Filtering out the Facts: Recommendations to Optimize Performance of In-Line Filters for Parenteral Nutrition and Intravenous Fat Emulsion Infusions

**Problem Statement**
The use of an in-line, 1.2-micron filter is recommended for the infusion of total parenteral nutrition (TPN), also known as 3-in-1 or all-in-one [AIO], and intravenous fat emulsions (IVFE) infused alone through a separate IV line. However, literature references and post market surveillance data cite occurrence of infusion pump occlusion alarms which may be indicative of a clogged filter. This paper provides an overview of filter recommendations for parenteral nutrition (PN) and IVFE, describes the challenges of filtration with PN and IVFE, and includes recommendations to minimize pump occlusion alarms that may occur from a clogged filter.

**Background**

**Filtering IVFE: Overview of Clinical Guidelines**
The administration of intravenous fat emulsions (IVFE) is an essential component of PN regimes for pediatric and adult patients. IVFEs are formulated to provide essential fatty acids for patients on parenteral nutrition and a dense source of calories to help reduce the volume required for PN. Long-chain triglycerides (LCT) including soybean oil (omega-6), olive oil (omega-9), fish oil (omega-3) and medium-chain triglycerides (MCT) make up the majority of the composition of the IVFEs available worldwide. In the United States until recently, only 100% soybean oil-based IVFEs (e.g. Intralipid®, Baxter; Nutrilipid®, B. Braun) were available. In 2016, SMOFlipid®, a four oil lipid emulsion (Soybean Oil 30%, MCT 30%, Olive Oil 25% and Fish Oil 15%) manufactured by Fresenius Kabi, was approved in United States. SMOFlipid® has been increasingly used for neonatal and pediatric population PN due to potential clinical benefits published in the medical literature (despite the fact it is indicated for adults only). According to its FDA approved package insert: “The safe and effective use of SMOFlipid® in pediatric patients, including preterm infants, has not been established”.

Undiluted IVFEs can be given separately from the PN admixtures or are added to the PN for an “all-in-one” (AIO) admixture. In either case, as AIO and IVFE are prone to precipitation, a 1.2-
micron, in-line filter is a recommended part of the administration setup to help reduce large particulate (e.g., enlarged lipid droplets) from entering the body leading to patient injury.\textsuperscript{1, 7, 8} Special populations, such as the critically ill, neonatal and pediatric patients are at a higher risk from large particulates due to their co-morbidities and size, serious injuries up to and including death can occur.\textsuperscript{5}

Practices regarding filtering IVFE have historically varied. IVFE prescribing information outside of the United States does not consistently include the recommendation to use a 1.2-micron in-line filter. For example, the package leaflet for Lipofundin MCT/LCT 20%, advises, "Infusion sets with in-line filters are not to be used for administration of fat emulsions."\textsuperscript{6} In recent years, consensus promoting the use of a 1.2-micron filter for IVFE is growing from organizations such as A.S.P.E.N\textsuperscript{7} (American Society of Parenteral and Enteral Nutrition) and INS\textsuperscript{8} (Intravenous Nursing Society) to reduce the potential for patient harm that may occur due to infusion of particulate, precipitates and air emboli. Since the 2014 A.S.P.E.N recommendations for filter usage, all prescribing information for IVFE sold in the United States includes the recommendation for a 1.2-micron filter.\textsuperscript{18} ESPGHAN (European Society for Paediatric Gastroenterology Hepatology and Nutrition) recommends filtering lipid emulsion or AIO mixes with filter pore size "around 1.2-microns to 1.5-microns".\textsuperscript{9} A 0.22-micron filter is recommended for a dextrose/amino acids formulation.\textsuperscript{7, 8} One should avoid having the IVFEs infuse through a 0.2 micron filter as the fat will occlude the filter. In a publication that discusses PN and IVFE infusions for the pediatric / neonatal population, Hardy, \textit{et al}, state an in-line 1.2-micron filter should be used for all AIOs, but acknowledge it is not uncommon for filters to occlude during administration of an apparently "stable" mixture.\textsuperscript{1} Hardy further states the difference between what is an acceptable admixture and what will pass through an in-line filter is still not clearly defined.\textsuperscript{1} Christensen, \textit{et.al.}, in a Gap Analysis survey sent to ASPEN members, reported between 9.7\% to 19.4\% of users do not use filters for IVFE infusions (9.7\% for pediatric patients, 15.1\% for adult patients, 19.4\% for infant patients.)\textsuperscript{10} These clinicians reported having occlusion issues during the infusion of IVFE with a 1.2-micron filter, with no root cause identified in 54 to 80\% of the cases.\textsuperscript{10}

