Parenteral Nutrition and Sepsis

Subjects: Medicine, General & Internal

Contributor: Antonio Tota, Amato Serra, Pauline Raoul, Antonio Gasbarrini, Emanuele Rinninella, Maria Cristina Mele

Parenteral nutrition (PN) is recommended in malnourished patients or those at risk of malnutrition in some conditions—such as gut functional unavailability or gut physical inaccessibility. The lipids are sepsis risk factors in patients receiving parenteral nutrition.

Keywords: clinical practice ; fatty acids ; infectious complications ; lipids ; parenteral nutrition ; sepsis

1. Introduction

Parenteral nutrition (PN) is the means by which nutrients are provided intravenously. It can be administered via a catheter with the tip located in a central vein—central PN—or via a cannula inserted into a peripheral vein—peripheral PN—depending on the osmolarity of the mixture. For patients for whom central catheterization is impossible, PN can also be administered via an arteriovenous shunt.

PN is recommended in malnourished patients or those at risk of malnutrition in some conditions—such as gut functional unavailability or gut physical inaccessibility [1]. Central PN may be associated with catheter-related bloodstream infections (CRBSIs). Indeed, an intravenous line can be colonized by bacteria or fungi, potentially seeding into the bloodstream. CRBSIs are associated with high morbidity and mortality [2]. Multiple mechanisms are known to increase the risk of infectious complications in patients receiving central or peripheral PN: poor central venous catheter care, contamination of the cannula and the cannula wound, infusate contamination, or colonization of other parts of the PN system by some varieties of microorganisms (bacteria and fungi) such as *Candida albicans* (*C. Albicans*). Enteral starvation may concur to increase this risk due to an impairment of the gut barrier and bacterial translocation [3]. Among many clinicians, there is a concern that adding lipid emulsions to PN could cause fungal infections [4]. This concern has spread across the decades among clinicians as a dogma. Hence, some of them still now exclude lipids emulsions (LEs) regardless of the nutritional status of patients.

2. Parenteral Nutrition and Sepsis

2.1. Generalities on Sepsis

Sepsis is a potentially life-threatening condition characterized by organ dysfunction caused by a dysregulated host response to infection. Septic shock is a complication of sepsis with circulatory and cellular/metabolic dysfunction, and thus is associated with higher mortality risk. Sepsis is associated with increased morbidity and mortality [2] and is considered a significant healthcare problem, affecting millions of people worldwide each year. This condition has a mortality risk ranging from moderate (e.g., 10%) to substantial (e.g., >40%) depending on the etiologic agent, biological characteristics of the host, the timeliness of recognition, and provision of adequate therapy [5]. Concerning its pathophysiology, sepsis occurs when the response to an infection causes the release of proinflammatory molecules, the so-called cytokine storm, that exceeds the boundaries of the local environment, leading to a more systemic reaction [6]. Most cases of sepsis are triggered by hospital-acquired Gram-negative bacilli or Gram-positive cocci and often occur in immunocompromised patients or patients affected by chronic diseases. Infrequently, it is caused by *Candida* or other fungi. Current therapies consist of adequate antibiotics/antifungal agents targeting the underlying infection, fluid repletion to improve stroke volume, vasopressors if needed in refractory hypotension, and high-quality supportive care [7].

Sepsis can be a complication of parenteral nutrition, as a consequence of phlebitis, the most common complication of peripheral parenteral nutrition, or as a complication of central venous catheters (CVCs) used for central parenteral nutrition. Usually, people refer to the septic complications of intravascular catheters with the term CRBSI. Bacteria or fungi can colonize a catheter, and when they grow significantly, they seed the systemic circulation causing clinical signs of infection to become apparent. These signs cover a broad spectrum from subfebrile status up to symptoms of MOF and

septic shock. It has also been hypothesized that TPN, by-passing the intestinal tract, causes mucosal gut atrophy and dysbiosis, and increases bacterial translocation thus promoting sepsis [8].

2.2. Parenteral Nutrition and Infectious Complications: A « Liaison Dangereuse »

The concept of peripheral parenteral nutrition (PPN) was first depicted by Brunschwig, in 1945. Together with his colleagues, he fed a patient suffering from multiple enteral fistulas, for eight weeks, using a protein hydrolysate and a 10% dextrose solution. Later, in the 1950s and 1960s, an amino acid solution and lipid emulsion were first introduced, respectively [9][10].

