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Management of Y-Site Incompatibility of Intravenous Medication: A Scoping Review

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ABSTRACT

Patients in intensive care units have a critical problem with Intravenous (IC) drug administration. The effort to decrease incompatibility or manage the incompatibility risks is paramount significant to reduce morbidity and mortality. This review collates all published studies about kinds of approaches to prevent or solve y-site incompatibility, evaluate the effectiveness of those approaches, and provide the recommendation. A scoping review was conducted in PUBMED in a time frame 1 Januari 2010- 28 February 2021. All type studies of randomised controlled trials, observational studies, before and after studies, also review articled were considered to include. We identified 944 studies; of these, 78 met the inclusion criteria, but 44 were excluded. A total 34 articles were included in the analyses. Six articles reported protocol, two-dimensional chart, database, or pH colour code to provide information of incompatibilities. Two-dimensional chart and pH code were comparable with a gold standard. Specific protocol markedly reduced the incompatibility event. Normal saline (NS) flushing effectively prolonged patency and reduced the incompatibility rate. NS was preferred over heparin associated with thrombocytopenia. In-line filtration has been proved to reduce particulate matter, as well as the precipitation, resulted from incompatibility. The filter also reduced inflammation, infection, and complication appreciably. Four studies used more than three lumen catheters which successfully decrease the number of precipitation and incompatibility events. Therefore, separating incompatible drugs using multi-lumens according to the chart should be preferred. However, when co-administration is inevitable, flushing or filter is needed.

Keywords: scoping review, intravenous incompatibility, compatibility chart, flushing, filter, multi-lumen

INTRODUCTION

Critically ill patients usually suffer from numerous and severe diseases that require multiple medications (Hanifah, Ball *et al*., 2018). Complex disease states, a considerable number of medications, and limited venous accesses for the concomitant delivery of IV medications can result in intravenous (IV) drug incompatibilities which may affect the outcome (Hanifah, *et al*., 2018; Hanifah, *et al*., 2022). High amounts of IV drugs increase the potency of drug incompatibilities. Recent studies identified 1 of 10 critical care patients who experienced IV drug incompatibilities; the other study revealed that up to 25% of patients suffer from IV drug incompatibilities, and a quarter of them are clinically significant (Tissot *et al*., 1999).

The risks of incompatibility were identified from a technical problem such as line occlusion and local reaction to a systematic event such as infection, thrombosis, and failure organ, which is mostly categorized as high risk and deadly effect (Tissot *et al*., 1999). Besides, instability may also develop amongst the IV admixtures in a syringe (Hanifah, *et al*., 2018). Thrombosis in the catheter may cause inaccurate blood pressure measurement, pain due to repeated re-injections, which also lead to breakage of local vascular

structures and even to distal ischaemia (Tully *et al*., 2014). Furthermore, there was a report of morbidity following the calcium-ceftriaxone incompatibility (Bradley *et al*., 2009).

Unfortunately, incompatibility is often under-recognised by health care practitioners. Bertsche identified that health care practitioners commonly lack knowledge on drug incompatibility issues and ways on how to avoid them (Bertsche *et al*., 2008). Hanifah also showed that some hospitals in developing countries have not established a protocol in preventing incompatibilities (Hanifah, *et al*., 2018). Some practitioners tend to ignore this matter and rely on brochures or information from manufacturers to avoid incompatible medication. However, co-simultaneous medication is often inevitable because the number of medications is higher than the infusion line. Moreover, supply the additional infusion lines is problematic. This situation reminds that incompatibility matter needs to be addressed from several approaches. Therefore, studies that specify explore and verify how to handle y-site incompatibility events in critical care should be performed. This article portray the available methods for preventing and reducing the incompatibility also manages the risk. The significance of each typical approach is also assessed.

METHOD

We conducted a scoping review by mapping of the available literature in the particular field; those are studies on the incompatibility, the management and the significances to prevent or reduce the risks. Three steps were involved in this scoping review: study identification, study selection and data synthesis.

Study identification

A literature search for period 1 January 2010 to 28 February 2021 was conducted within PUBMED. The search strategy was implemented with the following individual or combined key terms. A combination of the following key terms was used for the search literature with the Boolean operator with AND for 'intravenous' AND 'compatibility', also with OR for 'y-site compatibility", chart', 'pH-colour code', 'multi-lumen, 'flushing', 'filter', 'in-line filtration.