Moreover, a 2019 Georgia Society for Parenteral and Enteral Nutrition (GASPEN) Newsletter on the "Considerations for Injectable Lipid Emulsion Administration: In-line Filters and DEHP-Free Tubing", caution that because lipid emulsions contain particles that can range from about 0.1 micron to 1 micron, some can pass through a 1.2 micron filter.\textsuperscript{11} Conversely, newer lipid emulsions (e.g. SMOFlipid\textsuperscript{®}) have larger lipid globules (greater than 5 microns) which can pose the greatest patient risk since particles of this size can lodge in pulmonary capillaries and cause
complications if filters are not utilized. However, filters can also become clogged due to the size of the lipid globules, which can result in an interruption in the infusion.

**Filter change intervals:**
There is a general consensus within most clinical practice guidelines for how often the 1.2-micron filter should be changed when infusing AIO parenteral nutrition and undiluted IVFE infusions. Ayers, et al, in a 2014 publication entitled, A.S.P.E.N. Parenteral Nutrition Safety Consensus Recommendations, specified replacing the tubing and filter with each new PN container (every 24 hours) for AIO and 2-in-1 infusions. This update also included changing the set and filter every 12 hours when IVFE is infused separately. If a prolonged IVFE is required, the fat emulsion dose should be divided into 2 parts, with a new container and tubing used every 12 hours. Previous A.S.P.E.N guidelines (1998 and 2004) did not include any information on set change intervals.

The 2016 INS Standard for administration of PN are consistent with the 2014 ASPEN update. INS further details changing the administration set for PN solutions at least every 24 hours, as well as recommendations to change the administration set with each new PN container, as the characteristics of IVFE (iso-osmotic, near neutral-alkaline pH, and containing glycerol) are conducive to the growth of microorganisms.

The Royal College of Physicians of Ireland Clinical Practice Guidelines for neonatal and paediatric units in Ireland, state that amino acid/glucose infusion sets can be left in situ for up to 48 hours, with lipid sets changed every 24 hours.

**Clinical Practice Challenges with filtering IVFE**
The consensus for in-line filter use as it relates to PN and IVFE infusions is evident in the literature. What is not well described are methods to maximize the life of an in-line filter. For valid reasons previously discussed, filter blockage can occur from retention of particulate matter, which is one of the primary reasons 1.2-micron filters are used. As the filter is “doing its job” of trapping particulate matter before it is infused to the patient, the pressure upstream of the filter may increase over time due to the filter retaining particulate matter, and in the case of IVFE, large amounts of enlarged lipid droplets. Filter blockage may result in a patient-side occlusion alarm, as higher pressures exist upstream of the filter vs downstream. In these cases, the clinician is needed to respond to the audible / visual infusion pump alarm and investigate the root cause of the occlusion.
The A.S.P.E.N PN Safety Consensus Recommendation states that an occluded filter should never be removed in response to occlusion alarms, thus allowing the unfiltered formulation to infuse. Rather, nurses must be well versed in the appropriate actions and trouble-shooting steps in response to high-pressure alarms or an occluded filter. The A.S.P.E.N Consensus recommendation emphasizes that "a filter that becomes occluded during PN administration should raise suspicions that the incorrect filter size was used or that a precipitate or particulate is present in the formulation. Before resuming PN, a pharmacist should review the PN formulation to determine if incompatibility issues are the cause of the problem and to identify actions to prevent further occurrences." Recommendations similar to A.S.P.E.N on occluded filter causes is noted throughout the literature.  