In the early days of PN in the United States, glucose and amino acids solutions with all other nutrient components were mixed, initially by the physicians and/or nurses, in 1-L glass bottles; then, a short time later, by pharmacists in more extensive (1–2 l) glass bottles and eventually in PVC bags. Fat emulsions, when given, were infused separately through Y-connectors, and this method was later called “2 + 1” [11].

On the other hand, in Europe, a multiple (double or triple) bottle (MB) system was used, in which amino acid, glucose, and lipids were administered in parallel or sequence using multiple different bottles. It was common at that time to change the bottle with the preparation for PN up to 6–8 times a day, to make many other additions, and numerous peripheral vein punctures, thus increasing the risk of solution administration errors, hyperglycemia, electrolyte disorders, and infectious complications.

Nowadays, the All-in-One (AIO, 3-in-1) system incorporates all the elements of PN mixed in one container [12]. This system has many advantages, among which is a reduced risk of contamination of the infusion system by multiple manipulations and interventions. Furthermore, due to fewer connections and bottle changes, the use of a closed system, the rate of sepsis is decreased [13].

Since its birth, PN has been related to the possibility of metabolic, mechanical, and infectious complications. PN is often considered an ideal microbial growth medium, since its slow administration at room temperature permits microbes to proliferate and cause adverse effects [14].

The risk of infectious complications in patients receiving PN is related to multiple mechanisms: central venous catheter care, contamination at different levels (cannula, infusate, other parts of the PN system), and cannula wound infection. This results in various microorganisms (bacteria and fungi) potentially associated with infectious complications

Multiple approaches prevent PN’s inadvertent microbial contamination and limit microbial growth, including PN preparation with an aseptic technique and reducing the times of bag changes [15].

In addition, the Healthcare Infection Control Practices Advisory Committee (HICPAC) hypothesized that lipid addition in PN constitutes a specific risk for microbial growth [16], recommending that administration sets linked to lipid-containing PN (or lipid emulsion) should be changed within 24 h after infusion beginning or up to 48 h for lipid-free PN. This recommendation was supported by the Cochrane Collaboration and the UK Epic Project after finding no evidence to challenge them [17].

The European Society for Clinical Nutrition and Metabolism (ESPEN) also considers lipid PN as an infection risk factor if administration sets are used beyond 24 h [18].

These recommendations have been applied in clinical practice by restricting the administration of lipid PN from a single bag to no more than 24 h, even in favorable conditions, such as when starting PN or weaning from PN, when it might have been infused over more prolonged periods [1].

Recommendations reported above are supported by evidence derived from a few studies, of variable quality, which sometimes did not compare lipid and lipid-free PN, sometimes reporting contradictory results and giving little or no regard to confounding variables or methodologies used. Furthermore, other recommendations are based on expert opinion alone.

Major clinical nutrition societies never stated that administering PN without the lipidic component could reduce the rate of infectious complications related to PN [19].

Contrariwise, in the standard clinical practice, many clinicians prefer administering the PN solution without the lipidic component, especially in septic patients, those at risk of infectious complications, or even those without particular risk

factors. This practice is supported by the belief, not validated by any scientific evidence, that the lipid component of PN increases the rate of infectious complications and sepsis above all [14].

3. Lipids in Parenteral Nutrition: Biochemistry and Properties

Lipids are essential energy substrates and are the primary energy stored in our body. Moreover, phospholipids are crucial structural components of cell membranes, including the plasma membrane, vacuoles, and other organelles; fatty acids (FA) may affect cell functions and are precursors of eicosanoid synthesis, while cholesterol is a precursor for steroid hormones' synthesis. In addition, lipids alter transcription factor activity, eicosanoids metabolism, cytokines production, and gene expression [20].

LEs provide high amounts of fuel calories and essential fatty acids, which are key components of PN regimens. Lipid intake should cover 20 to 40% of energy needs, depending on individual tolerance and clinical situation. In some patients, especially those with acute respiratory failure, in the presence of fat emulsion tolerance, up to 50% of total energy can be administered as a lipid emulsion to help maintain a usual respiratory quotient.

