Abstract: Purpose of review The routine use of intravenous in-line filters on infusion lines has been controversial for many years, with strong advocates, detractors and many fence-sitting observers. The purpose of this review was to examine the literature for new developments and to cast the net a little wider than in previous reviews in an attempt to draw useful parallels. Recent findings There were recent major policy statements or recommendations from a working party of the British Pharmaceutical Nutrition Group and from the US Centres for Disease Control. The first was focussed on filters and was broadly in favour, the second was not focussed on the subject but made quite a strong statement against, on microbiological issues alone. The major purpose of filters, however, is particulate contamination, and whilst there was little in the literature directly on this subject, useful parallels could be drawn from papers describing the therapeutic use of particles and also from their effects in intravenous drug users. Summary When all the available information is considered, and the role of filters in particulate contamination, in-line chemical precipitates, identifying problems in parenteral therapy practice, microbial contamination and entrapped air is examined, the case for routine use appears strong.

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IV in-line filters: filtering the evidence.

(3940 words)

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Abstract.

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Recent findings.

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Summary

When all the available information is considered, and the role of filters in particulate contamination, in-line chemical precipitates, identifying problems in parenteral therapy practice, microbial contamination and entrapped air, the case for routine use appears strong.
Keywords

Parenteral Therapy, Filters, Particles, Talcosis, Toxicity
**Introduction**

“To filter or not to filter? that is the question!” as Shakespeare didn’t say. It is generally held that the medical community was made aware of the issue of particulate contamination in the 1960’s[1], yet the following quote suggests the problem has been known for much longer: “Mackintosh described in great detail the saline injection procedure which he began to use in May of 1832....... ....He warned of the complications of injecting any solid saline particles into the circulation and recommended the solution be “carefully strained twice through leather” rather than linen or other materials which could allow “minute portions of flaky threads” to be injected”[2]. For years, the filter debate has continued with some strong advocates, some detractors and many sitting astride the fence and continuing as before, unconvinced by the arguments on either side. Some are waiting for the randomised controlled trial that selects patients to have intravenous in-line filters or not, and then follows their entire progress, probably for up to 30 years, with sufficient power to overcome the experimental noise from issues relating to the patient’s underlying condition and other procedural variations and complications.

Even if it were achievable, and it almost certainly is not, who would fund it? For the present, decisions must be based upon the available evidence, with all its limitations.
**Why filter?**

Appropriately chosen filter devices have the potential to remove particulate contamination, microbiological contamination and air from infusion solutions. (Not all devices in the marketplace can remove all three.)

**Why not filter?**

It is not custom and practice. It is perceived by many that particulate contamination is a low priority issue. Further; even if filters can stop microorganisms, patients can become infected by numerous other means, and these days, infusion pumps have air-in-line alarms. Filters cost money and it may be perceived that the benefits do not outweigh the costs.

**What is the state of the arguments**

Much of the background was again summarised recently in a position statement from the British Pharmaceutical Nutrition Group (BPNG) published in ‘Nutrition”[3**]. This sets out the major arguments and relevant bibliography very well. This group made four recommendations:

1. Solutions being added to Parenteral Nutrition (PN) that are removed from glass ampoules or vials should be added to the final PN admixture through a filter with a maximum pore size of of 5µm, to reduce the particle load from extrinsic and intrinsic contamination introduced from raw materials during PN production. It is not possible
to use filters with pores smaller than 25µm during the manufacture of PN when using automated compounding devices.

2. Appropriate filters should be used during the administration of PN to patients who require intensive or prolonged parenteral therapy, the immunocompromised, neonates and children, and patients receiving home PN because of the large volume of potentially particulate-contaminated fluid administered and their increased susceptibility to the detrimental effects of particulate contamination. These patients also would benefit from the use of filters during the administration of intravenous drugs and fluids.