Study selection

All full-text published original article including a clinical trial, observational, before and after study as well a review is included. Two authors screened the relevancy of studies with the goal of this scoping review. Firstly, the authors reviewed from the title and abstract for potential relevance. Secondly, further evaluation was conducted to examine the eligibility. The studies are included if they are related to how to avoid or manage the incompatibilities or prolong the intravenous (IV) line patency. Incompatibility assays between medications, animal studies, and duplication studies are excluded (Figure 1).

Data synthesis

A standardized form was used to extract the data. The lead of the author including year publication, methodology, the result, and/or conclusion was noted. All those were identified and tabulated. We categorized the studies according to the type of approach to managing incompatibility, a methodological trend also the findings. Then, the key findings were compared to find the similarities. The trend of the results was concluded.

RESULTS

Two main approaches were used to prevent incompatibility; first, studies that avoided incompatible drugs to meet each other and studies that managed incompatibility risk by reducing the precipitates entering the venous line. The results of the typical methods to prevent IV drug dwelling and incompatibility event are summarized in Table I, Table II and Table IV for provision information, flushing and multi-lumen approaches, respectively. The result of precipitation reduction following the filter is showed in Table III.

Very limited studies identified the alternative ways to ease incompatibility prevention. Of those should be applied as a complimentary with the above main approaches were as follows: 1) standardisation of the concentration (Nemec, 2008), 2) optimisation of administration schedule (Maison *et al*., 2019) and 3) accurate pharmacist intervention. The standardisation of concentrations ensuring the preparation and administration of intravenous admixture was compatible (8). However, this finding should be further explored to confirm the compatibility of various combinations. The optimisation of administration schedules might be irrelevant because numerous medications were used in intensive care units (ICUs) (9). Pharmacist intervention is also significant to improve safety particularly in ICUs(Franco Sereno *et al*., 2018). These three things should be used along with the approaches, which would be discussed below.