Spiers, et al., tested three different Pall Medical 1.2-micron filters with lipid-containing admixtures and undiluted lipids in a technical report titled: "Pall Lipipor IV Filters for PN: A Characterisation of Pumped Infusion Pressures." Their testing demonstrated that upstream pressures increased during the testing period; pressures below the filter stayed substantially lower. Additionally, the testing identified SMOFlipid® infusions consistently resulted in higher pressures above the filter than Intralipid, with a greater increase over time. Spiers theorized that pressures will increase over the service life of the filter and are dependent upon formulation of the lipid particulate size, filter type and flow rate. (See Table 1 below, adapted from Spiers, et al.) At the time of this publication, there was no available test data below 6.3 mL/hr, which presents a potential impact to slower infusion rates for the neonatal and pediatric population.

<table>
<thead>
<tr>
<th>Maximum upstream pressure recorded for each filter, lipid type and flow rate over a 24-hour period</th>
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<tbody>
<tr>
<td>Lipid Brand name</td>
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<tr>
<td>-------------------</td>
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<tr>
<td>20% SMOFlipid®</td>
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<td>20% Intralipid</td>
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Techniques to trouble shoot patient side occlusion alarms when filtering PN / IVFE:

Patient-side occlusion alarms can occur for reasons unrelated to the filter becoming clogged.
These issues should be thoroughly investigated first, before a clogged filter issue is assumed.

Some common causes for a patient-side occlusion alarm, irrespective of filter use, are:
- A closed clamp or stopcock below the infusion pumping mechanism
- A positional / kinked IV line or catheter
- A clogged needleless connector
- Occlusion of intravenous line
- Occlusion pressure limit is set too low

There are proactive measures and known best practices clinicians can take to reduce the occurrence of patient-side occlusion alarms during IVFE or PN infusions that result from a clogged filter. These measures include:
- Understanding how air-eliminating filters work
- Selecting the right filter appropriate for the type of PN formulation
- Being cognizant of correct filter placement in relationship to the patient
- Setting the most appropriate occlusion pressure limit on the infusion pump, i.e., start at a lower pressure limit and incrementally increasing as needed.
  - Before resuming PN after an occlusion alarm, it is important that a pharmacist review the PN formulation to determine if incompatibility issues are the cause of the problem and to identify actions to prevent further occurrences.
- If stored in refrigerator prior to use, remove in time to allow warming
- Examine the solution for signs of instability before hanging the bag and periodically throughout administration.

**How do air-eliminating filters work?**

Air-eliminating filters are used with infusion sets to retain particulates and inadvertent microbial contaminants (dependent on pore size) and eliminating air. Filters are comprised of a housing with an upstream vented side, separated from the downstream patient side by a filter membrane. Fluid enters the upstream inlet and fills the vented side first, then passes through the filter to the patient side. Air can pass out through the vents, but once the filter membrane is wet, it will not allow air to pass through to the patient, thereby preventing air from infusing to the patient. See image 1.
Selecting the right filter size / type for the infusion

Selecting the appropriate filter for the type of PN formulation is important for proper filter functionality including removal of particulates, precipitates, bacteria, endotoxins; fragments of glass, plastic or rubber; and large lipids. Most drug manufacturers, associations and official regulatory bodies provide specific recommendations on the use of in-line filters as described in this article. Filter manufacturers offer a variety of filter options and provide information on filter options and performance through their websites.

The Royal College Physicians of Ireland recommend when infusing PN and IVFE through the same line, prime the administration set and filter with the lipid solution first, followed by the dextrose/amino acid solution mixing at the point of entry to the access device.