3. When used, in-line filters should be placed as close to the patient as possible.

4. The 1.2µm filters should be used for the administration of lipid containing solutions including All-in-One (AIO) admixtures and changed every 24 h. The 0.2µm endotoxin-retaining filters should be used for the administration of non-lipid containing solutions and can be changed every 96 h.[3**]

Conversely, two recent reviews concentrating on the microbiological aspects of in-line filter use concluded: ‘No evidence was found to support the use of in-line filters as a means of reducing the incidence of line associated bacteremia’[4*] Also ‘No data to support their {in-line filters} efficacy in preventing infections associated with intravascular catheters and infusion systems[5**].

It seems clear therefore that on the available evidence, filters cannot be justified solely as a prevention of infection measure. This is hardly surprising. Both these reviews and in particular the CDC report, allude to all the mechanisms by which catheters may become infected, other than infusion of an infected solution. Infection can be introduced during the
set-change procedure that is still required at least once every 96 hours if endotoxin retaining filters are used, and more frequently if they are not. Infection can also track around the outside of the catheter, and the patient can become infected through bacterial translocation, the presence of other artificial intubations such as urinary catheters, endotracheal tubes and by inhalation.

However, although filters will not make an evidence-based or cost-effective difference on reduced infections alone, it has been convincingly shown that if microorganisms are present in the lines upstream of the filter membranes, even at viable counts far in excess of those likely to be seen clinically, the filters will retain organisms larger than the pore size of the filter[6,7]. For lipid filters (around 1.2µm pore size) this means the larger organisms such as pathogenic fungi like Candida albicans[8] and Malassezia furfur[7], and for the aqueous in-line filters (typically 0.22µm) just about everything except Mycoplasma spp and viruses.

If the use of filters could be argued on other criteria, as demonstrated below, then an additional case could then be made. This would be along similar lines to the arguments for the clean air hoods used for aseptic manipulations in pharmaceutical preparation (for example). The major factor protecting the product is Good Pharmaceutical Manufacturing Practice (GMP) with thoroughly trained and validated operators working to strictly monitored protocols and procedures[9]. The laminar flow hood or aseptic isolators used add to the chances that if the operators’ technique falls short of the required standard the product may still be sterile. Likewise, good hand washing and a high standard of aseptic manipulation at all stages of the process is the patient’s best protection against line infection[5**] but the presence of a filter affords some additional protection if things go wrong.
The CDC report[5**] refers to the possibility that filter blockages might lead to additional manipulations on the line increasing the risk of infection. This may be true if filters are introduced into a unit in a haphazard fashion, but not if there is a systematic introduction period, in which the problems that occur are logged, investigated and solved[10]. In 16 years of filter use, this author has never experienced a filter becoming occluded from the background particulate contamination present in infusion solutions and equipment (Ball PA 1987-2002, data on file). Having been involved in the implementation of filter use in a number of units, it has been found that in almost every case, blockages occurred during the initial phase of filter introduction. The details of the infusates and additions made to the lines were logged and the circumstances of each blockage thoroughly examined. In the majority of cases, the causes of the blockages were traced to problematic technique, causing chemical precipitates or emulsion instability. This does not necessarily mean breaches of protocols by staff, although that can certainly happen too. Problems such as retrograde flow of solutions at ‘Y’ connectors and 3-way taps has also been well documented.

**Blocked filters are serving a purpose.**

That the filters blocked in such situations meant that they were doing precisely what they were designed to do; protecting the patient from the infusion of particulates. A unit in which this occurs could make a knee-jerk reaction and remove the filter from the system, but that would be ignoring the problem. Confronting and solving the problems leads to better practice.
The effect of particulates

If problems with existing practices are leading to the infusion of chemical precipitates or oversize emulsion droplets, where are the problems? Since the effects are not immediately obvious, one could surmise that the particles are unimportant. Again, the frequent cry is where are the randomised controlled trials? There are no randomised controlled trials in humans, but realistically one might expect a proposal to randomise human subjects to receive either a regular infusion of particulates or a clean solution might have some difficulties getting past the ethics committee!