Intravenous lipid emulsions (IVLE) have been developed on the model of the intestinal chylomicron, with triglycerides and lipid-soluble vitamins in the core of the molecule and phospholipids, free cholesterol, and other lipid-soluble vitamins on the surface [21]. However, exogenous emulsion particles essentially differ from endogenous lipoproteins. For example, no apoproteins (apo B-48 and apo A-1) nor esterified cholesterol are contained in exogenous emulsions. The composition of their component, such as the FA pattern, differs from that of endogenous counterparts. Nonetheless, emulsion particles rapidly acquire exchangeable apoproteins (C-I, C-II, C-III, E, A-IV). At the same time, they are delivered to the bloodstream, following the same intravascular metabolic pathways of chylomicrons.

Significant differences exist between Europe and the USA regarding the use of IVLE. In the USA, the first lipid emulsions, mainly derived from cottonseed oils, were associated with side effects, so their use was limited until 1977, also explaining the low lipid content in their preparation for enteral nutrition.

Conversely, in Europe, Wretlind et al. developed a lipid emulsion based on soybean oil emulsified with egg phosphatides that was clinically well tolerated and has been widely used, not only to prevent a deficiency of essential FAs but also to supply significant energy intake (from 30 to 40% of infused calories) even in stressed patients with insulin resistance.

These "first generation" LEs contain a much higher proportion of (mainly ω-6) polyunsaturated FAs, such as linoleic acid and alfa-linolenic acid, but a relatively low amount of antioxidants such as alfa-tocopherol. Their disadvantage is that they can enhance the production of pro-inflammatory prostaglandins, leukotrienes, and thromboxanes and stimulate proinflammatory cytokine release, thus leading to inflammation [22].

In the last two decades, these unfavorable effects led to the development of the so-called "second generation" LEs. They contain a mixture of medium and long-chain triglycerides (MCT/LCT) instead of only LCT containing LEs. Medium-chain triglycerides, derived from coconut or palm kernel oil, have better solubility and are more readily hydrolyzed by lipases and more quickly taken up by peripheral tissues than LCT. Other "second generation" lipid emulsions are made of so-called "structured triglycerides," phased out in most countries, or olive oil/soybean oil, composed of 80% olive oil and 20% soybean oil. Olive oil contains fewer ω-6 FAs and a good amount of oleic acid (mono-unsaturated ω-9 FA), which is not a precursor for pro-inflammatory prostaglandin synthesis [23]. Compared to MCT/LCT IVLEs, an international, multicenter, prospective, randomized, open-label trial by Pontes-Arruda et al. found no difference in catheter-related bloodstream infections (CRBSI) rates between patients receiving an olive oil-based IVLE versus those receiving an MCT/LCT based IVLE (25 vs. 21, respectively; $p = 0.62$) [24].

References

1. Pironi, L.; Boeykens, K.; Bozzetti, F.; Joly, F.; Klek, S.; Lal, S.; Lichota, M.; Mühlebach, S.; Van Gossum, A.; Wanten, G.; et al. ESPEN guideline on home parenteral nutrition. Clin. Nutr. 2020, 6, 1645–1666.
2. Taeb, A.M.; Hooper, M.H.; Marik, P.E. Sepsis: Current Definition, Pathophysiology, Diagnosis, and Management. Nutr. Clin. Pract. Off. Publ. Am. Soc. Parenter. Enter. Nutr. 2017, 6, 296–308.
3. Rinninella, E.; Annetta, M.G.; Serricchio, M.L.; Dal Lago, A.A.; Miggiano, G.A.; Mele, M.C. Nutritional support in acute pancreatitis: From physiopathology to practice. An evidence-based approach. Eur. Rev. Med. Pharmacol. Sci. 2017, 2, 421–432.

