill patient. Both the European Society of Parenteral and Enteral Nutrition (ESPEN) and the American Society of Parenteral Nutrition (A.S.P.E.N.) promote early enteral support (i.e., within 24–48 h) in these patients [24, 25]. Along with the putative nutritional benefits, early EN has been thought to support the immune and metabolic responses to stress and play a key role in maintaining gut integrity.

Experimental Animal Evidence

Kudsk and colleagues reported the first clinical and laboratory evidence to support the notion that enteral nutrition affects the metabolic response to sepsis and improves host defenses in an animal model [26]. Several authors subsequently demonstrated that disuse of the gut in animals that were supported by parenteral nutrition resulted in decreases in GALT lymphocyte cell number. Once enteral feed was reinstituted these changes reversed within days [21, 27, 28]. Similarly IgA levels were seen to drop with an associated decrease in B and T cells in the lamina propria in animals fed exclusively by the parenteral route [21, 27, 28]. Associated with atrophy of GALT lymphoid tissues, a quantitative decrease in adhesion molecules (especially MAdCAM-1) has been observed in animals not fed enterally [29]. Parenterally fed animals demonstrated decreases in IL-4 and IL-10 levels in the small intestine [22, 23]. In order to establish the functional impact of these changes on immunity, the same authors studied the effects of parenteral nutrition on established immunity [19, 30]. Kudsk and King were able to establish a loss in established respiratory mucosal immunity for *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and influenza.

These animal studies show that lack of enteral feeding has a profoundly negative effect on the overall immunological status. Whilst difficult to prove this hypothesis in humans, the circumstantial evidence in animals is highly suggestive. Inability or other failure to use the gut for nutrition appears to cause cytokine imbalances, in turn activating the innate immune system, and contributing thereafter to an overzealous stress response. At least in theory, this may ultimately lead to systemic inflammation and SIRS [31]. Early enteral feeding may attenuate this over-response and so lead to improved immune tolerance [32]. The recommendations of the professional societies, supporting the use of early enteral nutrition, lean heavily upon this supportive animal data.

Postoperative Infections

The positive results seen in animal studies have been reflected in the findings of a large meta-analysis of elective gastrointestinal surgery, and surgical critical care patients undergoing a major operation who were given early postoperative EN [33]. Patients receiving early EN demonstrated a significant reduction in infections (RR 0.72 CI 0.54–0.98) when compared to a "nil by mouth" approach. Decreases in hospital lengths of stay and anastomotic dehiscence were also seen. This beneficial effect is even more pronounced when EN is compared to PN. In all, six different meta-analyses have consistently shown the beneficial effect of EN over PN with respect to infectious sequelae [34–39].

Active Sepsis

These studies appear to confirm the benefit of EN in preventing sepsis as a complication (perhaps) of feeding route; but what of patients that are already septic and in septic shock?

A recent study from a German group has attempted to address this question [40]. They performed a secondary analysis of a prospective cohort of severely ill and septic ICU patients where the primary endpoint was response to intensive insulin therapy with the use of pentastarch resuscitation. In their secondary analysis, they found that mortality rates were substantially lower in patients fed using the EN as opposed to the use of EN and PN. (26.7 % vs. 41.3 %, $p=0.048$), with a protective effect observed in the EN group alone for development of secondary infections (HR1.89 95 % CI 1.27–2.81). This data should be interpreted with caution. Patients given PN may have been more severely

ill, given that the study was not randomized to PN vs EN. But even with this caveat, the study lends further support to the beneficial impact of EN in septic patients, and in improving overall outcomes from infectious complications.

Underfeeding

Recently underfeeding in the first week of critical illness has received much attention following the publication of three prospective trials designed to address this issue [41–43]. Based on these trials, the Surviving Sepsis Campaign guidelines suggested avoiding mandatory full caloric feeding in the first week of illness [44]. This recommendation was surprising, because none of the trials showed any difference in infectious outcomes, ventilator days or mortality. Arabi et al. did note a non-significant trend towards decreased mortality [41]. All three groups reported that patients fed less had less GI intolerance.

There were concerns expressed about the demographics of recruited patients in these studies. All patients were reasonably young, largely male, and incorporated both septic and non-septic patients. Elke and Heyland published a secondary analysis of their nutrition database to assess outcomes in a critically ill septic cohort [45]. Using a statistical model, they were able to demonstrate a beneficial effect of improved nutrition on mortality in long stay ICU patients. They hypothesize that individual patient characteristics may play an important role in how patients respond to various feeding strategies (e.g., older age, low or high BMI may fare worse). But there exists no data to support this theory. Moreover, in an observational analysis such as this, one can also conclude that sicker patients are harder to feed, and therefore improved nutrition is only a marker for wellness.

There remains the possibility that trophic feeding is at least equivalent to full feeding with respect to all critically ill patients, but the role of trophic feeding in the septic and critically ill patient remains open to debate.

EN Formulations

The formulation of EN has been suggested to play a role in the modulation of sepsis. Much work has been carried out on micronutrients and is discussed in detail later. The macronutrient composition of EN and in particular the lipid component of EN has been of interest to many.

Lipid-rich nutrition has been shown in animal models to attenuate inflammation and reduce organ damage [46–49]. In these studies, deHaan and colleagues were able to demonstrate amelioration in the initial hyper-inflammatory response by administration of a lipid-rich enteral formula. They used a custom made lipid-rich formula in which 50 % of administered calories were derived from fat. The lipids themselves were sourced from lecithin, with less than 5 % of fat derived from omega-3 or omega-6 fatty acids. By administering this formula, they were able to demonstrate stimulation of the autonomic nervous system via activation of cholecystokinin 1, leading to parasympathetic suppression of cytokine release. They showed a decrease in the early inflammatory response mediated by decreases in IL-6 and IL-10, leading to a subsequent increase in IL-12 and IFN-γ. Restoration of this IL-12/IL-10 balance has been shown elsewhere to improve defense against opportunistic pathogens [50].

This work has been expanded to preclinical studies, with similarly encouraging results [51]. Lubbers et al. from the same Dutch group demonstrated the potential benefit of a lipid-rich, protein-rich enteral formula in a human model of endotoxemia. Healthy human volunteers were administered *E. coli* lipopolysaccharide intravenously. Feeding with a lipid rich formula (analogous to that used in

the previously mentioned rodent studies) was shown to lead to a reduction in circulating levels of the pro-inflammatory cytokines, IL-6, TNF-α and IL-1 receptor antagonist.