It has however been done in animals[1,11] and much of the historic data was reviewed and cited by the BPNG working party[3**].

The suggested adverse reactions resulting from the infusion of particles include physical occlusion, inflammatory responses, antigenic responses and neoplastic responses[12]. Such effects would be difficult to prove to be directly related to particle-contaminated infusions because in the clinical situation, they may well be attributed to the patient’s underlying condition.

There are useful parallels to be drawn from other branches of medicine however. Particles are deliberately injected with the purpose of causing localised inflammation and scarring in procedures such as talc pleurodesis and in the management of pelveco-ureteric reflux and urinary incontinence. There are also those who regularly inject themselves with particulate matter in illegal injecting drug use (IDU) where the drug is sourced from oral and/or rectal dosage forms. This latter group is not an ideal comparison as the amount and frequency of
particulates received is variable and may frequently be contaminated with bacteria and/or viruses that would hopefully be less prevalent in our hospitals, but useful information can still be derived.

Animal studies have demonstrated that the tissue distribution of infused particles is related to their diameter. Particles in the range 10-12µm lodged in the pulmonary capillaries, those in the range 3-6µm were found in the spleen and hepatic lymph nodes and 1µm particles in the liver. Small microspheres around 3-5µm are retained in the liver and spleen for prolonged periods, possibly due to phagocytosis by reticuloendothelial cells. Larger microspheres (>12µm) were not phagocytosed by pulmonary macrophages or reticuloendothelial cells within 4 weeks of administration, suggesting a size limit for the phagocytosis of inert particles[13]. What have we learned more recently?

Recent literature further confirms the ability of the human body to absorb massive amounts of particulate and continue to function, but it also serves to demonstrate the diverse and long-term effects produced. It also further demonstrates that real and long-term harm results.

**Particles in clinical use and therapeutic trials**

Prompted by a case of fulminant pneumonitis following talc pleurodesis, Rehse undertook a retrospective review of all patients who had undergone the same procedure between December 1993 and December 1997, documenting respiratory and other complications. The records of 78 patients who received a total of 89 talc pleurodesis procedures were included. Respiratory complications or death occurred in 33% of patients. Adult respiratory distress
syndrome developed in 9%. It was concluded that the true rate of complications was higher than generally reported[14*].

Following reports of cardiovascular complications in vertebroplasty (treatment of compression fractures by the augmentation of vertebrae with injections of polymethylmethacrylate), Aebli et al studied an animal model. In a study performed in 6 sheep, it was found that following a unilateral injection into L1 there was a rapid decrease in heart rate and a rapid increase in venous pressure. On transoesophageal echocardiography, showers of echogenic material appeared within 6 seconds and lasted for 138 seconds. There was also a decrease in plasma pH and an increase in pCO₂. The authors attributed these findings to fat emboli passing through the heart and becoming trapped in the lungs[15*].

Solomon recently revisited the issue of particle size and phagocytosis from the perspective of particulate injections used in urology for the treatment of incontinence and reflux. The particle size of three materials used in urology was determined. Also studied was their ability to adhere to tissues was assessed using a fibroblast cell line and their ability to undergo phagocytosis was assessed using human monocytes. Mean particle sizes of 209µm, 49µm and 14µm were found for the respective products. The small particles were commonly ingested by human monocytes, phagocytosis of the 49µm particles was rare and it was never observed with the largest particles. That there is an upper size limit fits well with previous studies, but this upper limit is much larger than reported previously[16*].

Further information on this came from Henley who injected 13 female dogs with a 60:40 polyvinylpyrrolidone:silicone-based injectable paste for peri-urethral injection. Six animals received 2 periurethral injections of large particle paste with a mean diameter of 110µm
(range 32-270µm), whilst 7 received similar injections with a paste of 73µm diameter (range 11-160µm), all radio-labelled with Cobalt-57. When the animals were examined at 4 or 9 months, those receiving the larger particles had two distinct peri-urethral blebs. The animals receiving the smaller particles had much smaller blebs and clear evidence of particle migration. In the animals receiving the smaller particles, migration was confirmed to lung (n=7), lymph nodes (n=5), kidney (n=3) and brain (n=2). Migration to lung was demonstrated in one animal only in the large particle group[17*].

