Editorial

JVA The Journal of Vascular Access

The Journal of Vascular Access
2022, Vol. 23(2) 179–191

DOI: 10.1177/1129729821989165
journals.sagepub.com/home/jva
SAGE

WoCoVA consensus on the clinical use of in-line filtration during intravenous infusions: Current evidence and recommendations for future research

Ton Van Boxtel[1], Mauro Pittiruti[2], Annemarie Arkema[3], Patrick Ball[4], Giovanni Barone[5], Sergio Bertoglio[6], Roberto Biffi[7], Christian Dupont[8], Caroline Fonzo-Christe[9], Jann Foster[10], Matthew Jones[11], Cornelia Keck[12], Gillian Ray-Barruel[13], Michael Sasse[14], Giancarlo Scoppettuolo[2], Agnes Van Den Hoogen[15], Gianluca Villa[16], Lynn Hadaway[17], Marcia Ryder[18], Gregory Schears[19] and Josie Stone[20]

Abstract

The need for filtering intravenous infusions has long been recognized in the field of venous access, though hard scientific evidence about the actual indications for in-line filters has been scarce. In the last few years, several papers and a few clinical studies have raised again this issue, suggesting that the time has come for a proper definition of the type of filtration, of its potential benefit, and of its proper indications in clinical practice. The WoCoVA Foundation, whose goal is to increase the global awareness on the risk of intravenous access and on patients' safety, developed the project of a consensus on intravenous filtration. A panel of experts in different aspects of intravenous infusion was chosen to express the current state of knowledge about filtration and to indicate the direction of future research in this field. The present document reports the final conclusions of the panel.

Keywords

In-line filters, in-line filtration, filtering intravenous solutions, endotoxin, bacteria, particles, inert particles, microparticles, phlebitis, neonates, biofilm, drug incompatibility

Date received: 24 August 2020; accepted: 24 December 2020

Introduction

The vast majority of hospitalized patients get some form of intravenous (IV) infusion, which carries the risk for different types of complications such as phlebitis, sepsis and adverse reactions against materials and fluids introduced into the circulation. In-line filtration has been proposed for

[1]WoCoVa Foundation, Utrecht, The Netherlands
[2]Catholic University Hospital, Rome, Italy
[3]Arkema Biomedical Consultancy, Soest, The Netherlands
[4]University of Wolverhampton, Wolverhampton, UK
[5]Infermi Hospital, Rimini, Italy
[6]University of Genova, Genova, Italy
[7]European Institute of Oncology, Milano, Italy
[8]Universite Paris Descartes, Paris, France
[9]Geneva University Hospital, Geneva, Switzerland
[10]Western Sydney University, Sydney, Australia
[11]East Kent Hospitals University NHS Foundation Trust, Canterbury, UK
[12]Universität Marburg, Marburg, Germany
[13]Griffith University, Brisbane, Australia
[14]Medizinische Hochschule Hannover, Hannover, Germany
[15]Universitair Medisch Centrum Utrecht, Utrecht, The Netherlands
[16]University of Florence, Florence, Italy
[17]Lynn Hadaway Associates, Milner, Georgia, USA
[18]Ryder Science, California, USA
[19]Mayo Clinic, Rochester, MN, USA
[20]Josie Stone Consulting LLC, CA, USA

Corresponding author:
Mauro Pittiruti, Catholic University Hospital, Largo Francesco Vito 1, Rome, 00168, Italy.
Email: mauropittiruti@me.com

many decades as a possible tool for controlling and/or minimizing the undesirable IV inoculation of bacteria, inert particles, endotoxins, and other potentially obnoxious items. Most current guidelines do not state the proper indication to use in-line filtration during IV administration of fluids. The most recent edition of the Infusion Nurses Society (INS) "Infusion therapy standards of practice" (2016)[1] is an exception as it clearly addresses the issue of filtration. According to the INS recommendations, filtration should be adopted when infusing parenteral nutrition solutions (0.2- or 1.2-micron filters, depending on the absence/presence of lipids), blood and blood components (170- to 260-micron filters) and medications withdrawn from glass ampoules (filter needles or filter straw); filtration is also recommended for intraspinal infusions (0.2-micron filters), which will not be discussed in this document. Regarding the potential indications for filtration in other situations, there is much more uncertainty. On the basis of a few clinical studies carried out in a pediatric intensive care unit,[2] INS standards suggest "considering" the use of 0.2- and 1.2-micron filters when infusing intravenous solutions in critically ill patients. On the other hand, on the basis of a 2010 review,[3] the routine use of in-line filtration for prevention of phlebitis related to peripheral IV cannulas is not recommended by INS.

However, in the last few years, an increasing number of clinical studies both in adult and pediatric patients have suggested some positive effect of filtration on reducing IV related complications. An important symposium on filtration was held at the World Conference on Vascular Access (WoCoVA) in Lisbon, Portugal on 24th June 2016. During the debate, in part published later in the British Journal of Nursing,[4] some relevant data were presented.

First, there is a growing evidence that any IV infusion carries the inevitable risk of delivering undesired material (for example, endotoxins, bacteria, inert particles and microbubbles of air) into the bloodstream. This typically happens during complex infusions in the intensive care unit (ICU).[2,5] Inert particles include drug precipitates, silicon fragments and other foreign materials,[4] but also precipitates with inorganic sources containing calcium and phosphorous[6,7] and to a lesser extent participates with organic sources.[8]

Second, we now have commercially available filters (particularly 0.2 micron), which are proven to be effective. They can dramatically reduce the number of microparticles entering the bloodstream, by stopping the majority of them[4,9] and they can also eliminate the passage of bacteria.[10] Third, there is some clinical evidence that filtration carries potential outcomes benefits, particularly for some at-risk populations, such as critically ill and immunecompromised patients. The consistent use of 0.2-micron filters—which reduces the administration of endotoxin, bacteria and inert materials (which may not be so "inert", after all, as there is some evidence on their effect on immune state and cytokine formation)—seems to be associated with a clinical benefit in critically ill children, in terms of reduction of the incidence of systemic inflammatory response syndrome and organ failure.[5]

Based on the need for clarification, the WoCoVA Foundation (WoCoVA = World Conference on Vascular Access) decided to develop a project for international consensus on the use of in-line filtration. A carefully selected group of experts in both infection prevention and/or vascular access complication management has been formed to so to examine the current available evidence and prepare a consensus document stating the actual indications for IV filtration and defining the future clinical studies needed for further clarification of this issue, both in adult and in pediatric patients. The overall goal of this consensus paper was to increase global awareness on the risks of IV therapy and patient safety, which is one of the main goals of the WoCoVA Foundation.