Despite this intriguing research, evidence for a clinical role for enteral immunonutrition, especially lipid formulations, remains underwhelming and indeed divisive. Nevertheless, keen interest continues about the putative benefits of fish oils as a source of fat in enteral diets. Meta-analyses initially failed to observe any significant effect with the use of immunonutrients (including fish oils) despite recognizing a signal towards decreased infectious complications [52]. However, subsequent reviews (often from the same authors) initially suggested significant benefit and recommended the routine use of immune-nutrients (without differentiating between which ones) in critical care populations, only to rescind those recommendations with the exception of a benefit with fish oils in later reviews [53, 54].

Legitimate concerns have been raised about the heterogeneity of the studies reported and similarly the heterogeneity of interventions included. Put simply, a "well" postoperative patient receiving glutamine is not the same as a profoundly septic patient receiving omega-3 enriched enteral feeding formula.

Omega-3 fatty acids are predominantly derived from fish oils, but may also be obtained from some plant oils (walnut, chia, flaxseed etc.). Interest in their use in enteral nutrition has stemmed from the suggestive observation that omega-3 has anti-inflammatory effects. This effect was first observed in animal models and has led to several large clinical trials [55–57]. In these trials, omega-3 enriched diets appeared to be beneficial, leading to decreased time on ventilators, decreased length of stay and better outcomes in septic patients. However, concerns were subsequently raised about the validity of these findings. The concerns related to the use of enteral feeding formulas in the control groups that were high in omega-6, relative to the group that was given omega-3 enriched formulas. Omega-3 fats are felt to be pro-inflammatory and alterations in the omega-3/omega-6 ratio are potentially deleterious. As mentioned above, other elements of immune-nutrition have also been suggested to be beneficial. These are addressed separately.

At the present time, there remains insufficient evidence to promote one form of enteral nutrition (i.e., formula, amount, etc.) over another with respect to prevention of infectious complications.

Parenteral Nutrition

As described earlier, EN is associated with fewer complications than parenteral nutrition PN, and is more cost-effective to deliver nutrition to critically ill patients [58]. Consensus guidelines from A.S.P.E.N. have recommended that for adequately nourished patients who have contraindications to enteral nutrition, PN should be initiated only after 7 days of intensive care unit care [24]. On the other hand, for patients with clinical signs of protein–calorie malnutrition on admission to the ICU, A.S.P.E.N. guidelines recommend that it is appropriate to start PN as early as possible, once adequate fluid resuscitation has been completed. In contrast, ESPEN (European Society of Parenteral and Enteral Nutrition) have advocated commencing PN in patients within 2 days of ICU admission to meet 100 % of estimated calorie and protein needs not met by EN [25]. The disparity between the professional societies can largely be explained by differences of opinion both on the risk of PN and the benefits of full caloric and protein feeding.

Central Line Associated Infections

There is unequivocal evidence that patients receiving parenteral nutrition are at increased risk of catheter-related blood stream infections [59]. This risk is higher than patients who have central venous catheters but do not receive parenteral nutrition [60]. An observational study demonstrated that PN

administration can increase the risk of not only blood stream infection but also pneumonia, surgical site infection, and urinary tract infection [61]. Minimization or reduction of these complications can best be achieved by utilizing strategies to reduce the overall use of PN wherever possible. When PN is required, best practices to minimize catheter related blood stream infection should be strictly observed. Aseptic technique should be used for central catheter placement, and proper hand hygiene and maximal barrier precautions should also be used during the procedure. Introduction of care bundles has been shown to be effective in implementing these changes [62]. The site of central venous catheters has been shown to be an independent risk factor for development of blood stream infection (BSI). A large retrospective analysis of PN related BSI in a single Irish university hospital suggested that use of femoral lines increased the risk of BSI over the use of subclavian or internal jugular lines [63]. In general, single lumen catheters are preferred to multi lumen catheters, and the subclavian approach is a preferred location for central catheter placement. After central catheter placement, the single lumen of the catheter should be dedicated, and used solely, for parenteral nutrition [64].

Timing of PN

Timing of commencement of PN has been suggested to be a significant (and modifiable) risk factor for the development of sepsis related to PN use. A large randomized trial from Australia and New Zealand has attempted in part to address this issue [65]. They found no benefit to very early PN (<24 h) in patients with short term relative contraindications to EN, as compared to "standard of care", who received no nutrition. Of the patients in the "standard of care" group, only 51 % ever required PN. Interestingly, 40 % of the "standard of care" patients received no supplemental nutrition at all, either PN or EN, during their ICU stay (median 3.72 days). No adverse outcomes were observed. A post hoc analysis of a subgroup of patients from the EPaNIC study (discussed in more detail below) also examined the role of early vs. late initiation of PN in patients who had a contraindication to EN (i.e., where calories were derived from PN only, with no enteral component). This analysis found a statistically significant reduction in infection and a trend towards early discharge in the late initiation arm [66]. These results, while less reliable by their nature, seem to clarify that at least in the first 48 h of critical illness, there is no benefit to early provision of PN as far as infection is concerned. Indeed, the EPaNIC trial suggested that early PN may even be harmful.

Supplemental PN

Supplemental use of parenteral nutrition (in addition to EN) has been suggested as a solution to the perceived problem of delivery of inadequate calories, while simultaneously maintaining the benefit of EN with respect to impact on sepsis and other outcomes. A recent large multicenter prospective trial from Belgium (EPaNIC) investigated this approach [67]. In this study, early PN was used to reach 100 % of calories (within 48 hours) in patients unable to receive all their required calories enterally (for whatever reason). The control group did not receive PN until later in their ICU stay (i.e., 7 days). There was no associated effect on mortality. On the other hand, there was an observed increase in incidence of infection, prolonged mechanical ventilation and prolonged intensive care unit stay in the early PN cohort compared to the delayed PN cohort. But in the control group, a majority of patients never received PN at all. The data clearly supported the conclusion that if the patient doesn't need to receive PN, it is better not to give it early. A Canadian-led observational study using a similar approach documented an improvement in calorie provision but also failed to show any clinical benefit with the adoption of this strategy [67]. In the face of this data it would appear that supplemental PN is not to be recommended.

