

Post-Symposium Digest



Time to rethink filtration

New understandings in IV filtration
relevant to patient care
(WoCoVA Lisbon, 22 – 24 June 2016)



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The symposium was held at the World Congress for Vascular Access 2016 in Lisbon, 22–24 June

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Introduction



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To filter or not to filter?

Filtration of intravenous (IV) infusions is an old topic that has been forgotten for almost a decade, but it is now being discussed again and there is more interest than ever in the world of venous access devices.

An important symposium on filtration was held at the last World Conference on Vascular Access (WoCoVA) in Lisbon, Portugal on 24 June 2016.

Considering that need for filtering IV solutions has been underestimated in recent years, many of the symposium attendees may have been surprised to learn the new concepts and the new data accumulating on the importance of filtration. During the debate, some relevant data were presented:

First, any IV infusion carries the inevitable risk of delivering a high amount of undesired material (for example, endotoxins, bacteria, inert particles) into the bloodstream. This typically happens during complex infusions in the intensive care unit (ICU) (Braun's presentation). Inert particles include drug precipitates, silicon fragments and other foreign materials (Lankers' presentation), but also precipitates containing calcium and phosphorous when delivering parenteral nutrition (Gomis Muñoz's presentation).

Second, commercially available filters (particularly 0.2 micron) are definitely effective. They can dramatically reduce the amount of microparticles, by stopping the majority of them (Keck's presentation) and they can also eliminate the passage of bacteria (Ryder's presentation).

Third, filtration carries potential clinical benefits. There is a growing evidence that using 0.2 micron filters—thus reducing the amount of endotoxin, bacteria and inert materials (which may not be so 'inert' after all as there is some evidence of their effect on immune state and cytokine formation)—can be associated with an improved clinical outcome in paediatric ICU patients, in terms of reduction of the incidence of systemic inflammatory response syndrome and organ failure (Sasse's presentation).

Last but not least, most of this information, though often overlooked, is already available in the most recent guidelines on venous access devices. The 2016 Infusion Standards of the Infusion Nursing Society (INS) (Stone's presentation) recognise that there is evolving evidence documenting the effect of particulate matter (rubber, glass, latex) on capillary endothelium. The INS' final recommendation is (a) to filter parenteral solutions, both with lipids and without lipids, (b) to filter blood and blood components, and (c) to consider the filtration of all fluids and medications in critically ill patients.



SIRS is reduced by in-line filtration in intensive care patients



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Introduction: Sepsis, systemic inflammatory response syndrome (SIRS) or organ failure often complicate the clinical course on an ICU. Particulate contamination of infusion solution may contribute to the clinical deterioration of these patients. Particles have been shown to induce thrombogenesis, deterioration of microcirculation and modulation of immunoresponse. The use of in-line filtration with micro-filters almost completely prevents particulate infusion. Jack et al (2012) assessed the effect of in-line filtration on the reduction of major complications in critically ill children (Clinical Trials.gov ID NCT 00209768).

Methods: In a randomised prospective trial, 807 paediatric patients admitted to the interdisciplinary paediatric ICU (PICU) of a tertiary university hospital were assigned to either the control or interventional group, the latter receiving in-line filtration (infusion filter Pall ELD96LLCE/NEO96E, Braun Intrapur Lipid/Intrapur Neonat Lipid) throughout whole infusion therapy. Prior to this study, the infusion regimen was optimised to prevent precipitation and incompatibilities of solutions and drugs. Primary objectives included a reduction in the incidence of sepsis, thrombosis, SIRS, organ failure (liver, lung, kidney, circulation) and mortality.

Results: 807 children (343 female, 464 male) with a heterogeneous background of underlying diagnoses and a normal distribution to either control (406 patients) or in-line filtration group (401 patients) were included. According to the study criteria, a significant reduction in the incidence of SIRS for the interventional group (95% CI, $p < 0.001$) was evident. In addition, organ dysfunction of lung, kidney and the hematologic system was significantly reduced in the filter group.

Through the reduction of SIRS and organ dysfunction, length of stay in the ICU and the

duration of mechanical ventilation was reduced significantly. The length of stay was shortened by 25% from 4 to 3 days.