Methods

A literature search was done in PubMed and in the Cochrane library in September 2018, with subsequent updates in March and July 2019. Search terms used were as follows: in line (filter or filtration); filtering intravenous solution; filters endotoxin; filters phlebitis; filters neonates; filters biofilm; filters bacteria; intravenous filters; particles intravenous.

A panel of experts on vascular access with a focus on in-line filtration was selected, based on their competence as proven by the studies available in the scientific literature. The panel consisted of infection prevention experts, hospital and clinical pharmacists and physicians and nurses widely recognized as experts in the field of vascular access.

The panel of experts was divided into three working groups, each dealing with one of the three main topics that had previously defined: "Evidence about possible harmful effects of inert particles in intravenous infusions" (group 1), "Potential benefits of in-line filters in reducing peripheral phlebitis" (group 2), "Potential benefits of in-line filters in reducing systemic inflammation/infection" (group 3). A separate group of experts, not included in the working groups, was selected for the final peer review of the document. See Table 1 for the list of experts in each working group and the experts selected as peer reviewers.

A questionnaire was prepared for each group. The questions were formulated so that each group could answer from its own specific point of view. The purpose was to have a broad perspective on the use of in-line filters.

The questions for the experts of working group 1 (effects of inert particles) were as follows:

- Which are the types and dimensions of the particles potentially related to harmful clinical effects?
- Is there any evidence of harmful clinical effects due to particles?

Table 1. Panel of experts.

Coordinators
Annemarie Arkema
Mauro Pittiruti
Ton Van Boxtel
Working group 1 (effects of inert particles)
Patrick A. Ball
Caroline Fonzo-Christe
Jann P. Foster
Cornelia Keck
Working group 2 (peripheral phlebitis)
Sergio Bertoglio
Christian Dupont
Matthew Jones
Gillian Ray-Barruel
Gianluca Villa
Working group 3 (systemic infections)
Giovanni Barone
Roberto Biffi
Michael Sasse
Giancarlo Scoppettuolo
Agnes Van De Hoogen
Peer reviewers
Lynn Hadaway
Marcia Ryder
Gregory Shears
Josie Stone

- Which kind of filters is available for clinical use and which kind of particles are they expected to stop?
- Which basic research is currently warranted for further investigation in this area?

The questions for the experts of working group 2 (peripheral phlebitis) were as follows:

- Please provide an acceptable definition for peripheral catheter-related "phlebitis"
- Which are the commonly accepted causes of phlebitis?
- Is there evidence that phlebitis might be related to particles?
- Is there evidence that the clinical use of filters might reduce this risk?
- Which clinical research is warranted for further investigation in this area?

The questions for the experts of working group 3 (systemic infections)

- Please provide acceptable definitions for sepsis – systemic infection – SIRS – septic shock
- Which is the currently accepted pathogenesis of the pathophysiologic effects of systemic infection?
- Is there any evidence that particles might be involved in this pathogenesis?
- Is there evidence that the clinical use of filters might reduce systemic infection or systemic inflammatory response? And in which kind of patients?
- Is there any evidence that the use of filters can also improve clinical important outcomes (such as length of stay, survival, duration of mechanical ventilation etc.) through the reduction of SIRS?
- Which clinical research is warranted for further investigation in this area?

Each working group was provided with the most relevant papers found by searching the literature. Twenty-nine general papers on filtration were considered to be relevant for all working groups. More specific papers were also forwarded to each working group (32 papers to group 1, 17 to group 2 and 23 to group 3). Each expert was asked to formulate his/her answer to each question on the basis of available evidence and clinical practice.

Answers from the individual experts on each specific question were combined together in a narrative form, leading to a few final statements with a proper degree of consensus from the whole working group.

Results

(1) Evidence about possible harmful effects of inert particles in intravenous infusions

Discussion. What happens with particles when they are introduced into the body by IV infusion depends on the dimension (size and shape), the number and the surface properties of the particles.

More than 50% of particles in drug solutions are between 5 and 15 micron and sub-visible. Particles $>$ 12 micron cannot be phagocytosed by pulmonary macrophages or reticuloendothelial cells, suggesting a size limit for the phagocytosis of inert particles. The diameter of lung and tissue capillaries is 5–10 micron, thus all particles $>$10 micron may potentially cause obstruction[11]; 10–12-micron particles stay lodged in pulmonary capillaries. Also, 3–6-micron particles are lodged in spleen and hepatic lymph nodes for prolonged periods, possibly due to phagocytosis by reticuloendothelial cells; 1-micron particles are lodged in the liver.

About 5% of the particles in IV drug solutions are $>$50 micron[12–14]; these particles are visible. A maximum number of such particles is usually accepted. Some studies show that generic antibiotics have many more particles than the original preparation.[13,14] The presence of such a load of particles cannot be ignored, since they might be cytotoxic and have immune-modulating effects.[15] In addition to material

and size, particles also possess different shapes and surface properties (hydrophilicity or charge).

A special type of inert particles is that related to precipitate due to drug incompatibilities, which frequently occur because of the number of drugs administered through an inadequate number of infusion lines. Injected particles can be trapped in the lungs and micro-particles caused by drug incompatibility may lead to micro-emboli and granuloma in pulmonary vessels.[16]

As regards the potential harmful clinical effect of particles,[11] this depends on the accumulation of all particles and is therefore highly complex and, so far, not yet predictable.