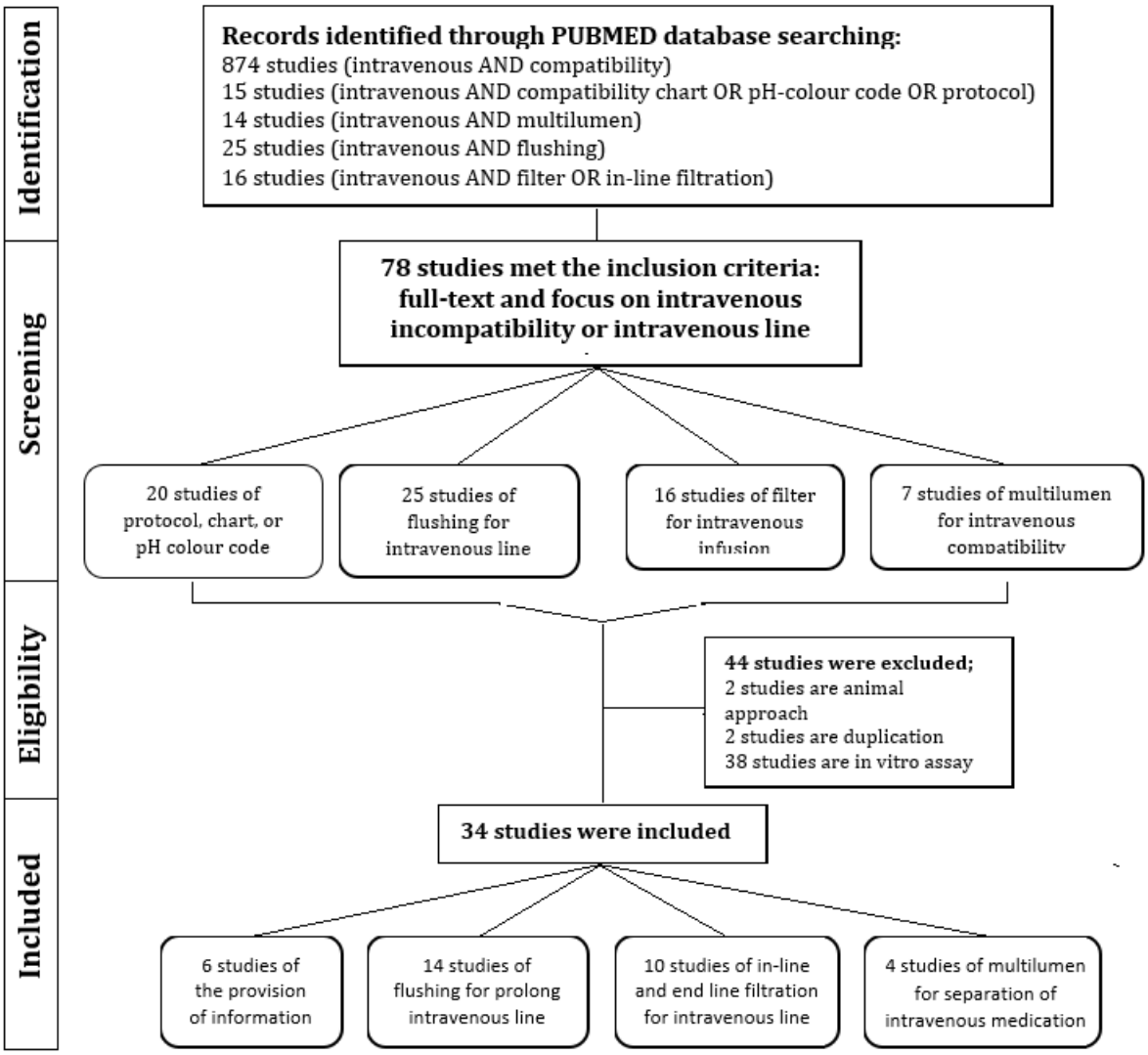

Figure 1. PRISMA Flow Diagram

Provision of information on compatibility

This provision underlines the importance of information about uses, warnings, and directions to avoid the concurrent administration of incompatible drugs. The prevention of the concurrent administration of incompatible medications can be managed when information on potential incompatibility is sufficient. Information about syringe instability of IV admixture may recommend to administer immediately after mixing (Husna *et al*., 2021).

A specific protocol has been proved to reduce incompatibility by 40% (Bertsche *et al*., 2010). The other advantage was found as a two dimension-chart (Lao *et al*., 2019)(Kanji *et al*., 2010). However, studies on the effectiveness of the provision of information in intravenous compatibility are limited (Table I). Manrique showed that charts are comparable with gold standards from Trissel's injectable drug and Micromedex (Manrique-rodríguez *et al*., 2012). Two-dimensional charts and cross-tables are the most familiar forms because they are easy to match the kinds of medications used and practice to follow for practitioners. This information can be a handy protocol and possible to attach to the wall or bed or included in patients' record.

Instead of the chart, an electronic database is also identified. Sweden is continuously validating the data of compatibility and comparing diluents, concentration, and other pharmaceutical aspects to use in hospitals (Collden, *et al.*, 2015).

Table I. Studies on the provision of drug compatibility information

Authors	Methods	Results
Bertsche, 2008, 2010	Evaluation after specific protocol on amiodarone, caspofungin, furosemide and linezolid that often cause incompatibility.	Specific protocol reduces the co-administration of amiodaron with incompatible drugs from 100% to 58%
Kanji, 2010	Developed a two-dimensional chart from the databases Medline, Embase and International Pharmaceutical Abstract	Systematic review—no evaluation on the impact
DeGiorgi *et al*., 2010	Compared 8 tools Theriaque 2007, Stabilis 3, Perfysi 2 databases; KIK 3.0 software; Neofax 2007 handbook; King 2008 Guide, CHUV 9.0, pH 2007 cross-table and Trissel's 14th Ed. handbook served as the gold standard	In range of 1000 score, the global scores of each database are as follows: Theriaque (840), pH (807), CHUV (803), Perfysi (776), Neofax (678), King Guide (642), Stabilis (584) and KIK (523)
Manrique-Rodriguez, 2012	Compared compatibility chart with the gold standard of Micromedex and Handbook injectable drug	Concordance value of two resources is >0.8
Collden *et al*., 2015	Developed incompatibility information from various databases considering diluents and concentrations	This will be applied for many hospitals in Swedia. There is no measurement of impact of implementation
Lao, 2019	Developed a two-dimensional chart using database Micromedex, handbook of injectable drugs and stability	Systematic review—no evaluation of the impact

Although this article did not measure the gap of incompatibility events before and after, the database have been implemented in many countries as a quick reference and positive results in reducing at least half of the incompatibilities have been obtained (Bertsche *et al*., 2010). Thus, this becomes a recommended protocol that may reduce incompatibility errors. It guides health care practitioners in specific medication-use practices to make health care practitioners be more well-informed about potential drug incompatibilities and assist them in deciding whether possible to administer concomitantly or not.

