


Update on the Use of Filters for Parenteral Nutrition: An ASPEN Position Paper

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Intravenous in-line filters play a critical role in promoting patient safety during parenteral nutrition (PN) administration. Guidelines for using filters for PN have been issued by a number of professional organizations and manufacturers of PN components. Yet despite this guidance, filter use remains controversial. Recent changes in recommendations for filtering lipid injectable emulsions have added to confusion and created considerable variation in practice. This Position Paper aims to review past guidance regarding the filtration of PN, examine the clinical consequences of infusing particulate matter, discuss the challenges and issues related to filtration, and clarify the American Society for Parenteral and Enteral Nutrition (ASPEN) recommendations for the use of filters for PN administration. This paper was approved by the ASPEN Board of Directors. (*Nutr Clin Pract.* 2021;36:29–39)

Keywords

filters; intravenous fat emulsions; lipid injectable emulsion; parenteral nutrition; patient safety

An ASPEN Position Statement: Update on the Use of Filters for Parenteral Nutrition Executive Summary

- In-line intravenous filters serve a critical purpose in reducing exposure to particulate matter during parenteral nutrition (PN) therapy.
- Particles greater than 2 microns, which are retained by 1.2 micron filters, appear to pose the most serious risk for adverse consequences.
- Based on best available evidence and guidance from scientific and regulatory agencies, the American Society for Parenteral and Enteral Nutrition (ASPEN) recommends using a 1.2 micron in-line filter for administration of total nutrient admixtures (TNAs), dextrose-amino acid admixtures and lipid injectable emulsion (ILE). For TNAs, place the filter as close to the catheter hub as possible. For dextrose-amino acid admixtures below the Y-site where the dextrose-amino acid admixture and the ILE co-infuse.
- The safety of using a single 1.2 micron filter for PN administration is supported by decades of experience in hospital and homecare settings. This approach alleviates the confusion and errors associated with using 2 filters with different pore sizes. Simplifying filtering practices could potentially increase compliance with recommendations for filter use with PN administration.

- Although 1.2 micron filters are not recommended for use as a routine infection control measure, these devices are effective in preventing *Candida albicans*, a

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pathogen frequently associated with PN administration, from reaching the patient.

- ASPEN recommends that healthcare organizations that do not filter PN admixtures or ILE reevaluate these decisions and consider the small price of filters in comparison to increased morbidity and mortality that may result from not filtering ILE or PN.

Introduction

The administration phase of Parenteral nutrition (PN) is the all-important part of the PN process that directly involves the patient. This phase is not without associated risks to the patient from errors or lapses in following best-practice recommendations.^{1–3} In particular, the use of intravenous in-line filters represents a key practice aimed at enhancing patient safety during PN administration.

In the United States, intravenous in-line filters are required for PN administration. Guidelines for PN filter use have been issued by the United States Food and Drug Administration (FDA), the American Society for Parenteral and Enteral Nutrition (ASPEN), the Infusion Nurses Society (INS), and manufacturers of PN components.^{4–8} International organizations such as the British Pharmaceutical Nutrition Group (BPNG) and European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)/European Society for Clinical Nutrition and Metabolism (ESPEN)/European Society of Pediatric Research (ESPR)/Chinese Society of Parenteral and Enteral Nutrition (CSPEN) also address the use of filters for PN administration, but PN filtration practices vary throughout Europe, Asia, and Australia.^{9–11} In several countries, in-line filters are not used for all patients but are reserved for at-risk groups such as neonates, children, immunocompromised patients, and those who require intensive PN therapy.¹¹

Recent updates to recommendations for filtering lipid injectable emulsion (ILE) have led to confusion and considerable variation in practice. A survey of institutional practices for prescribing, preparing, and administering ILE products indicated that 10%–20% of respondents did not adhere to current guidelines for filtering ILE.¹² Lack of compliance with filtering guidelines may be related to questions about the strength of available evidence; poor understanding of the risks posed by particulate contamination; a belief that filters are not effective in screening microbes; concerns about costs; and the incidence of clinical problems such as low flow rates and occlusions that may occur during filter use.^{12,13} Overall, the gap analysis suggests that clinicians underestimate the importance of filters, seeing them as preventing a relatively rare problem rather than considering the impact of these devices on safety outcomes on a day-to-day basis.

Guidelines and policy statements for intravenous filter use have been updated and revised against a backdrop of evolving knowledge regarding their role in promoting patient safety. Over the years, the focus has shifted away from using filters as a defense against microbial contamination, moving instead toward their ability to remove ever-present particulate matter.^{13–15} This Position Paper aims to review past guidance regarding the filtration of PN, examine the clinical consequences of infusing particulate matter, discuss the challenges and issues related to filtration, and clarify ASPEN recommendations for the use of filters for PN administration. Any recommendations in this paper do not constitute medical or other professional advice and should not be taken as such. To the extent that the information published herein may be used to assist in the care of patients, this is the result of the sole professional judgment of the attending healthcare professional whose judgment is the primary component of quality medical care. The information presented here is not a substitute for the exercise of such judgment by the healthcare professional. Circumstances in clinical settings and patient indications may require actions different from those recommended in this document, and in those cases, the judgment of the treating professional should prevail. This paper was approved by the ASPEN Board of Directors.

Methodology

Literature searches were performed with keywords related to the topics “intravenous filters,” “ILEs,” “parenteral nutrition,” and “intravenous therapy,” both as individual terms and in combination with modifiers such as “indications,” “outcomes,” “adverse events,” and “particulate matter.” The literature search included MEDLINE, PubMed, the Cochrane Database of Systemic Reviews, and a query using the Google Scholar search engine for scholarly articles, as well as manual searches of bibliographies for full-text articles published in English through an end date of January 2020. Product literature from the manufacturers of intravenous filters and ILE products was included in the search. The panel also examined relevant guidelines from other professional societies to assess congruence and variations in practice among other countries. Abstracts, theses, conference reports, and other forms of non-peer-reviewed sources were not included.

Although the use of filters with PN has appeared in the literature for decades, relatively few high-level controlled studies address outcomes related to filter use with PN. Due to obvious ethical considerations, no controlled trials have examined the effects of the infusion of particulate matter in human patients. As a result, information regarding the consequences of particulate infusion relies heavily on the results of *in vitro* studies, animal data, case studies, and autopsy reports.