**Particles in injecting drug users**

The recent publications in this area can be subdivided into those representing longer term issues and those likely to give rise to more immediate presentation.

**Longer term issues**

Ward et al evaluated the computerised tomography (CT) appearance of talcosis associated with IDU in a retrospective analysis of 12 patients with a confirmed diagnosis of the condition. The diagnosis had been made histologically in 11 patients and on fundoscopy in 1. In five patients they reported that emphysema was the only abnormality seen (lower lobe panacinar: n=4, upper lobe: n=1). They reported a diffuse, fine nodular pattern (n=2), a combination of nodules and lower lobe panacinar emphysema (n=3) and ground-glass attenuation (n=2)[18*].

Segal reported a previously unrecognised renal complication in three IDU patients who had been injecting material derived from oxycodone suppositories. The patients presented with an unusual granulomatous glomerulonephritis and interstitial nephritis. Granulomas were
seen in the intraglomerular mesangial and interstitial locations. In both sites, the granulomas were associated with an unknown filamentous material. All three patients had some degree of renal failure with two requiring haemodialysis, the first 20 months after presentation, the second at 30 months[19**].

Lynn reported five cases of IDU patients presenting with glomerular deposition of lipid-like material. Three presented with the nephritic syndrome, one with hypertension and an active urinary sediment and one with acute renal failure. All were using opiates intravenously, derived from oral dosage forms. Renal biopsy showed large vacuolated areas consistent with heavy deposition of lipid-like material in all glomerular cells and infiltrating macrophages[20*]

**More immediate problems**

There is also evidence of more immediate problems; McColl looked at 322 consecutive women presenting with objectively confirmed, symptomatic venous thromboembolism. In 21.4% of all cases of DVT and 52.4% of cases of deep vein thrombosis (DVT) in women under 40 years of age, IDU via the femoral vein was a common risk factor[21*]. He suggested that IDU may be the most common risk factor for DVT in his region.

Thorne described the case of a 49 year old male who died suddenly. He had a known history of crack cocaine abuse. His lungs were of increased weight and appeared oedematous. On examination of the heart a section of a broken hypodermic needle was found in the right ventricular chamber. The right ventricle was dilated and hypertrophied and microscopic
examination showed hyperaemic myocardium surrounding the needle. Sections of the lungs showed numerous foreign-body type giant cells containing foreign material[22].

Cook described advanced pulmonary disease as ‘an unusual consequence’ of IDU involving oral medications however, his paper describes the case of an IDU patient who presented with talc granulomatosis of the lungs. The patient successfully underwent lung transplantation and subsequently presented with a recurrence of the condition in the transplanted lung 18 months later[23**].

Khanna described a case of a known asthmatic patient who presented with signs and symptoms suggesting an uncomplicated asthmatic exacerbation. However, a chest x-ray compared with one from six months previously revealed new, diffuse, reticulonodular interstitial infiltrates. There was no evidence of infective aetiology. Arterial blood gas measurements showed severe hypoxaemia. High resolution CT revealed extensive, diffuse centrilobular interstitial disease. Bronchoalveolar lavage with transbronchial biopsy showed non-specific chronic inflammation and was negative for tuberculosis and Pneumocystis carinii. Later, after a second exacerbation, open-lung biopsy was performed. There were multiple foreign bodies seen throughout all microscopic fields. There were two distinct types, larger particles resembling cotton fibres and smaller birefringent particles. Although the patient had fiercely denied IDU, she later died of a morphine overdose and was found to have foreign material in the lungs, liver, kidneys and spleen[24**].

There are also numerous reports in the literature of patients presenting with acute rhabdomyolysis and compartment syndromes[25*,26*]. The authors do not yet appear to
connect these with infused particle loads, but extrapolating from the work of Kirkpatrick[27], it seems likely that they are a factor.