Conclusions: Particles in infusion solutions modulate the immune system in terms of SIRS. The occurrence of SIRS often complicates treatment in intensive care medicine. In-line filtration is most effective reducing the incidence of SIRS and other severe complications. The stabilisation of patients through the in-line filtration leads to a significant reduction of length of stay on the ICU and is therefore an important economic factor.

Jack T, Boehne M, Brent BE et al (2012) In-line filtration reduces severe complications and length of stay on pediatric intensive care unit: a prospective, randomized, controlled trial. *Intensive Care Med* 38(6): 1008–16. doi: 10.1007/s00134-012-2539-7

How particles and endotoxins may affect patient health



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Normal infusion medications are nearly free of endotoxin contaminations. Contamination of sterile infusions can occur during production, transport or use. In real life, most of the contaminations will occur during clinical use. To evaluate the amount of contamination, measurements of contamination have to be performed on site in the clinic. In a study performed in 1995 in Ulm, Germany, bacterial colonisation and endotoxin contamination of IV infusion fluids and catheter systems were examined in a surgical ICU. The overall rate of bacterial colonisation of bottles/burettes was up to 15.7% at 96 hours, while colonisation rates of catheter fluid were 34.0% and 24.1% respectively. These high rates of colonisation, despite regularly reinforced hand disinfection practices, may be explained by the high frequency of manipulations of the catheter systems, during acute interventions in emergency situations (Trautmann et al, 1997).

In humans endotoxins can induce severe systemic health effects ranging from mild fever to endotoxic shock. Cytokines like tumor necrosis factor (TNF- α) and Interleukin (IL-6) will be elevated and

Abstract Summary

subsequently induce a rise in body temperature and pulse rate while a significant decrease in blood pressure will occur.

Cases of bacterial or endotoxin contamination during production and transport are extremely rare. Most of the contaminations occur during use of the often complex infusion systems.

Particle contamination of infusion solutions exists despite a stringent infusion regimen. The number and composition of particles depends on the complexity of the applied admixtures. The biological effects of particles are dependent on particle characteristics like size, shape and concentration. Beyond possible physical effects, immunological effects like the suppression of macrophage and endothelial cell cytokine secretion in vitro suggests that particle infusion in vivo may have relevant immune-modulating effects (Jack et al, 2010). These effects might be important for the toxicological effects of particle infusion.

Most of the contaminations of infusions by particles, as well as by endotoxins, occur during use of the often complex infusion systems. This might be avoided by careful use of the systems and strict execution of hygiene plans. An additional possibility to protect patients is the use of filter systems retaining bacteria as well as endotoxins.

Jack T, Brent BE, Boehne M et al (2010) Analysis of particulate contaminations of infusion solutions in a pediatric intensive care unit. *Intensive Care Med* **36**(4): 707–11. doi: 10.1007/s00134-010-1775-y

Trautmann M, Zauser B, Wiedeck H, Buttenschön K, Marre R (1997) Bacterial colonization and endotoxin contamination of intravenous infusion fluids. *J Hosp Infect* **37**(3): 225–36

How many nanoparticles enter a patient during infusion therapy?



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Introduction: Infusion therapy has substantial clinical importance but also involves risks of introducing particles into the body, which can lead to serious complications. The particles may

be present in the IV solutions or derive from the infusion system. To avoid particle contamination, many clinical institutions use filters at the point of infusion. The focus in these experiments was on the number of submicron particles found in the infusion fluid after perfusing an infusion system with and without filters.

Method: The experimental design simulated a real clinical situation in a clinical ICU. Instead of real patients, glass vials were used, in which the infusion fluids that are typically used in a regime for intensive care patients were infused over a period of 72 hours (Figure 1). The experiment was carried out without and with in-line IV filters (Pall®) at the point of infusion. The particles were counted with the NanoSight NS300 (Malvern Instruments).



Figure 1: Setup of the experiment without filters

Results: In the experiments without filters, particle counts fluctuated widely and revealed particle counts to up to $1.9 \cdot 10^8$ particles/mL. From the results it could be calculated that a total number of about 76 billion submicron particles would have entered a patient during 72 hours of infusion therapy. The total number of infused particles could be reduced by 87% by using in-line IV filters.