In general, large particles can block capillaries. On the other hand, smaller particles – depending on their surface properties – interact with blood plasma proteins. Hence, blood proteins will stick to the surface of the particles and will create so-called "protein corona". Which types of blood proteins will stick to the particles is not predictable – even though more than 25 years of research has been conducted in this field. In general, we can discriminate between two scenarios. In the first case, opsonin is bound to the particles and this leads to a recognition of the particles by the immune system and the activation of inflammation mechanisms (acute toxicity). In the second scenario, the particles are bound to dys-opsonin and are not recognized by the immune system: this leads to a long-lasting circulation of the particles. Depending on their properties, these particles can enter various parts of the body, including brain and bone marrow, and create a deposit. Whether these particles might cause late immune responses and/or inflammation (sub-acute and chronic toxicity), triggering oxidative stress-related diseases (e.g. Alzheimer's disease, Parkinson or tumors) cannot be predicted and should be addressed in further studies.

Schaefer et al.[14] warned that through the increased use of cheaper generic and false medicines with substandard manufacturing qualities, the contamination of parenteral fluids and drugs by particulate matter poses an increasing health hazard worldwide.

Occlusions due to particles can result not only in drug delivery problems for the patient (which may be harmful particularly in the critical care setting) but also may have potentially harmful consequences. Granulomas, respiratory distress syndrome/pulmonary embolism, thrombosis, multi-organ dysfunction, fatal bowel necrosis, phlebitis, systematic inflammatory response syndrome, sepsis, systemic infection and septic shock are all possible harmful clinical effects of particles.

Several case reports have described the effect of particulate matter on the pulmonary system during parenteral nutrition (PN). Hill et al.[17] reported drug incompatibilities involving PN, leading to amorphous material containing calcium and obstructing the pulmonary micro vasculature, as an autopsy finding. McNearney et al.[18] reported on a patient receiving PN with multiple diffuse lung nodules. Reedy et al.[19] also reported apparently unexplained chest tightness, shortness of breath and fever in a patient on PN.

Felton et al.[20] observed life-threatening pulmonary hypertension which was attributed to calcium and phosphate replacement and particulate contamination. Bradley et al.[21] reported deaths of seven neonates after receiving IV ceftriaxone and calcium. Four of the five infants were found to have crystalline material and white precipitates in lung vasculature.

Although the specific relation between inflammation and thrombosis remains unclear, catheterization of any vein is often associated with thrombus formation.[22] In particular, the endothelium damage induced by the venous catheterization produces accumulation and activation of clotting intermediates, thus leading to thrombosis. Histopathology studies of veins following peripheral catheter-related phlebitis demonstrate swelling of endothelial cells, leukocyte infiltration and other changes consistent with inflammation of the vein wall,[22,23] fibrin deposition and thrombus formation.[23] It is not known if and how inert particles may play a role in favoring this local inflammatory process.

In one case reported by Cant et al.,[24] fatal bowel necrosis occurred in a neonate, apparently because of plastic particles from a syringe (a thrombus contained irregular 50–200 micron fragments of plastic identified as polypropylene was found on histopathological examination and laser spectroscopy). Bavikatte et al.[25] reported systemic embolization of cotton fiber particles in two neonates, demonstrated at post-mortem examination. Puntis et al.[26] reported two cases of infants with pulmonary granulomas in the pulmonary arterial system. Occasional fragments and visible cotton fibers were identified on post-mortem examination.

Several types of filters are currently available for clinical use. They can remove lipid aggregates, larger molecules, fibrin complexes and micro-organisms. In-line filters are expected to remove all particles over 0.2 (or 1.2 micron). In experimental studies, 0.2-micron filters can retain 550 particles/cm^2, most particles being between 5 and 50 micron and silicon a major component.[15] In other studies, retention of particles was of 97.6%. Smaller particles (0.05 micron) were also retained, with an efficacy ranging from 63 to 99%.[9] Recently, using a dynamic particle counter, Perez et al.[27] showed that in-line filters were effective in reducing overall particulate matter and in reducing particles $>$10 micron and 25 micron. The number and composition of particles that will be formed and retained depend on many factors such as type of filter (pore size, type of membrane), type of drugs (pH, charged or not), volume of eluents (dissolution of precipitates), number of drugs (high risk of drug incompatibilities), complexity of infusions (parenteral nutrition) and position of the in-line filter in the infusion set. Possible physical limitations of these filters have to be mentioned. According

to Ball,[28] hospitals have reported that in-line filters interfere with therapy delivery because they might be blocked and require removal or replacement so to continue therapy delivery. This misses the point that in most cases, the filter has become blocked because their current practice for medication administration is resulting in-line precipitate formation: without using the filter, such drug precipitates would have been infused into the patient. In this context, the filter is doing precisely what it was meant to do; to prevent the infusion of particles and to warn the user that their practice is unsafe.

Conclusions of the panel

Which are the types and dimensions of the particles potentially related to harmful clinical effects? The types and dimensions of the potentially harmful particles are extremely variable. The types include particles coming from the infusion line and from the containers (fiber, glass, rubber, etc.) or particles coming from the environment (drug precipitates, lipid aggregates, bacteria, endotoxin, dust, etc.). Most of these particles are <50 micron and are not visible; the majority is between 5 and 15 microns.

Is there any evidence of harmful clinical effects due to particles? Particles < 10–12 micron can be phagocytosed by macrophages and may potentially act by modifying cell activities. Particles > 10–12 micron can occlude the microcirculation and may potentially be associated with local tissue damage, particularly in the lung. A great variety of pathological conditions (granulomas, respiratory distress syndrome/pulmonary embolism, venous thrombosis, multi-organ dysfunction, fatal bowel necrosis, phlebitis, systematic inflammatory response syndrome, sepsis, systemic infection and septic shock) has been potentially ascribed to the effect of particles, with different mechanisms, though most of the evidence is anecdotical and described as single clinical case reports.

Which kind of filters is available for clinical use and which kind of particles are they expected to stop? Different types of in-line filters with different pore diameters are commercially available. Filters with 0.2 micron are expected to stop the vast majority of particles, including bacteria and air bubbles; 1.2-micron filters are used for removing lipid aggregates during administration of PN. Larger filters are also available (8-micron, 15-micron) but they are unlikely to remove most of the potentially harmful particles.