Characteristics of Intravenous Filters

Depending on pore size and device design (filter material, housing dimensions), intravenous filters can block particulate matter, microbes, air, and enlarged lipid droplets from reaching the patient's circulation. A filter's pore size determines not only its retention characteristics but also its functional attributes, such as flow rate and throughput. For example, filter membranes with larger pore sizes will possess faster flow rates and increased throughput, which is the amount of fluid that will pass through a filter before blockage occurs or flow drops to an unacceptable rate. Filters with the same pore size, but made of different polymers and casting methods, can exhibit different flow rates and throughput performance. Furthermore, the number of pores will also impact flow rate and throughput. Device manufacturers combine the correct membrane pore size into the best filter housing to preserve the integrity and flow characteristics of the membrane.¹⁶

Intravenous filters come in a variety of pore sizes, ranging from 0.22 to 5 microns. The smallest, 0.22-micron filters, were originally designed to retain microorganisms, but they are also effective in trapping precipitates found in dextrose–amino acid PN admixtures (without ILE).¹⁷ Manufacturers caution against using 0.22-micron filters with lipid-containing infusions because compression of lipid droplets through small-size pores can disrupt the stability of the emulsion.^{18,19} Instead, a 1.2-micron filter is recommended for lipid-containing PN admixtures and for ILE given as a separate infusion.⁷ The 1.2-micron filter is capable of retaining particles obscured by the opaque fluid, trapping *Candida albicans* and enlarged lipid droplets without compromising the stability of total nutrient admixtures (TNAs). Figure 1 illustrates an example of a typical air-eliminating intravenous filter.

Because of concerns about the potential for microbes trapped within the filter to release endotoxin into the circulation, most filters must be changed every 24 hours. Filter models with a positive charge on the membrane have the capacity to retain endotoxin, which extends the duration of use to 96 hours.⁹ However, this feature is of limited value for PN administration in which container and tubing changes must take place every 24 hours.² In addition, a study in newborns receiving ILE demonstrated significantly higher microbial contamination rates (3.54% vs 1.35%, $P = .001$) when assigned to 72- vs 24-hour administration set changes. Logistic regression analysis that controlled for birth weight, gestational age, and type of venous access showed that only the tubing-change interval was significantly associated with ILE set contamination (odds ratio, 2.69; 95% CI, 1.40–5.13; $P = .003$). A higher proportion of infants randomized to the 72-hour group died (8% vs 4%, $P = .05$), although the increased deaths could not be directly linked to bacteremia.²⁰

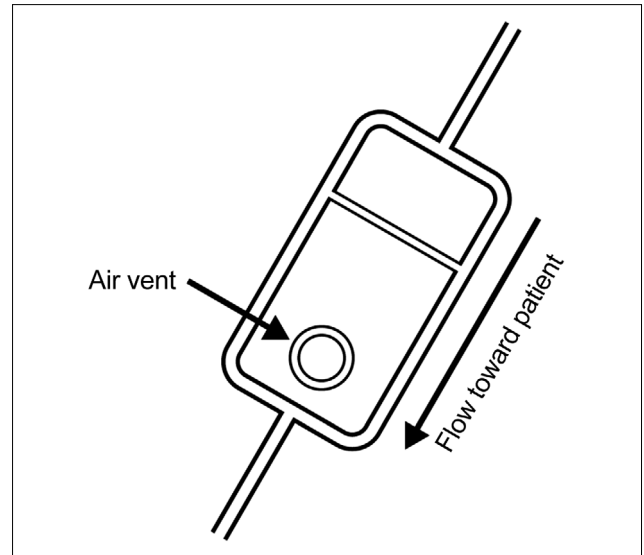


Figure 1. An example of an air-eliminating in-line intravenous filter.

Chronology of Recommendations for Filter Use for PN Administration

Concern over particulate matter in intravenous fluids and PN admixtures has long driven recommendations for in-line filtration during administration.^{21–24} However, noteworthy events that brought national prominence to the risks associated with infusing PN without a filter led to specific professional recommendations.

1994: FDA Alert

In 1994, the FDA issued a safety alert to clinicians after receiving a report of 2 deaths and at least 2 cases of respiratory distress related to calcium phosphate precipitation (CaHPO_4 [calcium monohydrogen phosphate]) in an unfiltered TNA peripheral PN.^{4,25} Autopsies revealed diffuse microvascular pulmonary emboli containing calcium phosphate, a finding that was subsequently reproduced in a laboratory investigation.²⁵ The authors concluded that using a 1.2-micron filter during PN infusion would prevent further morbidity and mortality.

Prior to this incident, 1 other case report had described an adult with subacute interstitial pneumonitis associated with calcium phosphate precipitates.²⁶ Instances of calcium phosphate precipitates causing occlusion of vascular access devices (VADs) had also appeared in the literature before the FDA alert.^{27,28} With input from ASPEN, the FDA developed recommendations to reduce the hazards of precipitation associated with PN.¹⁸ In addition to specific guidance on compounding PN admixtures, the FDA stipulated the use of a 1.2-micron air-eliminating filter for lipid-containing

admixture and a 0.22-micron air-eliminating filter for lipid-free admixtures.^{4,18}

2002: Centers for Disease Control and Preventions Guidelines

Early interest in using filters for PN administration centered on their potential to reduce the infectious complications associated with the therapy.^{29,30} Filters with pore sizes of 0.2 or 0.22 microns, referred to as “sterilizing” filters, first came into use when research determined that a strain of pseudomonas (*Brevundimonas diminuta*) could pass through the 0.45-micron filters that were the standard of care at the time.^{29,31} However, subsequent evidence failed to conclusively demonstrate the efficacy of in-line filters in reducing infectious complications of PN therapy.¹³ Based on this information, in 2002, the Centers for Disease Control and Prevention (CDC) issued Guidelines for Prevention of Intravascular Catheter-Related Infections that recommended *against* routinely using filters for infection-control purposes.³²

The 2002 CDC guidelines acknowledged other theoretical advantages of filters, including removal of particulate matter, but suggested that filtering take place in the pharmacy as a more practical and less costly way to eliminate the most particulates. Given that precipitates often form hours after compounding, such a strategy would prove ineffective in reducing potential harm from particulate matter in PN admixtures.¹⁸ In addition, automated compounding devices widely used for preparing PN admixtures do not have the ability to filter PN during the compounding process.⁹ By highlighting the limited role filters play in reducing bloodstream infection, these CDC guidelines may have inadvertently created the impression that in-line filters serve no purpose for PN administration.^{13,33}

In making this recommendation, the CDC noted that the majority of catheter-related bloodstream infections arise from contamination at the insertion site of the catheter or through manipulation of the catheter hub, both of which occur after the fluid has passed through the filter. On the other hand, contamination of the fluid itself represents a rare cause of bloodstream infection.^{33,34} To a large extent, the quality assurance measures mandated by the *United States Pharmacopeia* (USP), in General Chapter <797>, Pharmaceutical Compounding—Sterile Preparations (USP <797>), act to ensure the sterility of compounded PN admixtures.³⁵