Discussion and conclusion: The experiments reveal that high numbers of submicron particles enter the body during infusion therapy. The fluctuation in the particle counts in the experiments without filters indicates that numerous effects, e.g. type of medication, set up of the infusion system or slightly different handling of nurses can have tremendous effects on the number of infused particles. The usage of filters can efficiently reduce these effects and reduce the number of particles introduced into the patient.



Identification of micro- and macroparticles entering a body during infusion therapy



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Infusion therapy is always accompanied by the risks of the application of unintentionally present particles into the patient causing serious complications. The goal of the study was to understand the amount of micrometre-sized particles as well as their composition found in the infusion fluid after perfusing an infusion system with and without filters. To simulate a clinical situation in a clinical ICU, glass vials were used to collect the infusion fluids typically used for intensive care patients during a period of 72 hours. The particles were isolated by filtration with a gold-coated membrane filter with a pore size of 0.8 μm . Counting and identification was performed by an automated system (rap.ID Single Particle Explorer) based on Raman spectroscopy.

The majority of particles originate from incompatibilities of different drugs because of pH shifts and oxidation processes. Another major source of particles is silicone, which can be released from the infusion equipment e.g. syringes and can interact with different kinds of drug substances forming stable particles with drug compounds e.g. antibiotics. The effect of silicone release was dramatically increased during bolus injections.

The particle load of the infusion set itself and infusion solutions like saline was also investigated. Varieties of plastic materials e.g. polypropylene, polystyrene, silicone as well as cellulose fibres were identified as main contributors of particulates for the infusion equipment. Cellulose fibres are in general the most observed foreign particle in drug products.

The experiments show particle numbers in the range of $1.6 \cdot 10^4$ to $25 \cdot 10^5$ particles $>2\mu\text{m}$ entering the body during infusion therapy. Particle numbers during the infusion experiment could be effectively reduced by 84-95% regardless of the chemical species for stabilised particles by the use of an in-line filter.

The large amount of silicone, as well as the amount of particles due to hardly visible incompatibilities was unexpected and should be further investigated. The usage of filters reduces most of the different kinds of particles efficiently and avoids the application of large numbers of particles into the patient.

Particles in parenteral nutrition



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Parenteral nutrition may contain glass, plastic, rubber, metal or fabric particles in suspension, either from the manufacturing process or from vials, ampoules and gauze manipulation. These particles can be avoided by filtering in the parenteral nutrition preparation, usually with 5 micron filters, when content from ampoules or vials are added to the bag of parenteral nutrition.

Parenteral nutrition may have enlargement of lipid droplets owing to emulsion destabilisation and can also generate calcium phosphate precipitates as a result of compatibility problems.

There are many factors that influence the precipitation of calcium and phosphorus. The risk of precipitation increases at high calcium/phosphorus concentration, low amino acid concentration and acidic pH. The source of calcium and phosphorus is also very important. Organic sources are more compatible than inorganic ones. There are many studies on precipitation with inorganic sources of calcium and phosphorus e.g. Wong et al (2006) and MacKay et al (2011), but not many with organic sources e.g. Anderson and Mackay (2015).

A study was conducted to investigate if precipitates occurred in parenteral nutritions commonly used in hospitals. Several paediatric parenteral nutrition solutions without lipids were compounded and stored at ambient temperature for 20 hours followed by 4 hours at 35°C to simulate a neonate incubator. After the storage time, the parenteral nutritions were filtered through a 0.2 micron filter and these filters were observed using scanning electron microscopy. This task was performed by Pall Corporation. Only 2.25%