**Particles today.**

There is little new in the literature examining particles in current infusion fluids but this author recently revisited parenteral nutrition admixtures. On the wards of a general hospital, samples were drawn from the infusion tubing of 20 adult and 20 paediatric parenteral nutrition admixtures just before they were connected to patients. Particle counts were taken[28*]. Some of the particles were further examined by electron microscopy and energy disperse spectroscopy (EDX). Similar levels of particulate contamination to those found ten years previously[29] were detected. Particles of talc, glass and plastic were identified.

**A complete package.**

Where does this leave the question of whether or not to filter?

The question needs to be examined as a complete package; particles, microbes, air and cost. It is very clear that all parenteral systems currently in use, yield unwanted particulate contamination. There have been major technical advances over the years that have reduced the level such as plastic ampoules and blow-fill seal technology[30]. Every sector involved has made some improvements, but all parts of the system; containers, tubing, connectors, cannulae, needles etc. yield particles[3**]. Consequently, the overall effect of this has been very much evolution, not revolution and there is still a way to go. Despite these endeavours,
for the foreseeable future, any patient requiring parenteral therapy, unless it is filtered, will receive with it a selection of plastic, inorganic and metallic material that is unintentional, has no therapeutic use and is known to be potentially harmful.

It has been well demonstrated that particles worsen infusion site thrombophlebitis, and use of in-line filtration reduces it\(^{3**,5**}\).

It is clear from previous literature and confirmed again from recent studies that particles spread to a number of sites throughout the body and persist for a very long time. Information from IDU patients shows us that the body can continue to function in the presence of enormous particulate loads, but tissue damage occurs and function is compromised. Many of the signs and symptoms are similar to those seen in our patients today, but who is associating them with particulate contamination?

There is an increasing patient population receiving large-scale short-term (advances in critical care) and/or long term parenteral therapies; home parenteral nutrition, cancer chemotherapy, home intravenous antibiotics for conditions such as cystic fibrosis, endocarditis and cellulitis. There is very little evidence in the literature that these patients are suffering long-term sequelae from this, but from the evidence above, the most likely explanation for this is that very few people are looking for it. Detailed examination of long-term parenteral therapy recipients not using filters would in all probability show very similar findings to those in IDU patients, if such examinations were undertaken.

If and when these findings are confirmed in such a patient, there is surely enough evidence in the literature to provide the basis for legal action.
Chemical precipitates

We have clear evidence that the infusion of large boluses of particulate from in-line chemical precipitation can kill[31]. There is little evidence in the literature that in-line precipitation is a common hazard in practice, but again, experience strongly suggests that may be because nobody wants to go looking for it. Who amongst those who regularly administer intravenous drugs can honestly say they have never witnessed a transient change within the line when adding a drug to an infusion system? How many of us have actually stopped to investigate? If the patient showed no immediate signs of distress, it was probably assumed that what was seen was an illusion or the powder re-dissolved. Comfort would often be drawn from the fact that a procedure was being followed.

Yet clearly from the examples of IDU’s unless the initial load is enormous, or the patient unlucky enough to occlude an important vessel, obvious, immediate effects are unlikely. When implementing intravenous in-line filtration in a number of units, filters have become blocked and subsequent investigations have revealed problems in therapy. How many of the drug combinations commonly used in our patients have been properly validated in the laboratory? Much of the published literature on drug combinations in solution amounts to little more than mixing the drugs and observing. How does that relate to the variety of concentrations, flow rates and ambient temperatures seen in intensive therapy units or inside neonatal incubators?
If however an in-line filter is placed to protect the patient from background particulate contamination it will a) also protect the patient from particles arising from chemical precipitation, and b) bring the problem firmly to the attention of the staff so that it can be investigated and solved.