The 2002 CDC guidelines also expressed concern that management of occluded filters could increase manipulation of the line, thus adding to infection risk. An understanding of the pathogenic pathways for infectious complications of PN underscores the importance of adhering to the compounding practices as stipulated by USP

<797> and employing appropriate handling and aseptic techniques throughout all phases of the PN process.^{2,35}

2004: ASPEN Safe Practices for PN

The 2004 ASPEN document addressing Safe Practices for PN discusses the use of filters for PN administration.³⁶ The practice recommendations called for using a 0.22-micron filter for dextrose–amino acids (2-in-1) admixtures and a 1.2-micron filter for TNAs. These guidelines acknowledged that in-line filters can decrease flow rates, become occluded, develop air locks, and lead to excessive manipulation of the VAD. Recognizing that the CDC no longer recommended using in-line filters solely for infection-control purposes, the guidelines included a suggestion that when considering particulate and microprecipitate contamination only, a 1.2-micron filter can be used for all PN admixtures. However, the guidelines did not differentiate between adult and pediatric PN admixtures. As a result, some pediatric clinicians continue to use multiple filters, that is, a 0.22-micron filter for the dextrose–amino acids admixtures and a 1.2-micron filter below the Y-site with ILE.

2014: ASPEN PN Safety Consensus Recommendations

The 2014 ASPEN PN Safety Consensus Recommendations addressed the issue of filtration in conjunction with PN administration.² The recommendations in this document reiterated the guidelines promulgated by the FDA in 1994: Use a 0.22-micron filter for dextrose–amino acid admixtures and a 1.2-micron filter for TNAs, without specifically making alternative recommendations for using a 1.2-micron filter to manage precipitate contamination.

In addition, the recommendations indicate that clinicians should be aware that an occluded filter raises suspicions that the incorrect filter size has been used or that a precipitate or particulate matter is present in the admixture. The recommendations state that an occluded filter signals the need for a review of the formulation by a pharmacist to determine potential causes of the problem. Occluded filters must be replaced, never removed completely in response to occlusion alarms, thus allowing the unfiltered admixture to continue to infuse. The use of filters for ILE infusions is not addressed in these consensus recommendations.

2016: INS

The recommendations presented in the 2016 INS Infusion Therapy Standards of Practice are consistent with those outlined in the 2014 ASPEN Parenteral Nutrition Safety Consensus Recommendations.⁶ The INS practice criteria further state that filters should be used in accordance with the manufacturer’s directions and the filtration requirements for the therapy. The Standards also make note of

a growing body of evidence regarding the adverse clinical effects of particulate matter and microbubbles.

2016: Institute for Safe Medication Practices—Safety Alert

In 2016, the Institute of Safe Medication Practices (ISMP) notified clinicians of a change in the package insert for ILEs indicating that a 1.2-micron filter should be used for lipids infused alone or as part of an admixture; smaller 0.22-micron filters should not be used for ILE administration.^{7,8} The Safety Alert noted that filtering ILEs could prevent fat emboli, air emboli, microorganisms, and particulate matter from reaching the circulation. At the time of publishing the ISMP alert, ILE products with older labels and some drug information resources still stated that filters are not needed for ILE infused from the original manufacturer's container, which added to confusion about this new recommendation. Currently, all ILE package inserts in the United States carry the recommendation to use a 1.2-micron filter when infusing ILE administered separately or as part of a TNA.^{37–42} The package insert of one ILE product supports the directive to filter ILE by mentioning the possibility that fragments of the administration port membrane could be dislodged into the bag after spiking.⁴⁰

No specific evidence was cited to explain the change in labeling. The initial revision coincided with manufacturers' conversion, in June 2015, to a new type of container for ILE products.⁷ In January 2016, healthcare providers received a safety alert describing instances in which blue particles were observed in PN admixtures. An investigation determined that the particulate matter originated from the blue injection port of the new PN containers when the port was spiked at an angle. In addition to advising clinicians not to use these containers with automated compounding devices, the safety notice included a recommendation to filter *both ILE and ILE-containing admixtures*.⁴³ Table 1 provides more detail regarding the chronology of recommendations for filtering ILE and PN admixtures.

Particulate Matter in PN Admixtures

All intravenous fluids contain particulate contamination, defined as mobile undissolved particles, unintentionally present in a parenteral solution.⁴⁴ These particles may consist of dust, glass, rubber, plastic, silicone, fibers, metal, and precipitates resulting from drug incompatibility.^{45–47} The complex nature of PN admixtures and the need for multiple additives can induce alterations in the pH and concentration of nutrients in the solution that results in drug and mineral precipitation.^{9,36,48} Precipitates containing calcium and phosphate pose a serious risk during PN therapy.^{3,18,49,50} This may be related to the rigidity and irregular shape of calcium phosphate crystals.⁴⁶ The detrimental effects

of particulate infusion appear to be more pronounced in neonates, the critically ill, and those with preexisting tissue damage from trauma, surgery, or sepsis.^{17,46,51} The need for prolonged or intensive intravenous therapy, as is frequently the case for patients receiving PN, also increases the risk for adverse events related to particle infusion.^{9,52}

As stated earlier, for ethical reasons, no controlled trials have examined the effects of infusing of particles in human patients.^{46,51} However, animal studies and autopsy reports provide information regarding the consequences of particulate infusion. Infused particles can block small-diameter blood vessels; activate platelets, neutrophils, and endothelial cells; and modulate immune response.¹⁷ Heavy particle loads have also been associated with acute respiratory distress syndrome and systemic inflammatory response syndrome.^{9,17}

Pulmonary Complications Related to Particle Infusion

The diameter of pulmonary capillaries measures ~5–8 microns (average 6.3 microns).^{9,46,53} Therefore, particles larger than this will become trapped in these capillaries, posing the greatest potential for harm from particulate contamination. The capillary diameter of neonates is similar to those of adults, but the overall number and size of blood vessels is smaller in infants, which could explain the more severe effect of particulate infusion that has been reported in pediatric populations.⁵² Particles smaller than the size of pulmonary capillaries pass through the lungs, eventually depositing into organs such as the liver and spleen, where phagocytosis by cells of the reticuloendothelial system takes place.^{9,46,52} In some instances, the pulmonary vasculature is bypassed, such as in patients with an open foramen ovale between the right and left atrium, making infusion of particulate matter even more dangerous.⁵⁴ Little is known about the ability of the immune system to clear larger particles that are deposited organs or the clinical consequences that may occur because of long-term accumulation of such particles.^{15,46,55}

Respiratory compromise stands out as the predominant consequence of infusing particulate matter during PN administration.^{15,49} Case reports describe symptoms ranging from fever, dyspnea, cough, respiratory failure, and sudden unexpected death from cardiopulmonary arrest.^{14,25,26,55,56} Diagnostic studies have documented microvascular pulmonary emboli,^{25,57} granuloma formation,^{14,26,56} interstitial infiltrates,^{26,55} pulmonary artery occlusion, ground glass opacities, and miliary nodules.⁵⁶ The presence of a crystalline precipitate in the lung is a consistent finding for these adverse events. Of note, several of the case reports describe events that occurred in the years after the 1994 FDA alert about the danger presented by precipitates in PN admixtures.