Abstract Summary

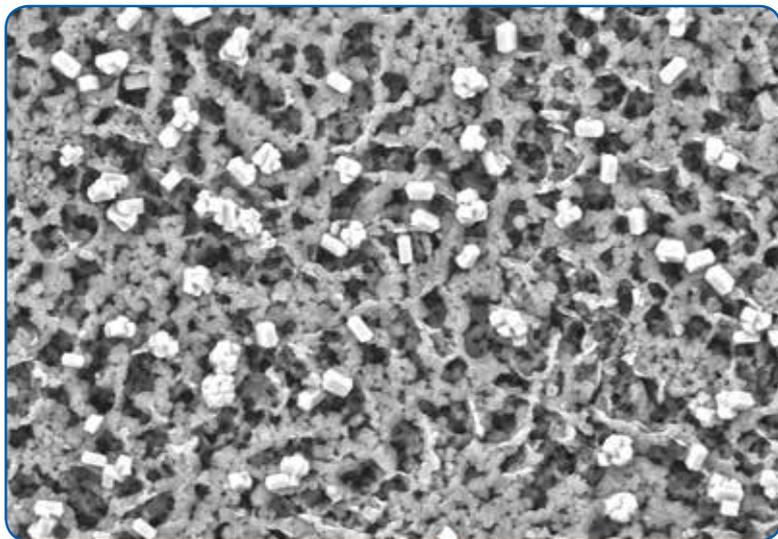


Figure 2. Particles found (magnification x 1000)

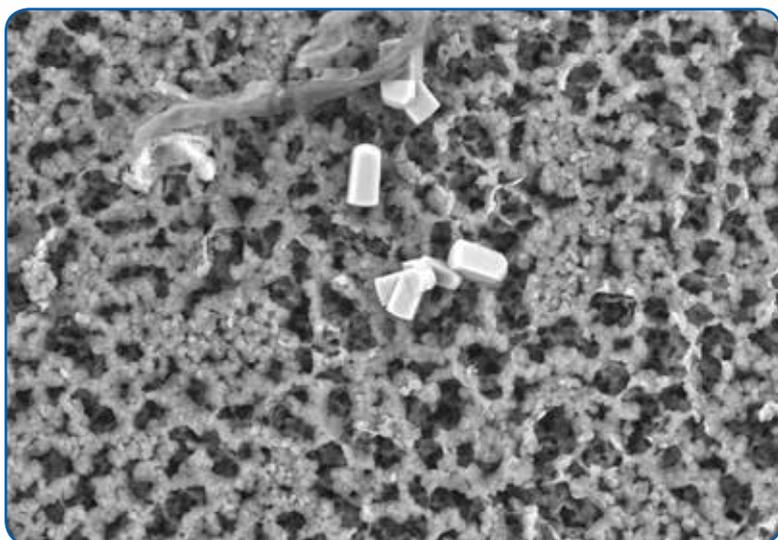


Figure 3. Particles found that could be a piece of gauze

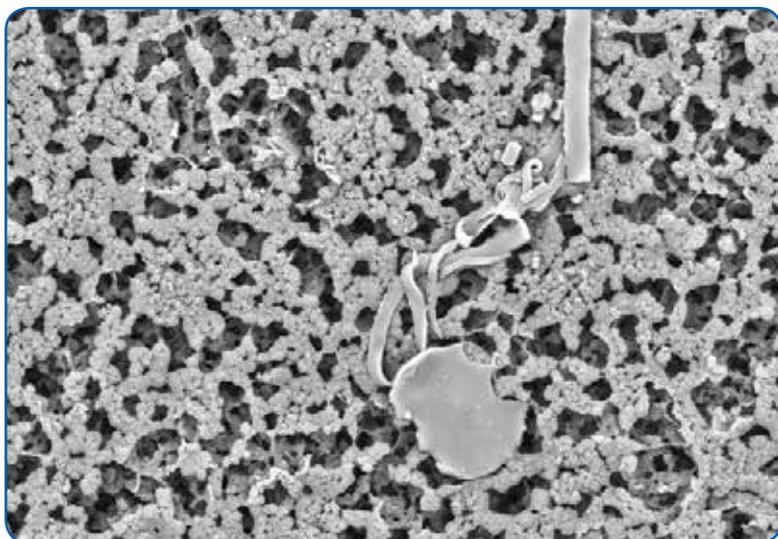


Figure 4. Particles found that could be a piece of rubber

of the filter was observed at magnification of 100. Many particles were found (Figure 2). More particles were observed at higher calcium and phosphorus concentrations. Also a decrease in the number of particles was observed when the amino acid concentration increased.

Particles that may have been a piece of gauze (Figure 3) or a piece of rubber from a vial (Figure 4).

Despite using organic phosphorous sources, parenteral nutrition solutions are not always free of particles. To prevent the passage of particles to the patient, health professionals should always use filters in administration.