The Y-siting of lipids into a neonatal PN can have an impact on the emulsion stability. Emulsion instability with aggregation of lipid droplets (greater than 5 microns) can occur at the interface between the emulsion and the PN solution within the line. Therefore, the Y-siting should be as close to the patient as possible, above the filter and narrow bore tubing with small priming volume should be used to minimize the lipid/PN contact time.

In-line air-venting filters are inherently known to back-siphon due to the filter design. Back-siphoning can result in blood backing up the IV line when the filter is lowered below the patient’s IV site and conversely, a loss of prime when the filter is raised above the patient’s IV site. This condition is exaggerated at very low infusion rates. Due to the back-siphon effect, the patient’s blood may stagnate in the IV line distal to the filter, and potentially cause a patient-side occlusion alarm (dependent upon the occlusion pressure limits set by the hospital). Back-siphoning can be better controlled by maintaining the filter at the level of the patient’s IV site, or by clamping the IV set below the filter if the filter will be moved above or below the level of the IV site. Remember to unclamp the IV set to avoid a patient-side occlusion alarm.

If external causes of patient-side occlusion alarms are ruled out, particulates or precipitates may have clogged the filter. Stability and formulation challenges remain in specialist therapeutic fields that require more patient-specific nonstandard pharmacy-compounded PN regimens (e.g., pediatrics). Pharmacy has an important role in to review the PN formulation to determine if incompatibility issues may be the cause of incompatibilities and/or particulate matter formation and to identify actions to prevent further occurrences. All clinicians should be aware that an occluded filter may be a sign of compatibility problems with the PN solution and that filters should
be replaced, but never removed, in order to ensure patient safety.

Close adherence to the drug manufacturer’s, associations, official regulatory bodies and filter manufacturer on filter usage and filter change policies are recommended for optimal filter performance and patient safety.

**SUMMARY**

The use of an in-line, 1.2-micron filter is recommended for all parenteral nutrition infusions that contain lipids (AIO) and for undiluted lipid emulsion infusions. Professional organizations such as the Infusion Nursing Society, American Society for Parenteral and Enteral Nutrition, and the Royal College of Nursing in large part, recommend a 24-hour filter change interval for AIO solution and a 12-hour filter change interval for undiluted lipid emulsions. However, end user post market surveillance data and published literature cite reports of patient side occlusion alarms and clogged filters when a 1.2-micron filter is used. These issues can lead to an interruption of the patient’s PN or IVFE infusion, which can be prolonged if efforts to resume the infusion are unsuccessful.

Clinical proficiency in air-eliminating filter technologies, their appropriate use, and adherence to manufacturer’s recommendations in the IV tubing set up support filter functionality. Pharmacy is needed to thoroughly investigate possible causes of a clogged filter, which have been associated with certain lipid formulations, particularly when infusing at lower infusion rates over longer periods of time. Further testing is needed to provide clinicians data on the impact of infusing certain lipid formulations at lower infusion rates. In situations where off label use may increase the likelihood of occlusion, considerations should be made to increasing the frequency of changing the filter. Finally, it is incumbent upon Pharmaceutical and Medical Technology companies to ensure end users have the appropriate resources and equipment available for use as new medications become available in the market.

Comments / Questions are welcomed via alarismedicalaffairs@bd.com
References:

4. ISMP Medical Safety Alert! Two unsafe practices: Administration of a product with a precipitate and reuse of a saline flush syringe. April 6, 2017 vol 22 Issue 7
8. Infusion Therapy Standards of Practice *Infusion Nurses Society* 2016; 39(1S) ISSN 1533-1458
11. GASPEN Newsletter Considerations for Injectable Lipid Emulsion Administration: In-line Filters and DEHP-Free Tubing. Issue 5 Winter 2019
12. Royal College of Physicians of Ireland Clinical Practice Guidelines: The use of parenteral nutrition in neonatal and paediatric units in Ireland. November 2018