Table 1. Chronology of Filter Use for PN Administration.

| Date | Guidance document | Recommendations |
|---------------------|--|--|
| 1994 ⁴ | FDA alert: Issued in response to 2 deaths related to calcium phosphate precipitation | Use a 1.2-micron, air-eliminating filter for lipid-containing admixtures Use a 0.22-micron, air-eliminating filter for non-lipid-containing admixtures |
| 2002 ³² | Centers for Disease Control and Prevention guidelines for the prevention of intravascular catheter-related infections: Revision of previous guidelines | Do not routinely use filters for infection-control purposes Consider filtration in pharmacy as a cost-effective alternative to in-line filters |
| 2004 ³⁶ | ASPEN safe practices for parenteral nutrition recommendations: Update of 1998 guidelines | A 0.22-micron filter is recommended for 2-in-1 admixtures A 1.2-micron filter should be used for TNAs When considering particulate and microprecipitate contamination only, a 1.2-micron filter can be used for all PN admixtures |
| 2014 ² | ASPEN parenteral nutrition safety consensus recommendations: Update of previous guidelines | Use a 1.2-micron, air-eliminating filter for lipid-containing admixtures Use a 0.22-micron, air-eliminating filter for non-lipid-containing admixtures Change filters and administration tubing with each new PN container An occluded filter must be removed and replaced with a new filter; do not allow an unfiltered admixture to continue to infuse Conduct a pharmaceutical review of the formulation to determine the cause of an occluded filter |
| 2016 ⁶ | Infusion Nurses Society infusion therapy standards of practice: Update of previous guidelines | Use a 1.2-micron, air-eliminating filter for lipid-containing admixtures Use a 0.22-micron, air-eliminating filter for non-lipid-containing admixture. Adhere to manufacturer's directions and filtration requirements for the prescribed therapy Change add-on filters to coincide with administration set changes Recognize evolving evidence concerning the hazards posed by particulates and microbubbles |
| 2016 ^{7,8} | ISMP medication safety alert: Change in manufacturer's directions for ILE infusion | Be aware of change in manufacturer's labeling indicating that a 1.2-micron filter should be used for ILE administration Some inconsistencies were found in labeling practices among manufacturers |

ASPEN, American Society for Parenteral and Enteral Nutrition; FDA, United States Food and Drug Administration; ILE, lipid injectable emulsion; ISMP, Institute of Safe Medication Practices; PN, parenteral nutrition; TNA, total nutrient admixture.

Size and Number of Particles in PN Admixtures

Overview

Both the size and the number of particles influence the risk associated with infusion of fluids containing particulate matter.⁴⁶ Particles >50 microns are considered detectable by visual inspection, but substantial variation exists among inspectors' ability to detect particles in parenteral fluids at this level. Therefore, many reports classify particles up to 100 microns as subvisible.^{58,59} Most infused particulate

matter falls into the subvisible range, defined as particles measuring 2–100 microns in diameter.^{46,52,60,61} However, advances in particle sizing technology now allow detection of submicron-sized particles. Although USP General Chapter <788> Particulate Matter in Injections requires parenteral products be free of visible particles (ie, >50 microns in diameter), there is currently no regulatory allowance for the number of particles <10 microns in diameter.⁴⁴

USP <788> describes 2 procedures for quantifying particulate matter in parenteral fluids: the light obscuration particle count test and the microscopic particle count test.⁴⁴ Of the 2, the light obscuration particle count is the

Table 2. Parameters for Light Obscuration Particle Count Test.⁴⁴

| Test A: Large Volume Injections | Test B: Small Volume Injections |
|---|---|
| Solutions for parenteral infusion or solutions for injection supplied in containers with a nominal content of more than 100 mL: The preparation complies with the test if the average number of particles present in the units tested does not exceed 25 per mL equal to or greater than 10 microns and does not exceed 3 per mL equal to or greater than 25 microns. | Solutions for parenteral infusion or solutions for injection supplied in containers with a nominal content of less than 100 mL: The preparation complies with the test if the average number of particles present in the units tested does not exceed 6000 per container equal to or greater than 10 microns and does not exceed 600 per container equal to or greater than 25 microns. |

predominant method used, whereas the microscopic test is performed in situations when the light obscuration test fails or produces unreliable results.⁴⁵ Table 2 provides further detail about the light obscuration particle count test.

While investigating the unexpected death of a 12-month-old infant who had received long-term PN, Puntis et al conducted an in vitro study of the particulate matter in a typical PN prescribed for a 3-kg infant.¹⁴ The analysis determined that with no filter, the infant would receive daily exposure to ~37,000 particles between 2 and 100 microns in diameter. Seventy percent of the particles measured less than 5 microns and 4% were greater than 25 microns. The authors calculated that their patient would have received ~5 million particles over the course of the PN therapy alone.

Following the 1994 FDA alert, Ball et al obtained samples from the infusion tubing of 20 adult and 20 pediatric PN admixtures just before they were connected to patients.⁶⁰ Particle counts were similar to those detected a decade earlier by Puntis,¹⁴ with the majority of particles measuring in the range of 3–5 microns.

In a multicenter study, investigators conducted a series of measurements of particulate matter present in 192 PN admixtures at the end of the infusion period. Standard PN admixtures contained an average of 960.9 particles per milliliter that measured 1.3 microns. In addition, 42.8 particles per milliliter were ≥ 5 microns and 6.4 particles per milliliter were ≥ 10 microns.³³ These measurements each represented a statistically significant increase in particle load compared with particle counts performed on control samples of PN components prior to admixing. The study also demonstrated significantly increased particulate contamination in admixtures that had been prepared using glass ampoules.