While it appears relatively clear that avoiding early PN in critically ill patients can reduce occurrence of infection, there are other questions that must be addressed. For instance, are there formulations and/or compounding methods of PN that may minimize infectious complications? Does type of central access device matter? These questions are further addressed in Chap. 7.

Role of Lipids

As with EN, the role of lipids in PN (with respect to sepsis) has been keenly debated. Joint guidelines from A.S.P.E.N. and Society for Critical Care Medicine (SCCM) recommended in their 2009 guidelines that soybean oil-based lipids should be omitted from PN in the first week of hospitalization in the ICU [24]. This recommendation was based on the results of a small study that suggested better outcomes in patients that did not receive lipids [68].

Early in vitro scientific studies demonstrated the ability of intravenous lipids to be used as a growth media for such organisms as *Staphylococcus aureus* and *Candida albicans* [69]. In contrast, PN formulations without added intravenous fat emulsion (IVFE) are quite hypertonic, and do not allow growth of microbial colonies (*Staphylococcus*, *Pseudomonas*, *E. coli*, and *Candida*) [70].

Several clinical studies have confirmed the association of intravenous lipids (in addition to dextrose/amino acids PN) with the occurrence of staphylococcal blood stream infections in pediatric cohorts. In the larger of the two, a case-control study demonstrated a 5.8-fold increase in staphylococcal bacteremia in pediatric neo-natal intensive care units (NICU) associated with lipid infusions [71]. This association was confirmed in a similar NICU-based study of very low birth weight infants [72]. This case-control study documented a ninefold increase in staphylococcal bloodstream infections in the cohort associated with the use of IVFE infusions.

In an analysis of a large database of patients (the Premier Perspective database, containing inpatient data from 45 million discharges from acute care facilities in the US) there was no increase in the risk of infectious morbidity when lipids were omitted from PN admixtures when adjusted for complexity and severity of illness [73]. The questions surrounding safety and infectious sequelae relating to intravenous lipids remain unanswered.

As with EN, alternative sources of lipid for PN has become of interest. In particular, the potentially positive benefits of omega-3 (and to a lesser extent omega-9) fatty acids relating to their anti-inflammatory properties has led to much work being done to assess their potential impact. It has also been suggested that omega-3 enriched PN may also slow or prevent progression of PN-related cholestasis and liver disease. Preclinical and small clinical studies have suggested the potential benefit of omega-3 fatty acids in reducing inflammatory burden in postsurgical patients [67, 74–76]. The results of these studies were summarized by Pradelli in a recently published meta-analysis of 23 studies [77]. While this analysis did not show any difference in mortality, they were able to demonstrate a reduction in infection rate (RR = 0.61, CI 0.59–1.33), with associated decreases in ICU and overall hospital length of stay. Omega-3 based lipids have been available in Europe for many years but as of yet remain unavailable in the US. This is likely to change pending the reporting of several trials to address the safety (and efficacy) of omega-3 lipids (Omegaven®, Fresenius Kabi, Hamburg, Germany) [78].

PN Compounding

PN compounding has been explored as a possible modifiable risk factor in decreasing the rate of blood-stream infections. Broadly speaking, PN may be compounded commercially, using multi-chamber bags, or locally, in a dedicated or hospital pharmacy. Turpin et al. were able to demonstrate

a decreased rate of blood stream infections with the use of multi-chamber bags compared to pharmacy compounded PN in a large retrospective database analysis [79]. This finding was further validated by the EPICOS study, a large, multicenter, prospective, open label trial [80]. In this study, a decrease in infections in patients was seen when the multi-chamber bags were used. The difference was small. It is likely that pharmacies that compound large amounts of PN solutions and adhere to appropriate safety measures will be able to minimize PN-related infections, similarly to manufactured multi-chambered PNs. Multi-chambered PNs are more likely to have benefit in settings where few PNs are prescribed. Moreover, the ease of prescribing a pre-manufactured bag may drive inappropriate use of PN upward. Further work is warranted with multi-chamber bags to assess their impact.

Infection Risk in the Community Setting

As discussed above, in the acute setting the type of line may have an important effect on BSI and overall risk of infection. What of patients in the home setting?

Buchman and colleagues have previously published their data on a large historical cohort of more than 500 patients infusing PN in the community [81]. They reported an overall infection rate of 0.37 per patient per year. Their study included patients over an 18-year period between 1973 and 1991. More recent data has suggested wide variations in incidence in BSI in home PN patients, ranging from 0.35 to 11 BSI per 1000 catheter-days [82–84]. Zhao and colleagues (who also reported a rate of BSI of 11/1000 catheter days) have suggested that the first 4 months of BSI are (not unsurprisingly) the time when most of these infections occur.

More recently Buchman et al. have reported on independent risk factors for developing BSI [85]. They identified use of subcutaneous ports (over tunneled catheters), multi-lumen catheters, increased frequency of lipid infusion, obtaining blood from the CVC and infusion of non-PN medications via the CVC as independent risk factors for BSI. Interestingly, increased PN frequency was associated with BSI in children but not with adults. All of this suggests that minimizing manipulation of the PN line is important in minimizing the risk of sepsis.

Central Access Devices

Historically, it was felt that tunneled catheters were the safest method to provide long-term PN [86]. This is particularly the case when compared to subcutaneous ports (as demonstrated by Buchman et al.) [85]. However, with the increasing use of peripherally inserted central catheters (PICC), this question needs to be readdressed. A recent uncontrolled and non-randomized but prospective French study compared occurrence of infections in home PN patients receiving their PN via Broviac catheter or PICC. The authors reported a significantly lower occurrence of infections in the PICC group when compared to the Broviac group (1.87 vs. 1.05 per 1000 catheter days, $p = 0.01$) [87]. Despite this, ESPEN still recommends that PICC be used for no longer than 3 months in the home setting for PN administration, acknowledging that the evidence base for this recommendation is weak [88]. A controlled and randomized study is required to address the issue of appropriate CVC in the home setting.

A multitude of other interventions have been suggested to reduce the risk of BSI [89–93]. They include (but are not limited to): different types of catheters impregnated with antibiotics, chlorhexidine, and a variety of catheter locks (heparin, vancomycin, citrate, ethanol and so on). Although questions remain over their efficacy, ethanol locks in particular show promise and are worthy of further investigation in an attempt to minimize BSI.