Which basic research is currently warranted for further investigation in this area? The harmful effects of inert particles are currently postulated on the basis of clinical expertise and knowledge of basic pathophysiology; clinical evidence, albeit scarce, is based mostly on single case reports of fatalities, with post-mortem documentation of particles in the microcirculation. Some experimental evidences exist, but it is widely recognized that data obtained by experimental studies cannot automatically extrapolated to clinical practice. Therefore, we recommend that future studies should be clinical trials, aiming to identify the occurrence of potentially particle-related complications in different groups of patients, with and without the implementation of in-line filtration, and preferentially – when ethically acceptable – under the structure of randomized controlled trials. In such clinical trials, possible undesired effects related to the use of filters should be carefully recorded and reported. In this regard, little is known about the expected rate of line malfunction secondary to the use of filters, which may vary depending on the overall management of the infusion line but also on the characteristics of the membrane, as the infusion flow rate decreases when the porosity of the membrane decreases. Other undesired effects to be investigated include the possibility of interaction between filters and the IV therapy (cellulose acetate membranes may retain proteins such as monoclonal antibodies and immunoglobulins, and this may alter the therapeutic efficacy). Last but not least, the actual indications for the use of filters should take into consideration also the evaluation of their cost-effectiveness (which depends on the cost of the device and on the frequency of its replacement).

(2) Potential benefits of in-line filters in reducing peripheral phlebitis

Discussion. Peripheral venous cannulation is the most common procedure performed among hospitalized patients worldwide and phlebitis represents a common and painful complication of peripheral IV cannulation.[29] As a matter of fact, phlebitis (i.e. thrombophlebitis) is the most frequent complication associated with peripheral intravenous cannulas (PIVC).[30] It often leads to vascular access malfunction, unwanted interruption to the prescribed IV therapy, requirement for insertion of a new vascular access device and thus increased equipment costs and staff time.[31]

A lot of data on incidence and/or risk factors is available on PIVC-related phlebitis. Most of the papers remark the pathophysiological role that the inflammation of the vein has in the definition of peripheral catheter-related phlebitis. However, a lack of consensus on its clinical definition has contributed to generating a chaotic disparity in the incidence of this condition across several studies.[3] A systematic review by Ray-Barruel et al.[29] described which diagnostic criteria are currently used to define infusion phlebitis in the clinical setting. Furthermore, they evaluated the current scales for assessment of infusion phlebitis in terms of reliability, validity, responsiveness and feasibility.[29] After the screening of more than 1000 studies, the authors found that, although the incidence of peripheral catheter-related phlebitis was reported in 233 papers, 53 papers (23%) failed to specify how they defined phlebitis. One hundred and eighty of the remaining studies described the method used for phlebitis

assessment; among these, 101 (56%) reported using a scale, while 79 (44%) used a definition alone.[29] Seventy-one phlebitis assessment scales were thus identified, including 15 symptoms, such as pain, tenderness, erythema or redness, edema or swelling, palpable venous cord, induration or hardness, straight thrombosis, streak formation or red line, purulence or exudate, local warmth, local coolness, infusion slowed or stopped, fever or pyrexia, tissue damage and impaired function. Although the prevalence of these symptoms was widely variable across different studies, erythema/redness, local pain, edema/swelling, warmth and palpable venous cord were undoubtedly the most common.[29] Interestingly, the authors observed a significant disparity among the 71 phlebitis assessment scales; some authors used a previously published scale, while others modified an existing tool or created their own. Furthermore, when an already existing scale was used – for example, the Visual Infusion Phlebitis (VIP),[32] Infusion Nurses Society (INS),[1] Maddox et al.[33] or Lipman[34] scale – the authors often failed to state which version they had used.[29] Among all scales already available for defining and grading of peripheral catheter-related phlebitis, only three of them gave any description of their psychometric adequacy: the VIP scale, the INS phlebitis scale and the PVC ASSESS.[29]

As a conclusion, the definition of peripheral catheter-related phlebitis, summarized as an inflammation of the vein, which may be mechanical, chemical or bacterial in origin, is based on a variable spectrum of symptoms, the most frequent of which are erythema/redness, local pain, edema/swelling, warmth and palpable venous cord.[35] In most cases, the inflammation concerns the tunica-intima of a superficial vein and it is almost always associated with a local thrombosis, secondary to endothelial damage. There is not one single cause of PIVC-related phlebitis. However, three causal categories, leading to local prostaglandin-mediated activation of the inflammatory cascade,[22] are usually described:

Chemical: Phlebitis caused by chemical agents (medications or infusions) that may be associated with inflammation or injury to the endothelium.

Mechanical: Phlebitis caused by physical trauma to the vein, leading to vein inflammation and thrombus formation, typically because of micro-movement of the catheter in the vessel due to inadequate securement at the insertion site or due to a chosen insertion located in an unstable area, or because of a catheter too large for the vein (i.e. exceeding 33–45% of the inner diameter of the vein).[36]

Infective: Bacterial contamination may occur by four different mechanisms:

1. Extraluminal contamination due to inadequate antisepsis of the skin or contamination of the catheter during insertion or during maintenance.
2. Intraluminal contamination through the hub (needle-free connector, stopcock, etc.) due to improper maneuvers when manipulating the infusion line.
3. Intraluminal contamination due to fluids or medications contaminated by bacteria.
4. Hematogenous seeding from an infection elsewhere in the body.

Infective phlebitis is commonly due to extraluminal contamination (the first of four these mechanisms). Several clinical studies have tried to define the risk factors for peripheral catheter-related phlebitis, but most of them are limited by small sample size, lack of a control group, use of retrospective design, and inadequate analyses. From an etiological point of view, significant risk factors for infusion-related phlebitis surely include the composition of the infusion set, the material of the catheter, the anatomic location of the catheter, the duration of catheterization, the pH and the osmolarity of the infused fluid, and the presence/absence of contaminants in the infusion solutions. In fact, infusion fluids may be contaminated with bacteria, endotoxins, precipitates, large lipid aggregates, and air.[3]

Risk factors are often identified as patient-specific or catheter-specific.[36] Female sex, "poor-quality" peripheral veins and the presence of underlying medical disease (cancer, immunodeficiency) appear to increase the risk of peripheral catheter-related phlebitis.[37,38] The duration of catheterization is probably the main risk factor for peripheral catheter-related phlebitis.[37,39] Critical importance was given to this predictor, and for a long period of time the Centers for Disease Control and Prevention (CDC) recommended rotation of catheter sites every 48–72 h to "minimize the risk of phlebitis"; current guidelines from INS, CDC and EPIC (EPIC = Evidence-based Prevention for Infection Control)[40] do not include this recommendation any longer, because the studies on clinically indicated replacement have shown no difference in phlebitis rates with longer dwell time.