ILE Considerations

Under stable conditions, parenteral ILE droplets range in size between 0.1 and 0.8 microns in diameter, with a mean diameter of 0.2–0.3 microns, similar to naturally occurring chylomicrons.^{9,63} USP standards stipulate that the mean diameter of lipid droplets must not exceed 500 nm (0.5 microns) and that droplets of 5 microns or greater

must not exceed 0.05%, a measurement referred to as the PFAT₅.⁶⁴ However, numerous factors such as pH, temperature, and the concentration of macronutrients, divalent cations, trivalent cations, and free fatty acids can cause ILE droplets to enlarge in TNAs, leading to coalescence of the droplets and, eventually, the release of free oil into the admixture.^{3,63}

ILE products can also be a source of particulate matter. A study of pediatric PN admixtures considered typical in the 1990s attributed 80% of the particulate matter in a PN regimen to the ILE component.¹⁴ Ball et al also detected large numbers of particles in the ILE component of the samples administered as a separate infusion for pediatric patients.⁶² In both of these studies, ILE was administered in a syringe, and an optical microscope was used to avoid counting lipid droplets. The investigators identified the particles primarily as glass and plastic fragments, which originated from the containers and infusion delivery sets.⁶²

In addition, concerns about ILE contamination with particulate matter or emulsion instability have periodically led to recalls of ILE products. For example, a 2009 recall was issued because of the presence of metallic particles in 1 brand of ILE, and in 2017, a nationwide recall was initiated when a shipment of ILE was exposed to subfreezing temperatures during transit, which could have compromised the integrity of the emulsion.^{65,66} As noted earlier, an issue with a blue injection port on the ILE container generated numerous complaints regarding the presence of visible particles in PN admixtures.⁴³

Drug Incompatibility

In recent years, the increasing complexity of intravenous therapy has brought renewed scrutiny to the presence of particulate matter in parenteral fluids. A number of in vitro studies have simulated multidrug protocols for neonatal, pediatric, and adult patients, many involving drug administration in conjunction with PN admixtures.^{47,48,52,60,67–70} Variation exists in the lower range of particle sizes evaluated in these studies, which may reduce the ability to accurately determine the total number of particles in a given solution. However, estimates of the number of particles infused in

critically ill neonates and children suggest that exposure to particles could approach or exceed 1 million particles measuring ≥ 2 microns each day.^{9,46,61,68} Several investigators have advocated more widespread use of filters, especially for the critically ill.¹⁵ However, a meta-analysis of randomized trials of filter use failed to demonstrate a clinical benefit to the practice.⁷¹

More recently, German investigators conducted a retrospective controlled cohort study to assess the effect of in-line filtration of intravenous fluids with 0.2- or 1.2-micron filters vs 5-micron filters in critically ill adult patients. From a total of 3215 adult patients, 3012 patients were selected by propensity score matching (adjusting for sex, age, surgery group) and assigned to either a 0.2-/1.2-micron filter group ($n = 1506$) or a control filter cohort using 5-micron filters ($n = 1506$). Comparing the fine filter vs control filter cohort, respiratory dysfunction, determined by the Horowitz index ($\text{PaO}_2/\text{FiO}_2$), was reduced in the fine filter cohort: 206 vs 191 ($P = .04$); pneumonia 11.4% vs 14.4% ($P = .02$), sepsis 9.6% vs 12.2% ($P = .03$), and length of intensive care unit (1.2 vs 1.7 days, $P < .01$) and hospital stay (14 vs 14.8 days, $P = .01$). Rate of acute kidney injury was not significantly different between the cohorts. The authors concluded that in-line filtration with 0.2-/1.2-micron filters may be associated with less organ dysfunction in critically ill patients.⁷² To date, no studies have assessed differences in particulate retention between 0.22-micron filters and 1.2-micron filters.

In some studies, medications were infused through the same vascular access lumen used for the PN admixture, simulating a clinical practice used in the setting in which the study took place.⁵² This practice is not optimal, but in situations when vascular access is limited, Y-site administration of medication through the line used for PN may be unavoidable.^{3,64,70} Given the high degree of patient-specific customization required for each PN admixture, not all instances of incompatibility or admixture instability can be predicted.^{3,50} Studies have documented sharp increases in particulate matter when medications are co-infused with PN, underscoring the importance of using appropriate administration techniques, including filters, when infusing medications in conjunction with PN.^{52,67,70} Strategies that limit contact time between drugs, such as avoiding the use of extension sets, reduces particulate contamination during multidrug therapies.^{50,66,68} ASPEN has issued guidelines designed to optimize admixture integrity and promote safety in all phases of the PN use process, including medication administration during PN therapy.^{2,3,36}

Challenges Associated With Filter Use

The use of intravenous filters may give rise to a number of clinical challenges, particularly with the low infusion rates typically used for neonatal populations.⁷²⁻⁷⁵ Examples of problems reported include decreased flow rates, increased

frequency of high-pressure alarms (also known as patient-side occlusion alarms), and air locks.^{13,36}

The cost of filters acts as a further barrier to their consistent use during PN administration. In a survey of ILE practices, many respondents reported not using 2 filters of different sizes when infusing ILE separate from the dextrose-amino acids admixture.¹² Instead, a single 1.2-micron filter was frequently used for both infusions, as shown in Figure 2. This practice not only stems from concern about the cost of 2 filters but also aims to reduce confusion and errors on the part of nurses, patients, and lay caregivers regarding the correct filter to use for the dextrose-amino acids admixture vs the ILE infusion.

Implementing recognized best practices for filtering PN admixtures and using specific techniques for priming filters can improve their function, particularly with low flow rates. Best practices for using filters for PN administration include the steps listed below:^{2,38,67,70,73,76}

1. Prior to compounding, a pharmacist must verify the stability and compatibility of the PN formulation.
2. Perform visual inspection of the PN container for evidence of particulate matter or admixture instability, including emulsion cracking for TNAs.
3. When administering the dextrose-amino acid component of the PN and the ILE as separate infusions, the first infusion must be completely set up and the pump programmed for that fluid before setting up the second infusion.
4. Avoid co-administration of medications with PN admixtures. When no other option exists, use appropriate flushing techniques before and after the medication is administered.
5. When co-administration of medications with PN cannot be avoided, the medication tubing should be attached at a Y-site above the filter. Medications that must not be filtered should not be administered with PN.
6. Select a 1.2 micron filter for all PN regimens including TNAs, dextrose-amino acid admixtures, and ILE.
7. Observe the manufacturer's directions for priming the filter before connecting to the patient's VAD.
8. Do not invert filter during priming to allow the vented side of the housing to fill before flowing to the patient side of the device.
9. To avoid clogging the filter during set up, consider allowing a small volume of ILE through the administration tubing allowing the ILE to enter the filter. Close the clamp on the ILE administration set. (Optional)
10. Prime the dextrose-amino acid admixture through the administration tubing completely filling the