The other types of information for intravenous incompatibility guidelines are standardised pH colour codes. The tool of a pH colour code system provides information on pH (basic or acid) to determine the safe line of medication administration. Maison recommended pH labelling to reduce incompatibilities under severe clinical conditions and complex interventions in ICUs and hematologic sterile units(Maison *et al*., 2019). This tool has been proven to decrease the number of incompatibility incidents during the 5 years (Vogel *et al*., 2003). Another study has shown that the global score (accuracy, completeness, comprehensiveness, and applicability) of pH cross-table is 807/1000, which is higher than that of other resources; Stabilis 3, Perfusi 2 databases; KIK 3.0; Neofax 2007 handbook and King 2008 Guide, CHUV 9.0 (De Giorgi *et al*., 2010). This finding is different from the other report that shows the higher concordance score of compatibility charts than the pH colour code (Manrique-rodríguez *et al*., 2012). A pH colour code system is more flexible when multiple lumen intravenous applied with various possible combinations and unavailability of drug compatibility information. However, it may be irrelevant unless a pH reaction is a cause. Therefore medication compatibility chart or database is more accurate to judge the incompatibility (Manrique-rodríguez *et al*., 2012).

Flushing the medication solution

Flushing can prevent the contact between medications or fluids by purging the solution of medications that may be left in the y-site or IV line. Studies on the effectiveness of flushing have indicated that it can prolong patency and prevent occlusion but will be problematic for patients with restricted fluid such as renal failure or oedema

(Hanifah 2016). However, studies on the effectiveness of flushing were mostly limited on comparing heparin and normal saline (NS) (Han *et al*., 2012; Kumar *et al*., 2013)(Table II). Only one study has examined the effectiveness of bolus flushing before and after IV drug administration that reduces incompatibility incidents (Bertsche *et al*., 2010). Even though studies on flushing began some decades ago, they focused on drug the thorough maintenance of line patency. Some studies have indicated that flushing can be applied to manage all types of particulate matter, maintain patency and prevent thrombosis and phlebitis problems as well as the precipitation as a result of incompatibility. No conflicting data on the effectiveness of flushing for line patency. However, findings on the important aspect of flushing are contradictory that is, the administration time and flushing regimen.

There are similar trends on how long the administration of flushing. Longer flushing seems beneficial than shorter. One scholar proved the benefit of intermittent rather than bolus (A. Perez *et al*., 2012). Continuous flushing was also more effective than intermittent (Hoff *et al*., 2019). However, continuous administration to manage incompatibility may be exaggerated. Therefore, Stok suggested using intermittent rather than continuous to save cost and reduce complications (Stok & Wieringa, 2016). No conflicting data on the effectiveness of flushing for line patency are available. However, findings on the important aspect of flushing are contradictory that is, flushing regimen. Recent studies mostly evaluated the effectiveness of 9% sodium chloride or purely normal saline [NS] compared with heparin added to NS. Even though heparin was common in the early 1980s, NS is currently more commonly used to flush IV lines in hospitals. Conflicting findings on regimens have been reported. One scholar stated that NS is superior(Sotnikova *et al*., 2020), some scholars have reported that saline is as effective as heparin particularly for maintaining patency (Ali *et al*., 2015; Dal Molin *et al.*, 2015; Gunes *et al*., 2018; Han *et al*., 2012; Sharma *et al*., 2019), but others have stated that heparin may prolong longer patency of IV lines (Tully *et al*., 2014; You *et al*., 2017). In response to this dispute, the first opinion presented here likely has stronger evidence and a more rigorous study conducted through randomisation and a double-blind approach (Ali *et al*., 2015). Moreover, a larger meta-analysis has shown that heparin does not prolong the patency significantly (Sotnikova *et al*., 2020). Meanwhile, the second opinion has a lower-quality study and not statistically significant results (Stok & Wieringa, 2016)(Gunes *et al*., 2018)(Sharma *et al*., 2019). Therefore, NS is considered safer than heparin in terms of avoiding adverse reactions. Adverse reactions, such as thrombocytopenia that occurs in almost 30% of patients, should also be considered in the use of heparin for flushing (McNulty *et al*., 2005). Therefore, hospital practitioners should involve heparin-induced thrombocytopenia in the differential diagnosis of patients who receive heparin flushing and suffer a platelet count drop while receiving heparin flushes.