Catheter material may further affect the risk for phlebitis. In particular, the older tetrafluoroethylene (Teflon) catheters were associated with a 30%–45% increase in the incidence of peripheral catheter-related phlebitis compared with polyurethane (PUR).[37,41] As expected, catheter size also increases the likelihood of phlebitis development. For example, large-gage catheters are associated with an increased risk for phlebitis compared with smaller devices.[42] The apparently negligible interaction between the IV cannula (comparable to a foreign body) and the vessel wall leads to friction and subsequent venous irritation due to mechanical insult.[36] Similarly, the selection of a PIVC too large related to the vein diameter, the insertion of a cannula near a joint or a venous valve, or inadequate securement of the cannula, may all increase the risk of mechanical phlebitis due to irritation of the vessel wall.[36]

Infusate characteristics also influence the occurrence of peripheral catheter-related phlebitis. Specific IV drugs infused through the cannula may cause chemical phlebitis. Causative factors include extreme values of drug pH and/or

osmolarity,[38,43] though some drugs may be irritant to the endothelium with mechanisms independent from pH and osmolality. Notably, the increased risk for phlebitis associated with IV administration of several antibiotics (e.g. vancomycin, amphotericin B, etc.)[37,44] may be attributable to the presence of micro-particles in the antibiotic solutions.[36]

The accidental introduction of bacteria into the vein may be secondary to poor skin cleansing technique before the cannulation, high frequency of manipulation of the cannula and more generally to inadequate adherence to the recommendations for infection prevention during IV infusion.[36]

As regards the potential benefit of the use of filters for prevention of phlebitis, the inadvertent intravenous infusion of micro-particles and nano-particles has been identified as a risk factor for phlebitis.[45] It has been speculated that micro-particles in the infusate may contribute to chemical and infective phlebitis. The research evidence for this is unclear. Most of the studies are very old (1970s, 1980s) and newer studies are at high risk of bias. The effects of the IV administration of particles were studied in a recent prospective, double-blind investigation, and a link between particles and phlebitis was demonstrated.[11]

Experimental studies have shown that IV in-line filters can reduce particle concentrations in infusates. A study in hamsters found that filters reduced capillary obstruction.[14] However, according to Pardeshi et al.,[46] even with in-line filters in place, high levels of sub-visible particles are delivered to patients and there is a need for improved, more effective filters and IV solutions with lower particle levels.

Contaminants in the infusates represent potential etiologic factors for peripheral catheter-related phlebitis. Particulates, bacteria, endotoxins, precipitates, large lipids and air bubbles may activate local inflammatory processes in the endothelium and subsequently increase the risk for phlebitis. In-line filtration is an effective approach to remove contaminants from the infused solutions, potentially reducing the rate of phlebitis. Although this pathophysiological rationale for the use of in-line IV filters is widely recognized in the literature, conflicting results are available on their clinical efficacy in reducing peripheral catheter-related phlebitis.

In a 2010 meta-analysis on 11 trials (1633 peripheral catheters), Niël-Weise et al.[3] assessed the effect of in-line filters in reducing the incidence of infusion-related phlebitis. Although the baseline risk for phlebitis was quite variable (ranging from 23% to 96% across the considered studies), in-line filters seemed to overall reduce the risk of infusion-related phlebitis (relative risk, 0.66; 95% confidence interval, 0.43–1.00). Nevertheless, the methodological shortcomings of the considered studies and the marked unexplained statistical heterogeneity ($p < 0.0005$, $I2 = 90.4\%$), severely affected the clinical importance of such observed benefit. The same authors conclude that although in-line IV filters appear to reduce the risk of phlebitis, they cannot be recommended for routine use because evidence of their benefit is controversial. Interestingly, in this meta-analysis, several clinical pitfalls on the use of in-line filters were evident in those studies that failed to demonstrate clinical benefits of in-line filtration. In particular, in a randomized clinical trial on 102 patients undergoing potassium chloride infusion, Adams et al.[47] observed no difference in the incidence of peripheral catheter-related phlebitis between patients treated with in-line filters and those treated with dummy filters. Even if purified of particles and/or other contaminants through in-line filtration, potassium chloride solutions are associated with phlebitis when infused through peripheral venous cannulation. So, the conclusions of this study are inconsistent: the inappropriate delivery of an irritant drug via a peripheral route is obviously associated with a high incidence of phlebitis, independently by the adoption of in-line filters. Similarly, 50% of surgical patients randomized by Maddox et al.[33] for in-line filtration received peripheral infusion of irritant drugs. Also in this study, in-line filtration failed to demonstrate a clinical benefit in reducing phlebitis (RR 1.03 95%CI [0.72; 1.45]).[6] In other trials considered in the meta-analysis by Niël-Weise et al.[3] misinterpretations of indication for in-line filtration can be recognized, potentially affecting results of the study. Again, a more appropriate proactive vascular planning might be more effective in reducing peripheral catheter-related phlebitis in patients requiring prolonged peripheral cannulation, rather than in-line filtration alone. In several other trials where in-line filtration was associated with an adequate choice and use of vascular access, a net reduction in catheter-related phlebitis was observed.

In a 2018 clinical trial, Villa et al.[30] randomized adult surgical patients undergoing peripheral venous cannulation to receive in-line filtration perioperatively. Interestingly, all patients enrolled in this study underwent careful evaluation before peripheral venous cannulation in order to guarantee an adequate proactive vascular planning (choice of the cannula, site of venipuncture, type of securement, etc.). Furthermore, patients' vascular access devices were continuously monitored and managed according to the up-to-date standard of care. In this trial, authors demonstrated a 25% reduction (95%CI 12–36%) in the occurrence of postoperative phlebitis in patients randomized to receive in-line filtration (OR 0.05, 95%CI 0.01–0.15).