- Anderson C, MacKay M (2015) Physical compatibility of calcium chloride and sodium glycerophosphate in pediatric parenteral nutrition solutions. *JPEN J Parenter Enteral Nutr.* doi: 10.1177/0148607115592673. [Epub ahead of print]
- MacKay M, Jackson D, Eggert L, Fitzgerald K, Cash J (2011) Practice-based validation of calcium and phosphorus solubility limits for pediatric parenteral nutrition solutions. *Nutr Clin Pract* **26**(6): 708–13. doi: 10.1177/0884533611426435
- Wong JC, McDougal AR, Tofan M, Aulakh J, Pineault M, Chessex P (2006) Doubling calcium and phosphate concentrations in neonatal parenteral nutrition solutions using monobasic potassium phosphate. *J Am Coll Nutr* **25**(1): 70–7

Advanced IV filtration technology: prevention of bacterial transfer and intraluminal biofilm formation



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Introduction: In 2002, the Centers for Disease Prevention and Control recommended to not use IV filters for the prevention of infection (O'Grady et al, 2011). The use of a 96-hour 0.2µm, air-eliminating, and bacteria and endotoxin retentive (ABE) filter challenges this guideline. An in vitro study was conducted in two laboratories to compare intraluminal bacterial transfer and biofilm formation when an ABE filter is placed between a needleless connector (NC) and catheter hub compared to a NC attached directly to the catheter hub.

Methods: In the test group, the NC was attached to



the filter attached to a 5Fr peripherally inserted central catheter (PICC). The NC was attached to the PICC in the control group. Three of each catheter system was used for the 96 hour study. At the start and middle of each day, the NC septum was inoculated with mean 5.8 log (CFU/inoculation) of *Staphylococcus aureus*. The connector/catheter sets were flushed for a total five 10 ml normal saline flushes per day and locked for 1 hour with a total parenteral nutrition solution after the first, third and fourth set of flushes. At the end of the last day, two sets were destructively sampled to measure biofilm within the connector, filter, catheter hub and catheter segment.

Results: When averaged across all flushes over 5 days, the ABE had a statistically significant mean log reduction of 3.24 of bacteria in the flush ($p = 0.009$). No bacteria were recovered from any of the hubs on the ABE systems. The mean log reduction of 1.55 was statistically significant ($p = 0.03$). No bacteria were recovered from any of the catheter segments on the ABE systems. The mean log reduction of 1.53 was statistically different ($p = 0.05$).

Conclusion: The use of the 0.2 μ m ABE filter eliminated the passage of bacteria through the filter and significantly reduced biofilm formation within the catheter hub and lumen.

O'Grady NP, Alexander M, Burns LA et al (2011) Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis* **52**(9): e162-193. doi: 10.1093/cid/cir257

Meeting the 2016 Infusion Therapy Standards of Practice



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The 2016 *Infusion Therapy Standards of Practice*, incorporated noteworthy additions to Standards and Practice Criteria for Filtration. The first change was their inclusion in the 'Vascular Access Device (VAD) Management' section and not in the 'Equipment' section as before, suggesting an emphasised clinical practice direction.

Additionally, there was recognition of 'evolving evidence' regarding the deleterious effect of both particulate matter on endothelium and μ m bubbles of air, causing pulmonary and cardiac damage. Also recognised were published articles (Jack et al, 2012; Boehne et al, 2013) that have shown the use of filters has had very positive results for fluid and drug delivery in the more critically ill paediatric patients in reducing the incidence of SIRS, time on the ventilator, length of stay in the ICU, and overall improved outcomes.

The INS practice guidelines recommend the use of add-on bacteria, particulate-retentive and air eliminating filters whenever possible to reduce tubing manipulation contamination risk, misuse and accidental disconnection/misconnection as well as placing them, whenever possible, close to the VAD hub.

As Chopra et al (2015) stated, as patients move between care settings, it is important to 'do what's right' for patients in terms of vascular access.

We have a responsibility to understand and adopt standards of practice in our complex industry today, incorporating them into our work environment and seeking out tools to make those practices cost effective, cost efficient and improve patient care and outcomes.