4. Seymour, C.W.; Liu, V.X.; Iwashyna, T.J.; Brunkhorst, F.M.; Rea, T.H. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016, 2, 762–774.
5. Singer, M.; Deutschman, C.S.; Seymour, C.W.; Shankar-Hari, M.; Annane, D.; Bauer, M.; Bellomo, R.; Bernard, G.R.; Chiche, J.D.; Coopersmith, C.M.; et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016, 2, 801–810.
6. Bosmann, M.; Ward, P.A. The inflammatory response in sepsis. Trends Immunol. 2013, 3, 129–136.
7. Spampinato, C.; Leonardi, D. Candida infections, causes, targets, and resistance mechanisms: Traditional and alternative antifungal agents. Biomed. Res. Int. 2013, 2013, 204237.
8. Jeejeebhoy, K.N. Total Parenteral Nutrition: Potion or Poison? Am. J. Clin. Nutr. 2001, 2, 160–163.
9. Dudrick, S.J. History of Vascular Access. JPEN 2006, 1, 47–56.
10. Messing, B.; Matuchansky, C. Techniques for the Provision of Parenteral Nutrition. Eur. J. Gastroenterol. Hepatol. 1995, 6, 507–513.
11. Dudrick, S.J.; Wilmore, D.W.; Vars, H.M.; Rhoads, J.E. Can Intravenous Feeding as the Sole Means of Nutrition Support Growth in the Child and Restore Weight Loss in an Adult? An Affirmative Answer. Ann. Surg. 1969, 6, 974–984.
12. Solassol, C.; Joyeux, H.; Etco, L.; Pujol, H.; Romieu, C. New Techniques for Long-Term Intravenous Feeding: An Artificial Gut in 75, Patients. Ann. Surg. 1974, 4, 519–522.
13. Didier, M.E.; Fischer, S.; Maki, D.G. Total Nutrient Admixtures Appear Safer than Lipid Emulsion Alone as Regards Microbial Contamination: Growth Properties of Microbial Pathogens at Room Temperature. JPEN 1998, 5, 291–296.
14. Austin, P.D.; Hand, K.S.; Elia, M. Systematic Review and Meta-Analyses of the Effect of Lipid Emulsion on Microbial Growth in Parenteral Nutrition. J. Hosp. Infect. 2016, 4, 307–319.
15. Kuwahara, T.; Kaneda, S.; Shimono, K.; Inoue, Y. Effects of lipid emulsions and multivitamins on the growth of microorganisms in peripheral parenteral nutrition solutions. Int. J. Med. Sci. 2013, 10, 1079–1084.
16. O'Grady, N.P.; Alexander, M.; Burns, L.A.; Dellinger, E.P.; Garland, J.; Heard, S.O.; Lipsett, P.A.; Masur, H.; Mermel, L.A.; Pearson, M.L.; et al. Guidelines for the Prevention of Intravascular Catheter-Related Infections. Clin. Infect. Dis. 2011, 9, 162–193.
17. Ullman, A.J.; Cooke, M.L.; Gillies, D.; Marsh, N.M.; Daud, A.; McGrail, M.R.; O'Riordan, E.; Rickard, C.M. Optimal Timing for Intravascular Administration Set Replacement. Cochrane Database Syst. Rev. 2013, 9, CD003588.
18. Pittiruti, M.; Hamilton, H.; Biffi, R.; MacFie, J.; Pertkieqicz, M. ESPEN Guidelines on Parenteral Nutrition: Central Venous Catheters (Access, Care, Diagnosis and Therapy of Complications). Clin. Nutr. 2009, 4, 365–377.
19. Sriram, K.; Meguid, M.M. Addition of lipids to parenteral nutrition does not cause fungal infections. Nutrition 2015, 31, 1443–1446.
20. Calder, P.C. Marine Omega-3 Fatty Acids and Inflammatory Processes: Effects, Mechanisms and Clinical Relevance. Biochim. Biophys. Acta 2015, 4, 469–484.
21. Dupont, I.E.; Carpentier, Y.A. Clinical Use of Lipid Emulsions. Curr. Opin. Clin. Nutr. Metab. Care 1999, 2, 139–145.
22. Chen, B.; Zhou, Y.; Yang, P.; Wan, H.; Wu, X. Safety and Efficacy of Fish Oil-Enriched Parenteral Nutrition Regimen on Postoperative Patients Undergoing Major Abdominal Surgery: A Meta-Analysis of Randomized Controlled Trials. JPEN 2010, 4, 387–394.
23. Webb, A.N.; Hardy, P.; Peterkin, M.; Lee, O.; Shalley, H.; Croft, K.D.; Mori, T.A.; Heine, R.G.; Bines, J.E. Tolerability and Safety of Olive Oil-Based Lipid Emulsion in Critically Ill Neonates: A Blinded Randomized Trial. Nutrition 2008, 24, 1057–1064.
24. Pontes-Arruda, A.; Dos Santos, M.C.F.C.; Martins, L.F.; Gonzàlez, E.R.R.; Kliger, R.G.; Maia, M.; Magnan, G.B.; EPICOS Study Group. Influence of Parenteral Nutrition Delivery System on the Development of Bloodstream Infections in Critically Ill Patients: An International, Multicenter, Prospective, Open-Label, Controlled Study--EPICOS Study. JPEN 2012, 5, 574–586.