Conclusions of the panel

Please provide an acceptable definition for peripheral catheter-related "phlebitis". Phlebitis is a very frequent complication of peripheral intravenous catheters, potentially provoked by many different causes (chemical, bacterial and mechanical) and with many different pathological features, which nonetheless almost always include venous thrombosis due to endothelial damage and various degrees of inflammation of the vein wall.

Which are the commonly accepted causes of phlebitis? Phlebitis is the final effect of many different harmful agents acting on the vein wall: chemical irritation, bacterial contamination and mechanical trauma. Chemical irritation is usually secondary to infusion of vesicant drugs or irritant solutions, i.e. solutions that are associated with potential endothelial damage when administered via a peripheral catheter. Bacterial phlebitis is usually caused by extraluminal contamination (from the skin flora). Mechanical trauma is usually secondary to inappropriate securement of the catheter or insertion of a large catheter in a small vein, with subsequent friction of the catheter on the vein wall and endothelial damage.

Is there evidence that phlebitis might be related to particles? Though scientific evidence is still missing, it has been postulated that the mechanisms by which infused solutions may cause damage to the endothelium might include the presence of micro-particles contaminating the drug, or the accidental infusion of drug precipitates (for instance, because of drug incompatibility), or the accidental contamination of the infusion with endotoxin or bacteria. All of these items (inert particles, drug precipitates, endotoxin, bacteria, etc.) might be successfully removed by in-line filters.

Is there evidence that the clinical use of filters might reduce this risk? Considering the multiple factors that may cause phlebitis, the results of clinical studies dealing with the potential beneficial effect of in-line filters is uncertain and controversial. Clinical studies and meta-analysis available in the literature are difficult to evaluate, since the design of the randomized trials very often does not include a complete control of all the different factors that may cause phlebitis (size and material of the peripheral catheter, site of insertion, skin antisepsis, securement of the catheter, proper disinfection of the hub, type of IV solution, etc.). Though, studies suggest that in-line filters may concur in reducing the risk of PIVC-related phlebitis.

Which clinical research is warranted for further investigation in this area? Further randomized clinical studies are warranted, as long as designed properly, i.e. taking into account all the factors which are known to be cause of phlebitis, not only to confirm the beneficial effects of in-line filters, but also to describe potential disadvantages (reduction of the flow of infusion, interaction with drugs, etc.) and to evaluate the final cost-effectiveness of their utilization in different patient populations.

It should also be noted that most studies of in-line filters are quite dated. Newer catheter materials, chlorhexidine skin antisepsis, needle-free connectors, etc. have all been introduced since the previous studies of in-line filters were conducted. Therefore, it's time to re-evaluate the evidence for in-line filters.

(3) Potential benefits of in-line filters in reducing systemic inflammation/infection

Discussion. The possibility of a systemic effect of the particles accidentally infused during IV drug administration has been postulated in studies of the last decade. In 2007, Brent et al.[48] reported using an IV in-line filter and capturing particles that were angular and crystalline in appearance. Drugs given included furosemide, spironolactone, hydrocortisone, ranitidine, paracetamol and cefazolin. The authors hypothesized that these micro particles may cause local endothelial damage, but also that they could possibly predispose to systemic complications such as respiratory distress syndrome, thrombosis and systemic inflammatory response syndrome, or, in the worst case, multi-organ dysfunction.

The more recent clinical studies on the systemic effect of particles have been carried out mostly on critically ill children, focusing on the potential effect of in-line filters. In 2012, Jack et al.[5] conducted a single-center RCT on pediatric patients ($N=807$): they found a statistical reduction in the rate of overall systemic complications – systemic inflammatory response syndrome (SIRS), sepsis, organ failure (circulation, lung, liver, kidney) – in the in-line filter group compared to controls. In 2013, Boehne et al.[2] further analyzed data from the same study, finding that the incidence of respiratory, renal and hematologic dysfunction was significantly decreased in the in-line filter group. The hypothesis of the authors was that in critically ill children the infused particles might lead to a deterioration of the microcirculation, with systemic hypercoagulability, systemic inflammation and organ failure.

In 2015, Sasse et al.[49] investigated the effect of in-line filtration on major complications in the subgroup of cardiac pediatric patients ($N=305$) from the 2012 study by Jack et al.,[5] finding that the incidence of SIRS, renal and hematologic dysfunction was significantly decreased in the in-line filter group compared to controls. The authors concluded that infused particles might aggravate a systemic hyper-coagulability and inflammation with subsequent organ malfunction in pediatric cardiac intensive care patients.

On the other hand, in 2015 Gradwohl-Matis et al.[50] conducted a prospective, randomized, controlled open-label study evaluating the effect of in-line filters on systemic immune activation in 504 critically ill adults and found a higher incidence of SIRS in the study group (99.6 vs 96.8 %, $p=0.04$). The authors concluded that filtration of particles from injections and infusions by in-line microfilters does not modulate the systemic immune response in adult critically ill patients and cannot prevent acute lung injury or reduce the duration of mechanical ventilation.

A Cochrane systematic review concluded that there was insufficient evidence for the use of in-line filters in the neonatal population.[51] Only one small RCT investigated

the rates of necrotizing enterocolitis (which theoretically could be related to the infusion of inert particles), while two RCTs investigated the incidence of sepsis[52,53]: no difference was found between the study group and the control group. However, the Van Lingen study was a small study ($N=88$) and van den Hoogen 2006 ($N=442$) did not report a sample size calculation and had approximately 14% loss to follow-up. All other outcomes from the two remaining RCTs were related to local complications such as extravasation, phlebitis, and cannula patency.

A French study addressing the blood concentration of cytokine in preterm infants with or without filter is currently in progress.[54]

The systemic effect of particles and the protective action of in-line filters have also been studied in relation to the administration of parenteral nutrition, which notoriously carries the risk of accidental inoculation of lipid aggregates and/or drug precipitates.

The very recent guidelines from ESPGHAN (European Society for Pediatric Gastroenterology Hepatology and Nutrition) state that in children and neonates PN solutions should be administered through a terminal filter (R 11.5, strong consensus).