Boehne M, Jack T, Köditz H et al (2013) In-line filtration minimizes organ dysfunction: New aspects from a prospective, randomized, controlled trial. *BMC Pediatrics* **13**: 21. doi: 10.1186/1471-2431-13-21

Chopra V, Flanders SA, Saint S et al (2015) The Michigan Appropriateness Guide for Intravenous Catheters (MAGIC): results from a multispecialty panel using the RAND/UCLA Appropriateness Method. *Ann Intern Med* **163**(6 Suppl): S1-40. doi: 10.7326/M15-0744

Infusion Nurses Society (2016) Infusion Nursing Standards of Practice. *J Infus Nurs* **39** (Supple I): S70-1

Jack T, Boehne M, Brent BE et al (2012) In-line filtration reduces severe complications and length of stay on pediatric intensive care unit: a prospective, randomized, controlled trial. *Intensive Care Med* **38**(6): 1008-16. doi: 10.1007/s00134-012-2539-7

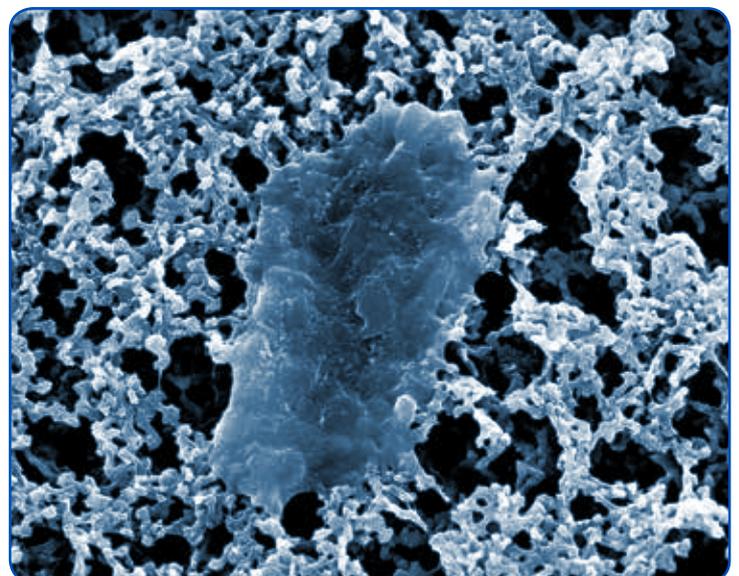
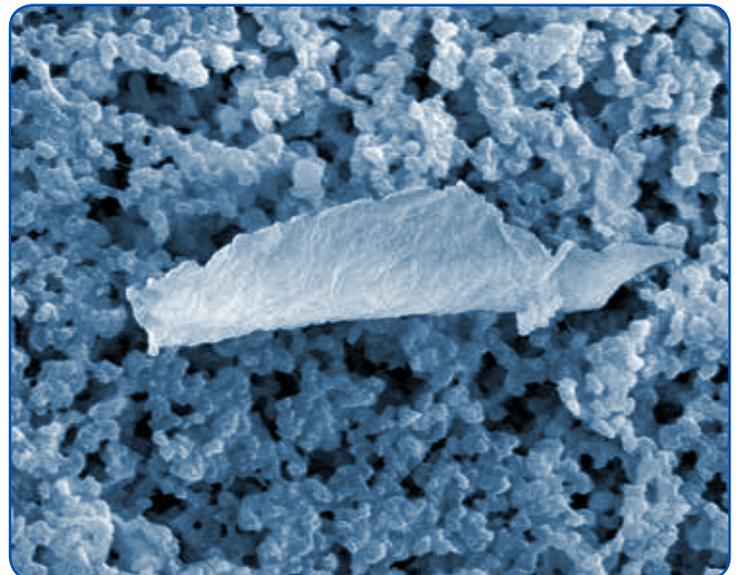
Conclusion



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Many aspects need to be verified by further research. In this regard, an international consensus of experts is much needed to identify the areas that deserve clarification (e.g. what is the clinical relevance of minimal amounts of endotoxin and bacteria getting into the bloodstream? Can we actually reduce biofilm formation inside the central venous catheter by a consistent use of 0.2-micron filters? Which are the inert particles that can really do harm, and by which mechanisms? Should we filter any intravenous infusion in the ICU, and which filters should we use?)

In the meantime, the answer to our Hamlet dilemma, to filter or not to filter, is yes, in most of these situations there is accumulating evidence that we should.





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