Immunonutrition

Immunonutrition is a term used to describe enteral feeds that have been supplemented with some combination of amino acids, omega-3 oils, and antioxidants in the belief that these components may have a beneficial impact upon immune function. Unfortunately, the evidence to date is conflicting; despite over 30 trials and at least three meta-analyses.

Omega-3 has been discussed in detail above with respect to both enteral and parenteral feeds. Here we concentrate on amino acids and antioxidants, both given enterally and parenterally.

Glutamine

Glutamine is the most abundant nonessential free amino acid in the human body. It plays an important role in nitrogen transport and provides the fuel for rapidly dividing cells (immune cells, enterocytes, hepatocytes, and others.). Low glutamine levels have been demonstrated in patients with critical illness [94, 95]. This observation led to the suggestion that replenishment of this amino acid may be beneficial in critical illness, and may ultimately lead to improved outcomes. A meta-analysis of six randomized trials published in 2002 which examined the role of glutamine in critical illness suggested a trend towards better outcomes [96]. While initially encouraging, some concerns were raised about the quality of this data.

Recently two large trials have refuted the suggestion that glutamine supplementation may be beneficial. The first study randomized patients in multiple Scottish centers to receive 20 g of Glutamine per day, with and without selenium [97]. They found no benefit with respect to mortality or infections. The second study, a large multicenter blinded prospective randomized controlled study recruited in excess of 1200 patients [98]. Patients were randomized in a 2×2 factorial design to receive glutamine (0.35 g/kg/day), a mixture of antioxidants (including selenium, zinc, beta-carotene, vitamin E and vitamin C), both glutamine and antioxidants, or placebo. Surprisingly, a statistically significant increase in mortality was seen at 6 months in the patients randomized to receive glutamine (with and without antioxidant supplementation).

Both A.S.P.E.N. and ESPEN recommend consideration of supplementary glutamine in their latest consensus guidelines, published prior to this study. However in the light of these new data, these recommendations are perhaps questionable. Research is ongoing.

Arginine

Arginine is a conditionally essential amino acid that has been demonstrated to have potential beneficial effects in improving nitrogen balance, and T-cell immune function [99]. As a consequence most of the commercially available immunonutrition feeds contain Arginine, although at widely ranging doses. One of the many meta-analyses performed suggested a dose-dependent benefit of supplemental arginine (i.e., >12 g/1000 kcal) [52]. Higher dose arginine led to a reduction in infections with no significant impact upon mortality. However, the widely different formulas and patient cohorts used to achieve this cumulative response means that this data should be interpreted with caution.

Selenium

Selenium is an endogenous antioxidant and an essential component of glutathione peroxidases, which can reduce free hydrogen peroxide and protect the organism from oxidative damage. Utilization of selenium is thought to increase in critically ill patients because critical illness is associated with generation

of oxygen free radicals and decreased selenium plasma concentrations. This has led some to postulate an increased requirement for selenium in critical illness. Patients from Europe and parts of Australasia are known to be prone to low pre-morbid levels of selenium due to low soil content. It has been suggested that this deficiency may predispose these patients to increased risk of oxidative damage and thus worsen clinical outcomes. This notion has (in part) been supported by animal models of sepsis and brain injury that worsen in the selenium deficient state [100]. Several investigators have tested the hypothesis that outcomes in sepsis could be improved with selenium supplementation with variable results.

Earlier smaller studies demonstrated that selenium supplementation may improve clinical outcomes by reducing illness severity, infectious complications, and decreasing mortality in critically ill patients [101–103]. However, a larger subsequent trial using high dose selenium (4000 μg on the first day, 1000 μg per day for the 9 following days) failed to show any improvement in clinical outcome [104]. Two more recent studies using lower doses of Selenium (500 μg/day) have shown some conflicting results. A Scottish multicenter prospective randomized control trial in which critically ill patients received selenium suggested a decrease in "new" infections if selenium was given for more than 5 days [97]. In contrast, an international multicenter trial found no benefit to administration of selenium [98]. Both trials were well designed, large multicenter trials using a 2×2 factorial design. However, the international trial recruited twice as many patients.

Unsurprisingly, questions remain about the appropriateness of provision of selenium supplementation. The European Society for Parenteral and Enteral Nutrition (ESPEN) recommended initiating selenium supplements (350–1000 mcg/day) with an initial bolus followed by continuous infusion in critically ill conditions in their 2009 guidelines [105]. A.S.P.E.N., on the other hand, included no such recommendation in their subsequent guideline for nutrition support of the critically ill. Expert consensus remains divided [106, 107]. It has been suggested that supplementation of selenium in the deficient state is beneficial, but potentially harmful for patients with normal/adequate status [107]. In any event, further work is required to clarify the role of selenium supplementation.

Vitamin D

Vitamin D, and it's associated endocrine system (calcium, PTH), is known to have effects on innate and adaptive immunity as well as lung, muscle, endothelial and mucosal functions. Deficiency of vitamin D is recognized as one of the most common mild medical conditions worldwide. Recent reports have demonstrated that vitamin D levels are decreased in patients in the ICU [108]. It is unclear however if low vitamin D levels reflect a surrogate for disease activity or true functional depletion. Given the relative ease and low cost of repletion of vitamin D, supplementation has become of interest in the critical care setting. It appears that large doses (100,000 I.U.) are necessary to quickly return 1,25 vitamin D levels to normal. Data suggests that such dosing is safe, but little data exists at present as to the utility of such an approach. Additionally, decrements in critically ill patients may be due entirely to systemic inflammation-related decreases in vitamin D carrier proteins.

Antioxidants (Including Vitamin E and C)

Vitamins E and C serve as important endogenous antioxidants. Therefore, like other antioxidants, it has been proposed that daily requirement of vitamins E and C are increased in critically ill conditions due to increased rates of biological oxidation in critical illness. A prior randomized trial revealed that early administration of vitamins C and E reduces the incidence of organ failure and shortens ICU length of stay in the surgical intensive care unit (1000 U α-tocopherol given enterally every 8 h and

1,000 mg ascorbic acid given parenterally daily) [109]. More recent randomized studies, however, have questioned this finding [97, 98]. As with other micronutrients the role and effectiveness of routine supplementation remains unclear.