In-line filtration for trapping precipitates

Previous interventions were useful to avoid the concurrent administration of incompatible medications. However, they are sometimes not convenient for critical care, considering that patients require multiple IV drug administrations and have limited vasculature. Therefore, further studies should focus on preventing the risk of incompatibility when simultaneous incompatible drug administration is inevitable. Discussions on in-line filtration dealing with particulate matter started in the 1970s; however, the benefit of filters for daily use is still conflicting. Some studies showed a benefit, and others could not prove the significance of filter use. Two systematic reviews, one observational study, and one clinical trial have failed to prove the effectiveness of filters significantly in reducing complications, and also doubt the value of the filter (Foster *et al*., 2015; Niël-Weise *et al*., 2010; Tanaka *et al*., 2016; Virlouvet *et al*., 2020). However, some studies have been performed under ideal conditions, considered well-controlled and compliant to protocols so the incompatibilities were not identified. More rigorous studies, which assign more patients than previous systematic reviews (807 versus 704 subjects), have proven the benefit of in-line filtration not only for reducing phlebitis and particulate contamination but also for suppressing the secretion of macrophages and endothelial cell cytokines (Boehne *et al*., 2013; Jack *et al*., 2012; Ku *et al*., 2010). In addition, a retrospective group-controlled cohort study performed the respected result on 3012 patients; lessen interleukin-6, pneumonia and sepsis. Other studies have confirmed that filters are statistically significant in reducing SIRS, phlebitis, and other infections on 155, 268, and 1500 patients, respectively (Sasse *et al*., 2015)(Villa *et al*., 2018)(Schmitt *et al*., 2019).

Table II Studies on the effectiveness of flushing to prevent incompatibility or prolong the patency of intravenous lines

Authors	Methods	Results
Bertsche, 2008, 2010	Prospective study on 53 patients as a control group and 58 patients with the intervention of flushing and multiple lumens	Flushing before and after administration of IV bolus reduces the incompatibility rate.
Han 2012; Kumar *et al,* 2019	Clinical trial analysing the effectivity of normal saline (NS) versus heparinised saline to maintain arterial lines	Both NS and heparinised saline maintains arterial lines. No statistical differences are found.
Perez, 2012; Hof *et al.,* 2019	Prospective observational study on 53 neonates (86 cannulas) with continuous saline compared with intermittent flushing of saline once a day.	Patients with intermittent flushing have a significantly longer patency.
Kumar, 2013; Perez *et al.,* 2012	Systematic review on 3 Randomised Controlled Trials (RCTs) of low-dose continuous infusion versus saline in neonates (N=228) 10 RCTs of intermittent heparin flushing versus saline (N=648) 3 studies performed in 2000 to 2011 10 studies published before 2000	Low-dose continuous heparin results in longer patency and significantly reduces the rate of infusion failure. No significant rates in intermittent heparin, phlebitis and side effects are observed.
Tully, 2014; Tully 2014	Observational study comparing the affectivity of NS versus heparinised saline (N=445)	Heparin prolongs the patency for 102 h compared with NS with patency for 72 h.
Gorji *et al.,* 2015; Gunes *et al.,* 2018	Clinical trial determining the effect of NS compared with heparinised saline	Adding of heparin does not increase patency during 21 days.
Gunes 2018; Sharma *et al.* 2019	Systematic review that evaluated time in situ, occlusion and thrombophlebitis	No significant difference is observed between heparin and saline.
Sharma et al. 2019; Dal Molin, 2019	Systematic review from 2012 to 2018 (nine studies) that compared heparin and NS	The patency of heparin for patency maintenance is slightly extended compared with NS, but the difference is not statistically significant.
Dal Molin, 2019; You 2017	Clinical trial on 430 patients to compare NS and heparin	No significant differences in the occlusion rate, time to occlusion and complication are observed.
Hoff, 2019; Stok 2016	Prospective cohort evaluated the effectiveness of intermittent versus continuous flushing on 113 neonates	The occlusion is significantly higher in the intermittent group. Complication of extravasation is significantly higher in the continuous group. No significant rate on the failure of intravenous line and complication is detected.
Sotnikova, 2020; Han 2012	Systematic review 2009 to 2019 (10 studies) NS versus heparin via peripheral intravenous catheters	NS is superior to heparin in terms of maintaining the patency of PIVC. NS is safer, lower cost-effective and easier to use than heparin.
Stok, 2016; Sotkinova *et al., 2020*	Prospective comparative cohort study on neonates with dextrose infusion compared with intermittent saline for peripheral intravenous patency maintenance	No significant difference in the patency duration of PIVC is observed between intermittent and continuous flushing. Complication, time and cost are significantly reduced with intermittent flushing.
Tao You, 2017; McNulty *et al.,* 2005	Meta-analysis that analysed 32 studies from 2006 to 2016. The study focused on the efficacy of heparin versus saline in maintaining patency and causing complications in peripheral intravenous catheters	Continuous heparin prolongs the duration of patency, reduces the occlusion rate of a peripheral intravenous catheter and markedly alleviates phlebitis.

