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Fungal Contamination in Lipid Emulsions of Parenteral Nutrition: A Review

Shalahuddin Al Madury [a,1*], Ana Maulida Septiani [a,2], Dwi Pujilestari [a,3], Monia Agni Wiyatami [a,4]

[a] Master Program of Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia
[1] shalahuddinalmadury@gmail.com *; [2] anamaulidasep@gmail.com ; [3] dwipuji.2007@gmail.com ; [4] moniaagniwiyatami@gmail.com

* corresponding author

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ABSTRAK

Introduction: Lipid emulsions in parenteral nutrition (PN) are commonly associated with fungal infections and an unexplained risk factor for the development of candidemia, which is a major cause of morbidity and mortality in hospitalized patients. Candida species are the most common fungal agents in patients receiving PN. Candida albicans commonly create biofilm on prosthetic materials as they were found on the surfaces of immanent medical catheters. The aim of this review was to evaluate fungal contamination in lipid emulsion of parenteral nutrition. **Method:** The databases used for this review were Google Scholar, JAMA, PubMed and ScienceDirect library. The inclusion criteria were covering any literature published from December 2006 - Desember 2021. **Conclusion:** Overall lipid emulsion infusion for longer periods of time can cause fungal contamination. Therefore, the recommended administration for lipid emulsion needs to be replaced within 24 hours after the infusion commencement. However, another study suggested that lipid emulsions did not increase the risk of fungal infection in patients receiving parenteral lipid emulsions.

1. Introduction

Intravenous fat emulsion (IVFE) has been used as a nutrition support for more than 50 years. The parenteral nutrition (PN) formulations are combined to achieve the required nutrient of each patient, consisting of sufficient energy supply and proper amount of protein, carbohydrates, fat, fluid, electrolytes, vitamins, and trace elements (Mirtallo *et al*., 2010). IVFE is a pivotal source of calories and fatty acids for patients who receive PN. Intravenous lipid emulsions (IVLE) have limited hang time due to the risk of infection. Lipid emulsions are associated with contamination, which can be induced by candida. Candida albicans commonly create biofilm on prosthetic materials as they were found on the surfaces of immanent medical catheters removed from patients (Jawa *et al*, 2019; Swindell *et al*, 2009).

Injectable lipid emulsions (ILEs) can be the source of energy for neonates admitted in NICUs. Aseptic environmental conditions and trained staff are required in combining the parenteral nutrition, either manually or using automated devices. Microbial contamination of lipid emulsions may occur at different stages of ILE manipulation. Replacing ILEs from the original bottles into

smaller-volume syringes may become a portal of microbial entry. Hands of healthcare workers may also contain microbial contamination, including the hands of pharmacists who prepare an ILE, and the nurses who administer it. Therefore, all manipulations of ILE should always follow the strict aseptic conditions in order to prevent infections in neonates, such as bacteremia and septicemia (Omran *et al*., 2020). Bacterial contamination is a crucial safety issue in lipid emulsions because the isosmotic and nutritional values of lipid emulsion can be an ideal environment for bacteria to grow (Bae *et al*., 2018). The aim of this review was to evaluate fungal contamination in lipid emulsion of parenteral nutrition.

2. Method

Google scholar, JAMA, PubMed and science direct databases were employed in order to collect the data. The keywords used were including parenteral nutrition, fungal contamination, lipid emulsions. The inclusion criteria were covering any literature published from December 2006 - Desember 2021.

3. Result and Discussion

3.1. Lipid in parenteral nutrition

Parenteral nutrition (PN) consists of a complex mixture of macronutrients (carbohydrates, proteins, lipids), micronutrients (vitamins, minerals, trace elements), fluid and electrolytes. Carbohydrates are supplied as dextrose, proteins as amino acids, and lipids as intravenous fat emulsions (IVFEs). All of which are nutritionally vital for those patients with intestinal dysfunction (Schwartz *et al.*, 2009). IVLEs are a source of essential fatty acids, In addition, lipids have multiple physiological roles in the body. Fatty acids form the major constituent of cellular bio-membranes and contribute to regulate permeability, membrane integrity, and are precursors to key modulators involved in cellular pathways of the immune system (Raman *et al.*, 2017). Lipid emulsions in parenteral nutrition are commonly associated with fungal infections and an unexplained risk factor for the development of candidemia, and it may cause the PN administration to be discontinued (Quesada *et al.*, 2017; Swindell *et al.*, 2009).