Conclusion

Artificial nutrition support plays a very real and pervasive role in the management of septic patients. Decisions on how best to feed patients when septic or at risk of developing sepsis are complex and not without significant risk. While many questions remain unanswered there is abundant evidence to suggest that starvation is to be avoided and where possible enteral nutrition should be the first strategy that is implemented.

When this is not possible PN remains a viable (and important) option, although recent evidence would support an adoption of an under-zealous approach to commencement, specifically avoiding the use of PN in the early stages of critical illness. While there have been a plethora of suggested strategies with respect to supplements, antioxidants, etc. we appear to be no closer to realizing a strategy that may have any beneficial impact on patient outcomes and in particular with respect to sepsis.

There remains much work to be done.

References

1. Phillips-Qualigiata JM, Lamm ME. Migration of lymphocytes in mucosal immune system. In: Husband AJ, editor. Migration and Homing of Lymphoid Cells, vol. II. Boca Raton, FL: CRC; 1988. p. 53–75.
2. McGhee JR, Mestecky J, Dertzbaugh MT, Eldridge JH, Hirasawa M, Kiyono H. The mucosal immune system: from fundamental concepts to vaccine development. Vaccine. 1992;10(2):75–88.
3. Schmitz H, Barmeyer C, Fromm M, Runkel N, Foss HD, Bentzel CJ, et al. Altered tight junction structure contributes to the impaired epithelial barrier function in ulcerative colitis. Gastroenterology. 1999;116(2):301–9.
4. Gitter AH, Wullstein F, Fromm M, Schulzke JD. Epithelial barrier defects in ulcerative colitis: characterization and quantification by electrophysiological imaging. Gastroenterology. 2001;121(6):1320–8.
5. Bürgel N, Bojarski C, Mankertz J, Zeitz M, Fromm M, Schulzke JD. Mechanisms of diarrhea in collagenous colitis. Gastroenterology. 2002;123(2):433–43.
6. Janeway Jr CA, Medzhitov R. Innate immune recognition. Annu Rev Immunol. 2002;20:197–216.
7. Medzhitov R, Janeway Jr C. Innate immunity. N Engl J Med. 2000;343(5):338–44.
8. Trinchieri G, Sher A. Cooperation of Toll-like receptor signals in innate immune defence. Nat Rev Immunol. 2007;7(3):179–90.
9. Sartor RB. Mechanisms of disease: pathogenesis of Crohn's disease and ulcerative colitis. Nat Clin Pract Gastroenterol Hepatol. 2006;3(7):390–407.
10. Renegar KB, Johnson C, DeWitt RC, King BK, Li J, Fukatsu K, et al. Impairment of mucosal immunity by total parenteral nutrition (TPN): requirement for IgA in murine nasotracheal anti-influenza immunity. J Immunol. 2001;166:819–25.
11. Johnson CD, Kudsk KA, Fukatsu K, Renegar KB, Zarzaur BL. Route of nutrition influences generation of antibody-forming cells and initial defense to an active viral infection in the upper respiratory tract. Ann Surg. 2003;237:565–73.
12. Bernstein CN, Sargent M, Rawsthorne P, Rector E. Peripheral blood lymphocyte beta 2 integrin and ICAM expression in inflammatory bowel disease. Dig Dis Sci. 1997;42(11):2338–49.
13. Bernstein CN, Sargent M, Rector E. Alteration in expression of beta 2 integrins on lamina propria lymphocytes in ulcerative colitis and Crohn's disease. Clin Immunol. 2002;104(1):67–72.
14. Vainer B, Nielsen OH. Changed colonic profile of P-selectin, platelet-endothelial cell adhesion molecule-1 (PECAM-1), intercellular adhesion molecule-1 (ICAM-1), ICAM-2, and ICAM-3 in inflammatory bowel disease. Clin Exp Immunol. 2000;121(2):242–7.
15. Chandra RK. Mucosal immune responses in malnutrition. Ann N Y Acad Sci. 1983;409:345–52.
16. Reddy V, Raghuramulu N, Bhaskaram C. Secretory IgA in protein-calorie malnutrition. Arch Dis Child. 1976;51:871–4.