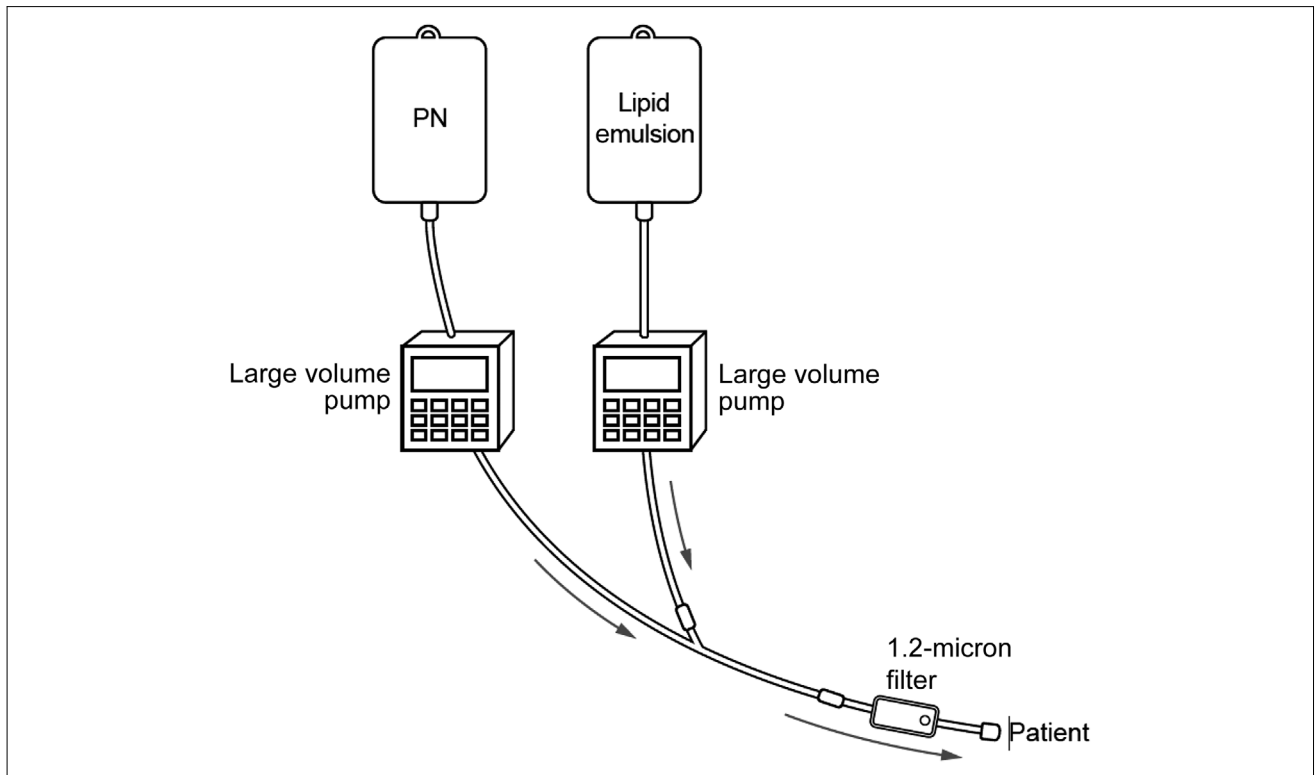


Figure 2. Setup for use of a 1.2-micron administration of dextrose-amino admixture with lipid injectable emulsion given as a separate infusion. PN, parenteral nutrition.

- tubing and filter to the distal end of the tubing. This will dilute the ILE present in the filter to avoid clogging.
11. Connect the filter to the hub of the patient's VAD. When administering the dextrose-amino acid component of the PN and the ILE as separate infusions, attach the filter below the Y-site where the infusions meet.
12. Release all clamps and initiate the infusion.
13. Schedule filter changes to coincide with the initiation of a new PN admixture and administration set.
- c. Assess the patency of the vascular access device according to organizational policies
- d. Inspect the dressing on the VAD to ensure that the catheter is not kinked or twisted under the dressing material
3. Verify that correct size filter has been used
4. If correct size filter is in place, assume that particulate matter is the cause.
5. Remember that precipitates can occur hours after compounding
 - a. Remove clogged filter and replace it with a new filter
 - b. Be alert for repeated episodes of occlusion
 - c. Never allow an unfiltered admixture to continue to infuse.
6. Conduct a pharmaceutical review of the PN formulation to determine the underlying of the occlusion and identify actions to prevent further occurrences.

In the event that a high-pressure alarm sounds during PN administration, clinicians must follow a series of steps to safely troubleshoot a potentially occluded filter. The following actions outline the appropriate response to high pressure alarms or a potentially occluded filter:^{2,6,77}

1. Verify that appropriate pressure setting has been used on the infusion pump
2. Rule out mechanical or thrombotic causes of high pressure infusion pump alarms:
 - a. Trace the administration tubing from the pump to IV catheter, checking for kinks
 - b. Confirm that all clamps are open

Further Research/Unanswered Questions

- What effect does the accumulation of particles in vital organs have over time?
- What, if any, level of particulate infusion could be considered acceptable?

- What effect does particulate matter have on the immune system?
- What is the risk to diverse patient populations posed by particles of various sizes, shapes, and composition that are infused intravenously?
- What difference occurs in particulate capture using a 0.22-micron filter vs 1.2-micron filter in a dextrose–amino acid admixture to determine whether there is an additional benefit of using 0.22-micron filter?