Candida species are the most common fungal agents in the patients receiving PN. Catheter-associated infections in such patients may result in candidemia, which is a major cause of morbidity and mortality in hospitalized patients (Guducuoglu *et al*., 2016). In a cohort study of fungemia and risk analysis in the Intensive Care Unit (ICU), Candida was reported as the main and only infectious agent, whereas Candida albicans was the most frequent, with a total of 63% of all isolated Candida (Yapar, 2014). The biofilm of Candida albicans develops in 3 phases, namely the early phase where the yeast cells adhere to the surfaces, divide and form a layer of microcolonies, the intermediate phase where the cells produce extracellular material and differentiate into pseudohyphae and hyphae, and the maturation phase where the extracellular material increases and the network of hyphal structures grows in parallel, adding structure to the biofilm (Swindell *et al*., 2009).

Based on study shows that lipid emulsion infusion for longer periods of time can cause either fungal or bacterial contamination. Therefore, the recommended administration sets linked to lipid PN should be replaced within 24 hours after the infusion commencement, and could be delayed for up to 48 hours for lipid-free PN replacement. The European Society for Clinical Nutrition and Metabolism (ESPEN) have also reported lipid PN to be an infection risk if the administration sets were used beyond 24 hours (Austin *et al*., 2016). However, another study concluded that lipid emulsions do not increase risk of fungal infections in patients receiving parenteral nutrition and that restricting lipids in parenteral nutrition because it could be detrimental to the patient's health (Quesada *et al.*, 2017; Sriram and Meguid, 2015).

3.2. Clinical study of fungal growth on lipid emulsion

A study by Kuwahara *et al* (2010) found that Candida species can grow rapidly in almost all Total Parenteral Nutrition (TPN) solutions despite their acidity and presence of lipids. Some

bacterial species that may grow in TPN solutions have lipids unless the pH value is 5.0 or less. Thus, all TPN solutions should be checked thoroughly to determine whether the bacterial species can proliferate. Microscopically, biofilms grown in standard growth media supplemented with emulsified lipids showed an increase in hyphal form in the early and mature phases compared to biofilms grown in standard growth media or biofilms grown in media supplemented with lipid emulsion (LE) without dextrose. These findings may help explain the increased risk of fungemia associated with administering parenteral nutrition including emulsified lipids to patients via medical catheters (Swindell *et al*, 2009).

The ability of Candida albicans and other pathogens to grow in parenteral nutrition formulations is known and considered a risk factor for the development of catheter-associated bloodstream infections in patients receiving parenteral nutrition. With regard to the growth of Candida albicans in parenteral LE, our findings agree with several studies, including those that are clinical guidelines for administration of Lipid Emulsion to patients via medical catheters. However, our findings broaden the understanding of the behavior of Candida albicans in LE by showing that exposure to LE also induces germination. In conclusion, lipid emulsion induced determinants of candidal virulence, such as germination and increased biofilm production, may help explain the increased risk of candidemia in patients receiving LE via a medical catheter (Swindell *et al*, 2009).

A study by Kim et al (2020) found that lipid emulsions induce Candida virulence determinants, such as germination and increased biofilm production, which may help explain the increased risk of candidemia. In a subject whose blood cultures were persistently positive for C. diddensiae while he was receiving TPN lipids. Although the blood isolate had a relatively high fluconazole MIC (8 g/mL), candidaemia disappeared after 3 days of fluconazole and discontinuation of TPN. These findings suggest that lipid emulsions containing TPN may increase the risk of C. diddensiae fungemia by providing a favorable lipid-rich environment for the survival of C. diddensiae in the blood. The use of TPN lipids has the potential to contribute to the development of nosocomial fungemia by C. diddensiae, an unusual Candida species.

According to research by Gouclou *et al* (2016), parenteral nutrition plays an important role in the proliferation of Candida species in patients undergoing it. This is due to the production of biofilms produced by candida species in the human body, which results in fungal proliferation and initiation of primary infection. Parenteral nutrition results in increased production of these biofilms, increasing the likelihood of developing fungal sepsis (Guducuoglu H, *et al*, 2016).