17. Okamoto K, Fukatsu K, Ueno C, Shinto E, Hashiguchi Y, Nagayoshi H, et al. T lymphocyte numbers in human gut associated lymphoid tissue are reduced without enteral nutrition. JPEN J Parenter Enteral Nutr. 2005;29:56–8.
18. Chang SS, Hsieh WH, Liu TS, Lee SH, Wang CH, Chou HC, et al. Multiplex PCR system for rapid detection of pathogens in patients with presumed sepsis – a systemic review and meta-analysis. PLoS One. 2013;8(5):e62323.
19. Kudsk KA, Li J, Renegar KB. Loss of upper respiratory tract immunity with parenteral feeding. Ann Surg. 1996;223:629–38.
20. Fukatsu K, Zarzaur BL, Johnson CD, Lundberg AH, Hanna MK, Wilcox HG, et al. Lack of enteral feeding increases expression of E-selectin after LPS challenge. J Surg Res. 2001;97(1):41–8.
21. Li J, Kudsk KA, Gocinski B, Dent D, Glezer J, Langkamp-Henken B. Effects of parenteral and enteral nutrition on gut-associated lymphoid tissue. J Trauma. 1995;39:44–52.
22. Wu Y, Kudsk KA, DeWitt RC, Tolley EA, Li J. Route and type of nutrition influence IgA-mediated intestinal cytokines. Ann Surg. 1999;229:662–8.
23. Fukatsu K, Kudsk KA, Wu Y, Zarzaur BL, Hanna MK, DeWitt RC. TPN decreases IL-4 and IL-10 mRNA expression in lamina propria cells but glutamine supplementation preserves the expression. Shock. 2001;15:318–22.
24. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically Ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2009;33:277–316.
25. Kreymann KG, Berger MM, Deutz NE, Hiesmayr M, Jolliet P, Kazandjiev G, et al. ESPEN guidelines on enteral nutrition: intensive care. Clin Nutr. 2006;25:210–23.
26. Kudsk KA, Carpenter G, Petersen S, Sheldon GF. Effect of enteral and parenteral feeding in malnourished rats with E. coli-hemoglobin adjuvant peritonitis. J Surg Res. 1981;31(2):105–10.
27. Tanaka S, Miura S, Tashiro H, Serizawa H, Hamada Y, Yoshioka M, et al. Morphological alteration of gut-associated lymphoid tissue after long-term total parenteral nutrition in rats. Cell Tissue Res. 1991;266:29–36.
28. King BK, Li J, Kudsk KA. A temporal study of TPN-induced changes in gut-associated lymphoid tissue and mucosal immunity. Arch Surg. 1997;132:1303–9.
29. Fukatsu K, Zarzaur B, Johnson C, et al. MAdCAM-1 expression in Peyer's patches: a mechanism controlling the gut-associated lymphoid tissue (GALT). Surg Forum. 2000;51:211–4.
30. King BK, Kudsk KA, Li J, Wu Y, Renegar KB. Route and type of nutrition influence mucosal immunity to bacterial pneumonia. Ann Surg. 1999;229:272–8.
31. Moore EE, Moore FA, Franciose RJ, Kim FJ, Biffl WL, Banerjee A. The postischemic gut serves as a priming bed for circulating neutrophils that provoke multiple organ failure. J Trauma. 1994;37:881–7.
32. Windsor ACJ, Kanwar S, Li AGK, Barnes E, Guthrie JA, Spark JI, et al. Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. Gut. 1998;42:431–5.
33. Lewis SJ, Egger M, Sylvester PA, et al. Early enteral feeding versus "nil by mouth" after gastrointestinal surgery: systematic review and meta-analysis of controlled studies, Br Med J. 2001;323:1-5.323:1–5.
34. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P, Canadian Critical Care Clinical Practice Guidelines Committee. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. JPEN J Parenter Enteral Nutr. 2003;27:355–73.
35. Braunschweig CL, Levy P, Sheean PM, Wang X. Enteral compared with parenteral nutrition: a meta-analysis. Am J Clin Nutr. 2001;74:534–42.
36. Simpson F, Doig GS. Parenteral vs. enteral nutrition in the critically ill patient: a meta-analysis of trials using the intention to treat principle. Intensive Care Med. 2005;31:12–23.
37. Gramlich L, Kichian K, Pinilla J, Rodych NJ, Dhaliwal R, Heyland DK. Does enteral nutrition compared to parenteral nutrition result in better outcomes in critically ill adult patients? A systematic review of the literature. Nutrition. 2004;20:843–8.
38. Moore FA, Feliciano DV, Andrassy RJ, McArdle AH, Booth FV, Morgenstein-Wagner TB, et al. Early enteral feeding, compared with parenteral, reduces postoperative septic complications: the results of a meta-analysis. Ann Surg. 1992;216:172–83.
39. Peter JV, Moran JL, Phillips-Hughes J. A metaanalysis of treatment outcomes of early enteral versus early parenteral nutrition in hospitalized patients. Crit Care Med. 2005;33:213–20.
40. Elke G, Kuhnt E, Ragaller M, Schädler D, Frerichs I, Brunkhorst FM, et al. Enteral nutrition is associated with improved outcome in patients with severe sepsis. A secondary analysis of the VISEP trial. Med Klin Intensivmed Notfmed. 2013;108(3):223–33.
41. Arabi YM, Tamim HM, Dhar GS, Al-Dawood A, Al-Sultan M, Sakkijha MH, et al. Permissive underfeeding and intensive insulin therapy in critically ill patients: a randomized controlled trial. Am J Clin Nutr. 2011;93:569–77.
42. Rice TW, Mogan S, Hays MA, Bernard GR, Jensen GL, Wheeler AP. Randomized trial of initial trophic versus full-energy enteral nutrition in mechanically ventilated patients with acute respiratory failure. Crit Care Med. 2011;39:967–74.

43. Rice TW, Wheeler AP, Thompson BT, Steingrub J, Hite RD, Moss M, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. JAMA. 2012;307(8):795–803. Apr;108(3):223–33.
44. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41(2):580–637.
45. Elke G, Heyland DK. Enteral nutrition in critically ill septic patients – less or more? JPEN J Parenter Enteral Nutr. 2015;39(2):140–2.
46. de Haan JJ, Thuijls G, Lubbers T, Hadfoune M, Reisinger K, Heineman E, et al. Protection against early intestinal compromise by lipid-rich enteral nutrition through cholecystokinin receptors. Crit Care Med. 2010;38(7): 1592–7.
47. de Haan JJ, Lubbers T, Hadfoune M, Luyer MD, Dejong CH, Buurman WA, et al. Postshock intervention with high-lipid enteral nutrition reduces inflammation and tissue damage. Ann Surg. 2008;248(5):842–8.
48. Lubbers T, de Haan JJ, Luyer MD, Verbaeys I, Hadfoune M, Dejong CH, et al. Cholecystokinin/Cholecystokinin-1 receptor-mediated peripheral activation of the afferent vagus by enteral nutrients attenuates inflammation in rats. Ann Surg. 2010;252(2):376–82.
49. de Haan JJ, Pastille E, Wirsdörfer F, Lubbers T, Greve JW, Zhang Y, et al. Lipid-rich enteral nutrition improves the defense against an opportunistic infection during polymicrobial sepsis. Shock. 2014;41(2):109–14.
50. Wen H, Hogaboam CM, Gauldie J, Kunkel SL. Severe sepsis exacerbates cell-mediated immunity in the lung due to an altered dendritic cell cytokine profile. Am J Pathol. 2006;168(6):1940–50.
51. Lubbers T, Kox M, de Haan JJ, Greve JW, Pompe JC, Ramakers BP, et al. Continuous administration of enteral lipid- and protein-rich nutrition limits inflammation in a human endotoxemia model. Crit Care Med. 2013;41(5):1258–65.
52. Heyland DK, Novak F, Drover JW, Jain M, Su X, Suchner U. Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. JAMA. 2001;286(8):944–53.
53. Montejo JC, Zarazaga A, López-Martínez J, Urrútia G, Roqué M, Blesa AL, et al. Immunonutrition in the intensive care unit. A systematic review and consensus statement. Clin Nutr. 2003;22(3):221–33.
54. Marik PE, Zaloga GP. Immunonutrition in critically ill patients: a systematic review and analysis of the literature. Intensive Care Med. 2008;34(11):1980–90.
55. Gadek JE, DeMichele SJ, Karlstad MD, Pacht ER, Donahoe M, Albertson TE, et al. Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with acute respiratory distress syndrome. Enteral Nutrition in ARDS Study Group. Crit Care Med. 1999;27(8):1409–20.
56. Pontes-Arruda A, Aragão AM, Albuquerque JD. Effects of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in mechanically ventilated patients with severe sepsis and septic shock. Crit Care Med. 2006;34(9):2325–33.
57. Singer P, Theilla M, Fisher H, Gibstein L, Grozovski E, Cohen J. Benefit of an enteral diet enriched with eicosapentaenoic acid and gamma-linolenic acid in ventilated patients with acute lung injury. Crit Care Med. 2006;34(4):1033–8.
58. Cangelosi MJ, Auerbach HR, Cohen JT. A clinical and economic evaluation of enteral nutrition. Curr Med Res Opin. 2011;27(2):413–22.
59. Koretz RL, Lipman TO, Klein S, American Gastroenterological Association. AGA technical review on parenteral nutrition. Gastroenterology. 2001;121(4):970–1001.
60. Ippolito P, Larson EL, Furuya EY, Liu J, Seres DS. Utility of electronic medical records to assess the relationship between parenteral nutrition and central line-associated bloodstream infections in adult hospitalized patients. JPEN J Parenter Enteral Nutr. 2014. [Epub ahead of print].
61. Yang SP, Chen YY, Hsu HS, Wang FD, Chen LY, Fung CP. A risk factor analysis of healthcare-associated fungal infections in an intensive care unit: a retrospective cohort study. BMC Infect Dis. 2013;13:10.
62. Pronovost P, Needham D, Berenholtz S, Sinopoli D, Chu H, Cosgrove S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med. 2006;355(26):2725–32.
63. O'Connor A, Hanly AM, Francis E, Keane N, McNamara DA. Catheter associated blood stream infections in patients receiving parenteral nutrition: a prospective study of 850 patients. J Clin Med Res. 2013;5(1):18–21.
64. Dimick JB, Swoboda S, Talamini MA, Pelz RK, Hendrix CW, Lipsett PA. Risk of colonization of central venous catheters: catheters for total parenteral nutrition vs other catheters. Am J Crit Care. 2003;12(4):328–35.
65. Doig GS, Simpson F, Sweetman EA, Finfer SR, Cooper DJ, Heighes PT, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. JAMA. 2013;309(20):2130–8.
66. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med. 2011;365(6):506–17.
67. Kutsogiannis J, Alberda C, Gramlich L, Cahill NE, Wang M, Day AG, et al. Early use of supplemental parenteral nutrition in critically ill patients: results of an international multicenter observational study. Crit Care Med. 2011;39(12):2691–9.