In line filtration is theoretically indicated for removing particulate contaminants of PN fluids, as well as to retain bacteria in the unlikely event the solution is contaminated. However, there is no data about the possible effect of filters on CRBSI during PN. PN solutions often contain particles and biochemical interactions can lead to chemical precipitates and emulsion instability; they also act as a media for microbiologic growth, should contamination occur. In theory, particles can harm the pulmonary endothelium and provoke a granulomatous pulmonary arteritis.[26] The routine use of in-line filtration has been advocated in children receiving large volume PN, and a randomized trial in a pediatric intensive care unit showed that filters were associated with a significant reduction in overall complication rate, a reduction in systemic inflammatory response syndrome, and a reduction in length of stay.[5] In critically ill children, infused particles may impair the microcirculation, induce systemic hyper-coagulability and inflammation.[2] Some endotoxin retaining 0.2 mm filters allow cost saving, through extended use of the administration set: in fact, it has been postulated that using appropriate in-line filters, administration sets could be used for 72–96 h. Still, little is known about the actual incidence of filter blockage, due to the interaction between the solution and the filter.

One of the most interesting aspects related to the systemic effect of in-line filters concerns the incidence of sepsis, SIRS and organ failure. The occurrence of these complications dramatically changes the prognosis of the critically ill. In more detail, SIRS is a widespread inflammatory response that may or may not be associated with infection. The presence of two or more of the following criteria (one of which must be abnormal temperature or leukocyte count) defines SIRS[55]: core temperature (measured by rectal, bladder, oral, or central probe) of >38.5°C or <36°C; tachycardia or bradycardia defined as a mean heart rate above or below two standard deviations for the age; mean respiratory rate more than two standard deviations above normal for age or mechanical ventilation for an acute pulmonary disease; leukocyte count elevated or depressed for age, or $>10\%$ immature neutrophils.

Neonatal sepsis is variably defined based on a number of clinical and laboratory criteria that make the study of this common and devastating condition very difficult. Diagnostic challenges and uncertain disease epidemiology necessarily result from a variable definition of disease. Pediatric sepsis criteria are not accurate for term neonates and have not been examined in preterm neonates for whom the developmental stage influences aberrations associated with host immune response. Thus, specific consensus definitions for both term and preterm neonates are needed. Such definitions are critical for the interpretation of observational studies, future training of scientists and practitioners, and implementation of clinical trials in neonates.

There is growing evidence that in pediatric patients admitted to intensive care unit the use of in-line filters may reduce the incidence of SIRS, although this is not associated with a reduction in the incidence of sepsis.[56] In a prospective, randomized, controlled trial including 807 critically ill children, the use of in-line filtration reduced the composite endpoint of "severe complications" including sepsis, SIRS and organ failure. SIRS, length of stay and mechanical ventilation were also reduced as single events.[2,5] As described above, the same authors analyzed the effect of in-line filtration in a subgroup of cardiac patients comprising 305 children ($n=150$ control, $n=155$ filter group). Again, risk of SIRS (−11.3%; 95% CI −21.8 to −0.5%), renal (−10.0%; 95% CI −17.0 to −3.0%) and hematologic (−8.1%; 95% CI −14.2 to −0.2%) dysfunction were significantly decreased in the filter group. No risk differences were demonstrated for occurrence of sepsis, any other organ failure or dysfunctions between both groups.[2,5]

Regarding the newborn population admitted to Neonatal Intensive Care Unit the quality of evidence is very low. In the above quoted Cochrane review on neonates, the use of in-line filters compared with unfiltered fluids for intravenous infusion had no statistically significant difference in effectiveness on overall mortality (typical RR 0.87, 95% CI 0.52 to 1.47; typical RD −0.01, 95% CI −0.06 to 0.04; two studies, 530 infants), proven and suspected septicemia (typical RR 0.86, 95% CI 0.59 to 1.27; typical RD −0.02, 95% CI −0.09 to 0.04; two studies, 530 infants), or other secondary outcomes (including local phlebitis and thrombus, necrotizing enterocolitis, duration of cannula patency, length of stay in hospital, number of catheters inserted and financial costs). The incidence of SIRS was not considered.

This difference between pediatric and neonatal populations might be related to the differences in the immune systems in these different populations, or more likely these different findings could be related to the low quality of evidence in the neonatal population.

During the preparation of the final version of this consensus document, an interesting paper has been published on the effect of filters in a population of adult critically ill patients[57]: in this retrospective study, 0.2–1.2 micron filters were compared with 5-micron filters in terms of clinical outcome, and the results suggested a decreased of respiratory dysfunction, sepsis and length of ICU length of stay in the patients with fine filters.

Conclusions of the panel

Please provide acceptable definitions for sepsis – systemic infection – SIRS – septic shock. Definitions of sepsis, septic shock and SIRS are available in the literature. For the purpose of our topic, it is interesting to stress that SIRS may occur in absence of sepsis, as a non-bacterial related inflammatory response. This is relevant, since the systemic benefits of in-line filters do not include the reduction of sepsis and septic shock, but may include the reduction of SIRS.

Which is the currently accepted pathogenesis of the pathophysiologic effects of systemic infection? The accurate pathogenesis of systemic infection is still largely unclear, though it appears that bacterial invasion may start a systemic inflammatory response, which – though probably finalized as a defense response – may imply obnoxious effects on circulation, respiration and organ function.

Is there any evidence that particles might be involved in this pathogenesis? At present, there is no clear and direct evidence that particles may be involved in this pathogenesis. This is partly due to the vast variety of agents included in the category of "contaminating particles" (drug precipitates, lipid aggregates, endotoxin, bacteria, inert particles), to their different size (only particles $>$ 12 micron may yield obstruction of the microcirculation, while only particles $<$ 12 micron can enter the macrophages and interact with their function) and to the pathophysiology of systemic infection, whose mechanisms are still largely unknown.

Is there evidence that the clinical use of filters might reduce systemic infection or systemic inflammatory response? And in which kind of patients? The available clinical evidence suggests that in-line filters may play a role in reducing systemic complications in the pediatric and neonatal populations, particularly in the critically ill or in children receiving PN. Though, data suggest some effect on the reduction of the incidence of SIRS and of organ failure, but not on mortality or on the incidence of sepsis. Furthermore, relevant differences exist between children and neonates, probably related to the different maturation of their immune system.