Many studies as mentioned above demonstrated that Candida species could grow rapidly in almost all PN solutions regardless of the presence of lipids. However, another published in vitro study showed that the lipid emulsion in parenteral nutrition has no effect on the growth of Candida albicans. Therefore, recommendations to limit infusion time of lipid-containing PN seem to be arbitrary and should be abandoned (Sriram and Meguid, 2015).

3.3. Candidemia or Fungemia Incidence in Recipients of Parenteral Nutrition

Tropicalis is the fourth most common cause of fungemia in the hospital. Patients with C. tropicalis fungemia were more likely to be older, or have cancer, and to have the abdomen as the portal of entry, and have a higher in-hospital mortality rate (Horn *et al*, 2009). The risk factors of candidemia showed that length of hospitalization, presence of a central venous catheter, previous episodes of candidemia or bacteremia, parenteral nutrition, and chronic renal. failures were variables independently associated with the development of candidemia. The analysis of prognostic indicators showed that the independent variables associated with poor prognosis were inadequate initial therapy and high Acute Physiology, Age, Chronic Health Evaluation (APACHE) III score (Bassetti *et al*., 2007).

According to research by Stratman *et al* (2010), the candidemia frequency is particularly related to the utilization of PN in an institution with strict rules for PN treatment. Identification of patients at high risk for candidemia has been a persistent challenge in healthcare. The Candida Score is a bedside scoring system for non neutropenic critically ill patients used to assess individual patient risk factors and to determine the risk of invasive Candidiasis. The most common candidiasis is

surgery at ICU admission, multifocal colonization, PN, and severe sepsis with a greater risk of proven Candida infection. PN is significantly associated with the development of invasive candidiasis. Patients with a Candida score >2.5 were 7.75 times more likely to develop invasive candidiasis compared to patients with a Candida score <2.5. When the score was applied retrospectively to candidemia risk in the present study, a progressive increase in the incidence of candidemia was noted as the Candida score increased. According to research by Jawa *et al* (2019), Hospitalized patients receiving TPN are at risk of candidemia, especially those on prolonged TPN or those on corticosteroids. Patients on TPN should be managed by a specialized and dedicated nutritional support team.

3.4. Management of the Fungemia Related to Parenteral Nutrition

The assessment of fungal contamination/fungemia in nutritional parenteral preparations should be studied properly and efforts should be made to prevent parenteral nutrition products from fungemia. The following is the management of Fungemia related to parenteral nutrition. Candida Colonization Index (CI) as a daily determination as the ratio of the number of different body parts colonized with the identical strain to the total number of body parts tested in 29 patients at high risk of Candida infection. However, CI has not been validated in large multicenter trials and its validity has been suggested almost exclusively in surgical patients, In addition, CI is expensive and time consuming (de Rosa *et al*, 2016).

Management of Fungemia Related to Parenteral Nutrition can be done by using the Candida score method. Candida score is a clinical scale used as a parameter to predict Candida infection. Four items were taken to evaluate the presence of fungemic contamination in TPN (1) parenteral nutrition (1 point), (2) surgery (1 point), (3) multifocal colonization (1 point), and (4) severe sepsis (2 points). . The test was considered positive when the total evaluated parameter was greater than 3 points, which is an indication for starting antifungal treatment. This diagnostic method has a diagnostic sensitivity of 81% and a specificity of 74%, with a negative predictive value of 98% (de Rosa *et al*., 2016).

In addition to the candida index and candida score, there are many methods for detecting Candida species. One of them is Culture and Biomarkers. However, none has been shown to be 100% specific for the presence of candidemia. Culture is the method of choice for the diagnosis of candidemia. This procedure has a sensitivity of 50-70%, obtaining results between the 3rd and 4th day. This method is very useful because it allows us to evaluate pharmacological sensitivity tests and better orientation of therapy for the good management of infected patients (Leon C *et al*., 2016).

4. Conclusion

Lipid emulsion infusion for longer periods of time can cause fungal contamination. Therefore, the recommended administration for lipid emulsion needs to be replaced within 24 hours after the infusion commencement. However, another study suggested that lipid emulsions did not increase the risk of fungal infection in patients receiving parenteral lipid emulsions. Further research is needed to prove the correlation between fungal contamination and lipid emulsions of parenteral nutrition.

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