68. Hayashi N, Tashiro T, Yamamori H, Takagi K, Morishima Y, Otsubo Y, et al. Effects of intravenous omega-3 and omega-6 fat emulsion on cytokine production and delayed type hypersensitivity in burned rats receiving total parenteral nutrition. JPEN J Parenter Enteral Nutr. 1998;22(6):363–7.
69. Melly MA, Meng HC, Schaffner W. Microbiol growth in lipid emulsions used in parenteral nutrition. Arch Surg. 1975;110(12):1479–81.
70. Gilbert M, Gallagher SC, Eads M, Elmore MF. Microbial growth patterns in a total parenteral nutrition formulation containing lipid emulsion. JPEN J Parenter Enteral Nutr. 1986;10(5):494–7.
71. Freeman J, Goldmann DA, Smith NE, Sidebottom DG, Epstein MF, Platt R. Association of intravenous lipid emulsion and coagulase-negative staphylococcal bacteremia in neonatal intensive care units. N Engl J Med. 1990;323(5):301–8.
72. Avila-Figueroa C, Goldmann DA, Richardson DK, Gray JE, Ferrari A, Freeman J. Intravenous lipid emulsions are the major determinant of coagulase-negative staphylococcal bacteremia in very low birth weight newborns. Pediatr Infect Dis J. 1998;17(1):10–7.
73. Pontes-Arruda A, Liu FX, Turpin RS, Mercaldi CJ, Hise M, Zaloga G. Bloodstream infections in patients receiving manufactured parenteral nutrition with vs without lipids: is the use of lipids really deleterious? JPEN J Parenter Enteral Nutr. 2012;36(4):421–30.
74. Yeh SL, Chang KY, Huang PC, Chen WJ. Effects of n-3 and n-6 fatty acids on plasma eicosanoids and liver antioxidant enzymes in rats receiving total parenteral nutrition. Nutrition. 1997;13(1):32–6.
75. Heller AR, Rössler S, Litz RJ, Stehr SN, Heller SC, Koch R, et al. Omega-3 fatty acids improve the diagnosis-related clinical outcome. Crit Care Med. 2006;34(4):972–9.83.
76. Gultekin G, Sahin H, Inanc N, Uyanik F, Ok E. Impact of Omega-3 and Omega-9 fatty acids enriched total parenteral nutrition on blood chemistry and inflammatory markers in septic patients. Pak J Med Sci. 2014;30(2): 299–304.
77. Pradelli L, Mayer K, Muscaritoli M, Heller AR. n-3 fatty acid-enriched parenteral nutrition regimens in elective surgical and ICU patients: a meta-analysis. Crit Care. 2012;16(5):R184.
78. Clinicaltrials.gov. A service of the US National Institutes of Health. Search of: omegaven. http://clinicaltrials.gov/ct2/results?term=omegaven. Accessed 21 Jul 2014.
79. Turpin RS, Canada T, Rosenthal V, Nitzki-George D, Liu FX, Mercaldi CJ, et al. Bloodstream infections associated with parenteral nutrition preparation methods in the United States: a retrospective, large database analysis. JPEN J Parenter Enteral Nutr. 2012;36(2):169–76.
80. Please provide details for reference [80]
81. Buchman AL, Moukarzel A, Goodson B, Herzog F, Pollack P, Reyen L, et al. Catheter-related infections associated with home parenteral nutrition and predictive factors for the need for catheter removal in their treatment. JPEN J Parenter Enteral Nutr. 1994;18(4):297–302.
82. Gillanders L, Angstmann K, Ball P, O'Callaghan M, Thomson A, Wong T, et al. A prospective study of catheter-related complications in HPN patients. Clin Nutr. 2012;31:30–4.
83. Reimund JM, Arondel Y, Finck G, Zimmermann F, Duclos B, Baumann R. Catheter-related infection in patients on home parenteral nutrition: results of a prospective survey. Clin Nutr. 2002;21:33–8.
84. Cotogni P, Pittiruti M, Barbero C, Monge T, Palmo A, Boggio Bertinet D. Catheter-related complications in cancer patients on home parenteral nutrition: a prospective study of over 51,000 catheter days. JPEN J Parenter Enteral Nutr. 2013;37(3):375–8.
85. Buchman AL, Opilla M, Kwasny M, Diamantidis TG, Okamoto R. Risk factors for the development of catheter-related bloodstream infections in patients receiving home parenteral nutrition. JPEN J Parenter Enteral Nutr. 2013;38(6):744–9.
86. Maki DG, Kluger DM, Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. Mayo Clin Proc. 2006;81(9):1159–71.
87. Touré A, Duchamp A, Peraldi C, Barnoud D, Lauverjat M, Gelas P, Chambrier C. A comparative study of peripherally-inserted and Broviac catheter complications in home parenteral nutrition patients. Clin Nutr. 2014;pii: S0261–5614(13)00340–3.
88. Pittiruti M, Hamilton H, Biffi R, MacFie J, Pertkiewicz M. ESPEN guidelines on parenteral nutrition: central venous catheters(access, care, diagnosis and therapy of complications). Clin Nutr. 2009;28:365e77.
89. Timsit J-F, Schwebel C, Bouadma L, Geffroy A, Garrouste-Orgeas M, Pease S, et al. Chlorhexidine-impregnated sponges and less frequent dressing changes for prevention of catheter-related infections in critically ill adults. JAMA. 2009;301:1231–41.
90. Camargo LF, Marra AR, Büchele GL, Sogayar AM, Cal RG, de Sousa JM, et al. Double-lumen central venous catheters impregnated with chlorhexidine and silver sulfadiazine to prevent catheter colonisation in the intensive care unit setting: a prospective randomised study. J Hosp Infect. 2009;72:227–33.
91. Toure A, Lauverjat M, Peraldi C, Boncompain-Gerard M, Gelas P, Barnoud D, et al. Taurolidine lock solution in the secondary prevention of central venous catheter-associated bloodstream infection in home parenteral nutrition patients. Clin Nutr. 2012;31(4):567–70.