Which clinical research is warranted for further investigation in this area? While this area of research appears very promising, more clinical studies are needed. In fact, the evidence suggesting a beneficial effect of in-line filters on systemic complication is limited to few studies on pediatric patients and it is still controversial. Critical points in the design of future studies are: the proper identification of the patient population (neonates vs. children), the type of treatment (PN solutions vs non-nutritional IV therapies), and the definition of the primary endpoint (organ failure; SIRS; systemic infection; mortality; etc.). Large randomized controlled trials in the neonatal population are recommended, as it is this population that may hugely benefit from the use of in-line filtration.

Final discussion and conclusions

The rationale for the use of in-line filters relies in the possibility of reducing the potential systemic effect of undesired micro-particles entering the circulation via the infusion line. Unfortunately, many studies on this topic are quite old and it is obviously difficult to draw conclusions from evidence accumulated in a span of almost four decades, considering the inevitable changes in product characteristics (both filters and infusate), techniques and knowledge about intravenous management. Nonetheless, after a thorough examination of the literature, the panel has concluded as follows:

(a) The adverse effects of micro-particles are postulated but not fully proven, since most of the speculation is based on in vitro and experimental studies. There is some evidence, however, that a link between infusion of micro-particles and phlebitis does exist, though this complication is also related to many other factors. Also, some clinical data in pediatric patients indirectly suggest a harmful systemic effect of microparticles on the clinical outcome, via the triggering and/or worsening of a systemic inflammatory response syndrome (SIRS). Considering the enormous variety of microparticles potentially involved (lipids, inert material, endotoxin, precipitates, microbubbles of air, etc.) and considering the multifactorial pathogenesis of SIRS, more clinical studies are warranted to consolidate such hypothesis.
(b) The actual effectiveness of filters in retaining microparticles depends of the physical characteristics of the filter and is largely based on in vitro studies. The uncertainty of the endpoint in terms of clinical outcome, the extreme variability of the type of infusate and of the policies of management,

Table 2. Summary of the conclusions of the panel.

(1) Evidence about possible harmful effects of inert particles in intravenous infusions
The types and dimensions of the potentially harmful particles are extremely variable. Particles <10–12 micron can be phagocytosed by macrophages and may potentially act by modifying cell activities. Particles >10–12 micron can occlude the microcirculation and may potentially be associated with local tissue damage, particularly in the lung. A great variety of pathological conditions has been potentially ascribed to the effect of particles, though most of the evidence is anecdotical.
Filters with 0.2 micron are expected to stop the vast majority of particles, including bacteria and air bubbles; 1.2-micron filters are used for removing lipid aggregates during administration of PN. Larger filters are unlikely to remove most of the potentially harmful particles.
Future studies should be designed to identify the occurrence of potentially particle-related complications in different groups of patients, with and without the implementation of in-line filtration, and preferentially – when ethically acceptable – under the structure of randomized controlled trials.
(2) Potential benefits of in-line filters in reducing peripheral phlebitis
Phlebitis is a very frequent complication of peripheral intravenous catheters, potentially provoked by many different causes (chemical, bacterial and mechanical) and with many different pathological features. It has been postulated that the mechanisms by which infused solutions may cause damage to the endothelium might include the presence of micro-particles contaminating the drug, or the accidental infusion of drug precipitates, or the accidental contamination of the infusion with endotoxin or bacteria. All of these items (inert particles, drug precipitates, endotoxin, bacteria, etc.) might be successfully removed by in-line filters.
The results of clinical studies dealing with the potential beneficial effect of in-line filters is overall uncertain and controversial. Though, some studies suggest that in-line filters may concur in reducing the risk of PIVC-related phlebitis.
Further randomized clinical studies are warranted, as long as designed properly, i.e. taking into account all the factors which are known to be cause of phlebitis, not only to confirm the beneficial effects of in-line filters, but also to describe potential disadvantages and to evaluate the final cost-effectiveness of their utilization in different patient populations.
(3) Potential benefits of in-line filters in reducing systemic inflammation/infection
The accurate pathogenesis of systemic infection is still largely unclear, though it appears that bacterial invasion may start a systemic inflammatory response, which – though probably finalized as a defense response – may imply obnoxious effects on circulation, respiration and organ function. At present, there is no clear and direct evidence that particles may be involved in this pathogenesis.
The available clinical evidence suggests that in-line filters may play a role in reducing systemic complications in the pediatric and neonatal populations, particularly in the critically ill or in children receiving PN. Though, data suggest some effects on the reduction of the incidence of SIRS and of organ failure, but not on mortality or on the incidence of sepsis.
More clinical studies are needed. Critical points in the design of future studies are: the proper identification of the patient population (neonates vs children), the type of treatment (PN solutions vs non-nutritional IV therapies), and the definition of the primary endpoint (organ failure; SIRS; systemic infection; mortality; etc.).

the little-known negative effect of filters on the infusion line, etc., account for the lack of good quality clinical studies and therefore for the lack of hard evidence about the effectiveness of in-line filters. Though, clinical studies suggest that the consistent use of filters may reduce phlebitis related to peripheral venous catheters. Further clinical studies should focus on specific endpoints, preferably under the design of randomized controlled studies.

(c) The issue of cost-effectiveness of in-line filters has been scarcely if ever addressed in the available literature. Filters do have a cost, related to the net cost of the device and to the frequency of its replacement. Also, filters may be associated with undesired effects (slowdown of the rate of infusion flow, blockage of the infusion, interaction with the IV therapy, etc.) which all have some cost. Future clinical trials should be designed to demonstrate the actual effectiveness of filters (in regards of a specific, well-defined clinical outcome) as well as their cost-effectiveness.

The final statements of the panel are summarized in Table 2.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Ton Van Boxtel https://orcid.org/0000-0002-3598-632X
Mauro Pittiruti https://orcid.org/0000-0002-2225-7654
Patrick Ball https://orcid.org/0000-0001-8918-2119
Sergio Bertoglio https://orcid.org/0000-0001-7235-3444
Roberto Biffi https://orcid.org/0000-0001-8548-323X

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