References

1. Sacks GS, Rough S, Kudsk KA. Frequency and severity of harm of medication errors related to the parenteral nutrition process in a large university teaching hospital. *Pharmacotherapy*. 2009;29(8):966-974.
2. Ayers P, Adams S, Boullata J, et al. American Society for Parenteral and Enteral Nutrition. A.S.P.E.N. Parenteral nutrition safety consensus recommendations. *JPEN J Parenter Enteral Nutr*. 2014;38:296-333.
3. Boullata JI, Gilbert K, Sacks GS, et al. A.S.P.E.N. clinical guidelines: parenteral nutrition ordering, order review, compounding, labeling, and dispensing. *JPEN J Parenter Enteral Nutr*. 2014;38(3):334-377.
4. Food and Drug Administration safety alert: Hazards of precipitation associated with parenteral nutrition. *Am J Hosp Pharm*. 1994;51(11):1427-1428.
5. American Society for Parenteral and Enteral Nutrition (ASPEN). Parenteral Nutrition—New Recommendations for In-line Filters. Accessed September 2, 2020. http://www.nutritioncare.org/News/General_News/Parenteral_Nutrition_%E2%80%9393_New_Recommendations_for_In-line_Filters/
6. Infusion Nurses Society. Infusion therapy standards of practice. *J Infus Nurs*. 2016;2016(1S):S11-S159.
7. Cohen MR, Smetzer JL. ISMP medication error report analysis. Selected medication safety risks to manage in 2016—Part I intravenous fat emulsion needs a filter. *Hosp Pharm*. 2016;51(5):353-357.
8. ISMP Medication Safety Alert. *ISMP Quarterly Action Agenda*. Accessed September 2, 2020. <https://www.ismp.org/sites/default/files/attachments/2018-02/ActionAgenda1602.pdf>
9. Bethune K, Allwood M, Grainger C, Wormleighton C. Use of filters during the preparation and administration of parenteral nutrition: Position paper and guidelines prepared by a British pharmaceutical nutrition group working party. *Nutrition*. 2001;17(5):403-408.
10. Puntis J, Hojsak I, Ksiazek J; ESPGHAN/ESPEN/ESPR/CSPEN working group on pediatric parenteral nutrition. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: organizational aspects. *Clin Nutr*. 2018;37(6 Pt B):2392-2400.
11. Martindale RG, Berlana D, Boullata JI, et al. Summary of proceedings and expert consensus statements from the international summit “Lipids in Parenteral Nutrition”. *JPEN J Parenter Enteral Nutr*. 2020;44 Suppl 1:S7-S20.
12. Christensen ML, Ayers P, Boullata JI, et al. Lipid injectable emulsion survey with gap analysis. *Nutr Clin Pract*. 2017;32(5):694-702.
13. Ball P. Intravenous in-line filters: filtering the evidence. *Curr Opin Clin Nutr*. 2003;6(3):319-325.
14. Puntis JWL, Wilkins KM, Ball PA, Rushton DI, Booth IW. Hazards of parenteral treatment: do particles count? *Arch Dis Child*. 1992;67(12):1475-1477.
15. Benlabed M, Perez M, Gaudy R, et al. Clinical implications of intravenous drug incompatibilities in critically ill patients. *Anesth Crit Care Pain Med*. 2019;38(2):173-180.
16. Filtration Devices for Infusion Therapy & Drug Delivery. Pall Corporation. Published 2020. Accessed September 2, 2020. <https://medical.pall.com/en/oem-manufacturing/filter-devices/liquid-filtration.html>
17. Boehne M, Jack T, Köditz H, et al. In-line filtration minimizes organ dysfunction: new aspects from a prospective, randomized, controlled trial. *BMC Pediatr*. 2013;13:21.
18. McKinnon BT. FDA safety alert: hazards of precipitation associated with parenteral nutrition. *Nutr Clin Pract*. 1996;11(2):59-65.
19. Driscoll DF, Bacon MN, Bistrrian B. Effects of in-line filtration on particle size in total nutrient admixtures. *JPEN J Parenter Enteral Nutr*. 1996;20(4):296-301.
20. Matlow AG, Kitai I, Kirpalani H, et al. A randomized trial of 72-versus 24-hour intravenous tubing set changes in newborns receiving lipid therapy. *Infect Control Hosp Epidemiol*. 1999;20:487-493.
21. Davis NM, Turco S, Sively E. Particulate matter in I.V. infusion fluids. *Bull Parenter Drug Assoc*. 1970;24(6):257-270.
22. Davis NM, Turco S, Sively E. A study of particulate matter in I.V. infusion fluids. *Am J Hosp Pharm*. 1970;27(10):822-826.
23. Davis NM, Turco S. A study of particulate matter in I.V. Infusion fluids—Phase 2. *Am J Hosp Pharm*. 1971;28(8):620-623.
24. Turco SJ, Davis NM. Particulate matter in intravenous infusion fluids—Phase 3. *Am J Hosp Pharm*. 1973;30(7):611-613.
25. Hill SE, Heldman LS, Goo ED, Whippe PE, Perkinson JC. Fatal microvascular pulmonary emboli from precipitation of a total nutrient admixture solution. *JPEN J Parenter Enteral Nutr*. 1996;20(1):81-87.
26. Knowles, JB, et al, Pulmonary deposition of calcium phosphate crystals as a complication of home total parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 1989; 13(2):209–213.
27. Robinson LA, Wright BT. Central venous catheter occlusion caused by body-heat-mediated calcium phosphate precipitation. *Am J Hosp Pharm*. 1982;39(1):120-121.
28. Breaux CW Jr, Duke D, Georgeson KE, Mestre JR. Calcium phosphate crystal occlusion of central venous catheters used for total parenteral nutrition in infants and children: prevention and treatment. *J Pediatr Surg*. 1987;22(9):829–832.
29. Maki DG, Goldman Dam Rhame FS. Infection control in intravenous therapy. *Ann Intern Med*. 1973;79(6):867-887.
30. Wilmore DW, Dudrick SJ. An in-line filter for venous solutions. *Arch Surg*. 1969;99(4):462-463.
31. Jornitz MW, Akers, JE, Agalloco JP, Madsen RE, Meltzer TH. Considerations in sterile filtration. Part II: the sterilizing filter and its organism challenge: a critique of regulatory standards. *PDA J Pharm Sci Technol*. 2003;57(2):88-96.
32. O’Grady NP, Dellinger EP, Gerberding JL, et al. Guidelines for the prevention of intravascular-catheter related infections. *Morb Mortal Wkly Rep (MMWR)*. 2002;51(RR-10):1-29.
33. Oie S, Kamiya A. Particulate and microbial contamination in in-use admixed parenteral nutrition solutions. *Biol Pharm Bull*. 2005;28(12):2268-2270.
34. O’Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infection. *Clin Infect Dis*. 2011;52(9):e162-e193.
35. United States Pharmacopeia. Pharmaceutical compounding—sterile preparations (Chapter 797). In: *The United States Pharmacopeia, 36th rev, and the National Formulary*. Rockville, MD: The United States Pharmacopeial Convention; 2008.
36. Mirtallo J, Canada T, Johnson D, et al. Safe practices for parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 2004;28(6):S39-S69.
37. Hirsch A. In line filters and injectable lipid emulsions. *GASPEN Newsletter*. 2019;(5):6-9.
38. *Intralipid 20%. Package insert*. Fresenius Kabi; 2015.
39. *Nutrilipid. Package insert*. B. Braun Medical Inc; 2017.
40. *Clinolipid. Package insert*. Baxter Healthcare Corporation; 2016.