**Air**

Air embolus is hopefully an extremely rare complication these days but regular air-in-line alarms waste considerable amounts of nursing time in hospitals and disrupt sleep for home patients[32]. Another recent problem brought to this department was persistent air-in-line alarms from the electronic pump used in an ambulatory infusion system used for pain control. The manufacturer was unable to provide drug reservoirs that were completely free of air bubbles and as patients moved around freely as was intended, the air bubbles passed into the tubing and triggered air-in-line alarms. This caused patients to have to return to the ward and occupy nursing staff time dealing with the problem. This was shown to have one important therapeutic benefit, since one of the major reasons for patients leaving the ward was to smoke cigarettes. The air-in-line alarms caused the patients to put out their cigarettes and return to the ward. This problem was overcome by fitting an air-eliminating filter into the line and turning off the air-in-line alarm (Ball PA, 2001 personal communication). Routine use of terminal filters, with appropriate procedural safeguards, would allow the wider application of this approach.

**Microbial contamination.**
Clearly the consensus is that filters cannot be justified on antimicrobial grounds alone, but if the filters are actually placed to deal with particles and air, they will still trap any microbial contamination that is present within the line. Provided the problems have been adequately addressed, as discussed above, they should not lead to additional disconnections of the line.

Cost

A number of studies have demonstrated that if integrated into a package of measures, the costs of filters can be offset against other savings[10]. Again the issues and relevant studies were included in the BPNG working party statement[3**].

Conclusion

Particulate contamination of parenteral fluids is a fact of life. The evidence is clear that its infusion is unlikely to cause immediate or severe signs and symptoms, but that adverse effects, tissue damage and loss of function are likely in the longer term. It is contamination, it serves no therapeutic purpose and the technology exists to remove the vast majority of it. In doing so, patients are provided with some protection against chemical precipitates, in-line microbiological contamination and air. Furthermore, institutions adopting filters appear to save money. Implementation of filter use often leads to initial problems, but the problems can be solved and better therapy usually results.

We have known about the problems since 1832, but the filter usage rates reported by the UK group [3**] were still very low. Are we going to change, or are we going to wait until the lawyers change us?
References


   Position statement by a working party from a UK expert group. This paper reviews most of the background material relating to this topic and cites the important references. It should be read in conjunction with this review.

*4* Fennessy PA, Antonis P, Anderson J. What is the efficacy of in-line filters in reducing microbiological contamination of intravenous fluids. Clayton: Centre for Clinical Effectiveness, Monash Medical Centre, 1999:pp11

   A well conducted review of the literature relating to the microbiological issues around filter use, but does not cover any of the other issues. Available on-line from www.med.monash.edu.au/healthservices/cce/evidence/pdf/c/old008.pdf

Detailed and comprehensive review of the literature relating to intravascular-related infections, with much valuable information. However, only really considers microbiological issues of filters. Refers to blocked filters increasing the microbiological hazard by causing additional manipulations but does not address the implications of what a blocked filter actually means.


Describes an adverse effect of the therapeutic use of injected particles. Adverse effects were found to be more common than perceived.


An animal study relating to localised injection of plastic material showing immediate cardiovascular effects.


Laboratory study on therapeutic particle injections used in urology providing updated information on the fate of injected particles and how their fate is related to their size.


Outside the review period but a useful animal study on particle injections in urology to compare with the findings of 16 above, and not yet cited in literature relating to IV in-line filtration,


Study of 12 patients with confirmed diagnosis, detailing computerised tomography appearance.


Outside the review period but important because kidney damage relating to particulates is not commonly described. Three patients with glomerulonephritis
related to particulate contaminated injections are described. Not previously cited with respect to inline filtration issues.

Useful adjunct to 19 above.

Study of 322 consecutive women presenting with venous thromboembolism.
Concludes that injecting drug use (with consequent particle contamination) is a major risk factor.


Interesting case study providing useful insight into how quickly this complication can develop.

Individual case report but demonstrates well the diagnostic challenge particle-related lung damage presents.

Is this particle related?


Is this particle related?


The most recent article in print showing the nature and extent of particulate contamination in parenteral nutrition solutions.