92. Opilla MT, Kirby DF, Edmond MB. Use of ethanol locks therapy to reduce the incidence of catheter-related bloodstream infections in home parenteral nutrition patients. JPEN J Parenter Enteral Nutr. 2007;31:302–5.
93. Jones BA, Hull MA, Richardson DS, Zurakowski D, Gura K, Fitzgibbons SC, et al. Efficacy of ethanol locks in reducing central venous catheter infections in pediatric patients with intestinal failure. J Pediatr Surg. 2010;45:1287–93.
94. Jackson NC, Carroll PV, Russell-Jones DL, Sönksen PH, Treacher DF, Umpleby AM. The metabolic consequences of critical illness: acute effects on glutamine and protein metabolism. Am J Physiol. 1999;276(1 Pt 1):E163–70.
95. Bongers T, Griffiths RD, McArdle A. Exogenous glutamine: the clinical evidence. Crit Care Med. 2007;35(9 Suppl):S545–52.
96. Novak F, Heyland DK, Avenell A, Drover JW, Su X. Glutamine supplementation in serious illness: a systematic review of the evidence. Crit Care Med. 2002;30(9):2022–9.
97. Andrews PJ, Avenell A, Noble DW, Campbell MK, Croal BL, Simpson WG, et al. Randomised trial of glutamine, selenium, or both, to supplement parenteral nutrition for critically ill patients. BMJ. 2011;342:d1542.
98. Heyland D, Muscedere J, Wischmeyer PE, Cook D, Jones G, Albert M, et al. A randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med. 2013;368(16):1489–97.
99. Daly JM, Reynolds J, Thom A, Kinsley L, Dietrick-Gallagher M, Shou J, et al. Immune and metabolic effects of arginine in the surgical patient. Ann Surg. 1988;208(4):512–23.
100. Agay D, Sandre C, Ducros V, Faure H, Cruz C, Alonso A, et al. Optimization of selenium status by a single intraperitoneal injection of Se in Se deficient rat: possible application to burned patient treatment. Free Radic Biol Med. 2005;39:762–8.
101. Angstwurm MW, Schottdorf J, Schopohl J, Gaertner R. Selenium replacement in patients with severe systemic inflammatory response syndrome improves clinical outcome. Crit Care Med. 1999;27(9):1807–13.
102. Angstwurm MW, Engelmann L, Zimmermann T, Lehmann C, Spes CH, Abel P, et al. Selenium in Intensive Care (SIC): results of a prospective randomized, placebo-controlled, multiple-center study in patients with severe systemic inflammatory response syndrome, sepsis, and septic shock. Crit Care Med. 2007;35(1):118–26.
103. Manzanares W, Biestro A, Torre MH, Galusso F, Facchin G, Hardy G. High-dose selenium reduces ventilator-associated pneumonia and illness severity in critically ill patients with systemic inflammation. Intensive Care Med. 2011;37(7):1120–7.
104. Forceville X, Laviolle B, Annane D, Vitoux D, Bleichner G, Korach JM, et al. Effects of high doses of selenium, as sodium selenite, in septic shock: a placebo-controlled, randomized, double-blind, phase II study. Crit Care. 2007;11(4):R73.
105. Singer P, Berger MM, Van den Berghe G, Biolo G, Calder P, Forbes A, et al. ESPEN guidelines on parenteral nutrition: intensive care. Clin Nutr. 2009;28(4):387–400.
106. Hardy G, Hardy I, Manzanares W. Selenium supplementation in the critically ill. Nutr Clin Pract. 2012;27(1):21–33.
107. Rayman MP. Selenium and human health. Lancet. 2012;379(9822):1256–68.
108. Lee P, Eisman JA, Center JR. Vitamin D deficiency in critically ill patients. N Engl J Med. 2009;360(18):1912–4.
109. Nathens AB, Neff MJ, Jurkovich GJ, Klotz P, Farver K, Ruzinski JT, et al. Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients. Ann Surg. 2002;236(6):814–22.