41. *SMOFlipid. Package insert.* Fresenius Kabi; 2015.
42. *Omegaven. Package insert.* Fresenius Kabi; 2018.
43. VA Comprehensive Pharmacovigilance Center. Intralipid IV fat emulsion products in Biofine containers: particulate matter observed. *Medication Safety Seconds.* 2016;6(1):3.
44. United States Pharmacopeia. Chapter <788>Particulate Matter in Injections. USP 35. In: *The United States Pharmacopeia, 36th rev, and the National Formulary.* Rockville, MD: US Pharmacopeial Convention; 2013.
45. Tran T, Kupiec TC, Trissel LA. Particulate matter in injections: what is it and what are the concerns. *Int J Pharm Compounding.* 2006;10(3):202-204
46. Langille SE. Particulate matter in injectable drug products. *PDA J Pharm Sci Tech.* 2013;67(3):186-200.
47. Perez M, Maiguy-Foinard A, Barthelemy C, Decaudin B, Odou P. Particulate matter in injectable drugs: evaluation to risks to patients. *Pharm Technol Hosp Pharm.* 2016;1(2):91-103.
48. Gordon S. Sacks, filtration of parenteral nutrition admixtures: friend or foe. *Nutrition.* 1997;13(10):936-937.
49. Newton DW, Driscoll DF. Calcium and phosphate compatibility: revisited again. *Am J Health Syst Pharm.* 2008;65(1):73-80.
50. Trissel LA, Gilbert DL, Martinez JF, Baker MB, Walter WV, Mirtallo JM. Compatibility of medications with 3-in-1 parenteral nutrition admixtures. *JPEN J Parenter Enteral Nutr.* 1999;23(2):67-74.
51. Lehr H-A, Brunner J, Rangoonwala R, Kirkpatrick CJ. Particulate matter contamination of intravenous antibiotics aggravates loss of functional capillary density in postischemic striated muscle. *Am J Respir Crit Care Med.* 2002;165(4):514-520.
52. Perez M, Decaudin B, Maiguy-Foinard A, et al. Dynamic image analysis to evaluate subvisible particles during continuous drug infusion in a neonatal intensive care unit. *Sci Rep.* 2017;7(1):9404. <https://doi.org/10.1038/s41598-017-10073-y>
53. Townsley MI. Structure and composition of pulmonary arteries, capillaries and veins. *Compr Physiol.* 2013;2(1):675-709.
54. Krishna A, Rice M, Kester T, Waters M, Wilson T. Particulate study on NeoProfen, a neonatal injectable product. *PDA J Pharm Sci Technol.* 2016;70(1):76-92.
55. Shay DK, Fann LM, Jarvis WR. Respiratory distress and sudden death associated with receipt of a peripheral parenteral nutrition admixture. *Infect Control Hosp Epidemiol.* 1997;18(12):814-817.
56. McNearney T, Bajaj C, Boyars M, Cottingham J, Haque A. Total parenteral nutrition associated crystalline precipitates resulting in pulmonary artery occlusions and alveolar granulomas. *Dig Dis Sci.* 2003;48(7):1352-1354.
57. Reedy JS, Kuhlman JE, Voytovich M. Microvascular pulmonary emboli secondary to precipitated crystals in a patient receiving total parenteral nutrition: a case report and description of the high-resolution CT findings. *Chest.* 1999;115(3):892-895.
58. Melchore JA. Sound practices for consistent human visual inspection. *AAPS Pharm Sci Tech.* 2011;12(1):215-221.
59. Das T, Nema S. Protein particulate issues in biologics development. *Am Pharm Rev.* 2008;11(3):52-57.
60. Corvari V, Narhi LO, Spitznagel TM, et al. Subvisible (2-100 μm) particle analysis during biotherapeutic drug product development: Part 2, experience with the application of subvisible particle analysis. *Biologicals.* 2015;43(6):457-473.
61. Jack T, Brent BE, Muller M, et al. Analysis of particulate contamination of infusion solutions in pediatric intensive care unit. *Intensive Care Med.* 2010;36(4):707-711.
62. Ball PA, Bethune K, Fox J, et al. Particulate contamination in parenteral nutrition solutions: still a cause for concern. *Nutrition.* 2001;17:926-929.
63. Hardy G, Puzovic M. Formulation, stability, and administration of parenteral nutrition with new lipid emulsions. *Nutr Clin Pract.* 2009;24(5):616-25.
64. United States Pharmacopeia. Chapter <729>. Globule Size Distribution in Lipid Emulsions. In: *The United States Pharmacopeia, 36th rev, and the National Formulary.* Rockville, MD: United States Pharmacopeia; 2019.
65. FDA Intralipid Alerts. Drugs.com. Accessed December 16, 2019. <https://www.drugs.com/fda-alerts/1067-9297.html>
66. Food and Drug Administration. Intralipid 20 Percent IV Fat Emulsion by Baxter: Recall - One Shipment of Product Exposed to Subfreezing Temperatures. Published October 5, 2017. Accessed September 2, 2020. <https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/baxter-initiates-voluntary-nationwide-recall-one-shipment-intralipid-20-iv-fat-emulsion-due-product>
67. Perez M, Decaudin B, Abou Chala W, et al. In vitro analysis of overall particulate matter contamination exposure during multidrug IV therapy: Impact of infusion sets. *Pediatr Blood Cancer.* 2015;62(6):1042-1047.
68. Perez M, Decaudin B, Chahla WA, et al. Effectiveness of in-line filters to completely remove particulate contamination during a pediatric multidrug infusion protocol. *Sci Rep.* 2018;8(1):1-8.
69. Jack T, Boehne M, Brent BE, et al. In-line filtration reduces severe complications and length of stay on pediatric intensive care unit: A prospective, randomized, controlled trial. *Intensive Care Med.* 2012;38(6):1008-1016.
70. Benlabed M, Martin Mena A, Gaudy R, et al. Analysis of particulate exposure during continuous drug infusion in critically ill adult patients: a preliminary proof-of-concept in vitro study. *Intensive Care Med Exp.* 2018;6(1):38.
71. Foster JP, Richards R, Showell MG, Jones LJ. Intravenous in-line filters for preventing morbidity and mortality in neonates. *Cochrane Database Syst Rev.* 2015;(8):CD005248.
72. Schmitt E, Meybohm P, Herrmann E, et al. In-line filtration of intravenous infusion may reduce organ dysfunction of adult critical patients. *Crit Care.* 2019;23:373.
73. Gill M. Filtering out the Facts: Recommendations to Optimize Performance of In-Line Filters for Parenteral Nutrition and Intravenous Fat Emulsion Infusions. BD. Published August 2019. Accessed January 27, 2020. <https://www.bd.com/en-us/clinical-excellence/bd-institute-for-medication-management-excellence/blog/key-insights-from-a-recent-white-paper-on-the-performance-of-in-line-filters-for-parenteral-nutrition-and-intravenous-fat-emulsion-infusions>
74. Chau D, Gish B, Tzanetos D, Zhang C. A dangerous side of in-line filter when used for vasoactive infusions in infants. *APSF newsletter.* 2013;28(2):43
75. IV in-line Filter FAQs. CareFusion 2010. Published 2010. Accessed October 5, 2020. https://www.bd.com/documents/faq/IF_Alaris-Pump-Module_FQ_EN.pdf
76. Newton DW. Y-site compatibility of intravenous drugs with parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2013;37(3):297-299.
77. Canadian Vascular Access Association. Occlusion management guideline for central vascular access devices (CVADs). *J Can Vascular Access Assoc.* 2013;7(Suppl. 1):3-31.