Table II. Studies on the effectivity of filters in reducing incompatibility risks

Authors	Methods	Results
Niel-Weise, Stijnen & van den Broek, 2010; Niël-Weise 2010	Systematic review 7 RCTs In-line filter attached to a peripheral catheter of 275 patients (children, general hospital, surgical, oncological, or urology and cardiac patients)	Phlebitis rates of the filter group vs. the non-filter group. Nilai Relative Risk (RR)= 0.66 (0.43–1.00). Filter decreases the risk by 34%, but uncertain results and unexplained heterogeneities are noted.
Ku, *et al* 2010	Systematic review In-line filter 7 studies 924 surgical patients	In-line filter reduces 39% of phlebitis. RR =0.61 (95%, 0.41–0.90, p<0.12). In-line filter markedly reduces the phlebitis incidence.
Jack *et al*. 2012; Boehne *et al*. ,2013	Randomised controlled trial In-line filtration 807 subjects in a paediatric intensive care unit	There were significant reduction in the group non-filter versus filter (n =166 [40.9%] vs. n =124 [30.9%]; P = 0.003) Incidence of Systemic Inflammatory Response Syndrome (SIRS) non-filter vs. filter (n =123 [30.3%] vs. n = 90 [22.4%]; P = 0.01). Length of stay non-filter vs. filter (3.89 [95% confidence interval 2.97–4.82] vs. 2.98 [2.33–3.64]; P =0.025) Duration of mechanical ventilation non-filter vs. filter (14.0 [5.6–22.4] vs. 11.0 [7.1–14.9] h; P = 0.028) Reduction of respiratory complication (−5.06%; 95% CI, −9.52 to −0.59%) renal complication (−3.87%; 95% CI, −7.58 to −0.15%) haematologic complication (−3.89%; 95% CI, −7.26 to −0.51%) Frequency of complication of filter vs. non-filter groups Respiratory dysfunction (9.5% [n=38] vs. 14.5%, Incidence rates −5.06%; 95% CI, −9.52 to −0.59%) Renal dysfunction (6.0% [n=24] vs. 9.9% [n=40], incidence rates=−3.87%; 95% CI, −7.58 to −0.15%) Haematologic dysfunction (4.5% [n=18] vs. 8.4% [n=34]; incidence rates=−3.89%; 95% CI, −7.26 to −0.51%) Cardiovascular dysfunction (13.5% [n=54] vs. 14.8% [n=60]; incidence rates=−1.31%; 95% CI, −6.12 to 3.49%) Hepatic (5.0% [n=20] vs. 6.4% [n=26]; incidence rates=−1.42%; 95% CI, −4.61 to 1.78%) Neurologic dysfunction 0.7% [n=3] vs. 0.5% [n=2]; incidence rates=0.26%; 95% CI, −0.83 to 1.34% Cardiovascular complication (-1.31%; 95% CI, -6.12 to 3.49%) filter vs. control group), hepatic (5.0% [n=20] vs. 6.4% [n=26]; difference in incidence rates=−1.42%; 95% CI, −4.61 to 1.78%; filter vs. control group) and neurologic dysfunction (0.7% [n=3] vs. 0.5% [n=2]; difference in incidence rates=0.26%; 95% CI, −0.83 to 1.34%; filter vs. control groups) Filters can reduce the overall complication rate of systematic inflammatory response syndrome, decrease the length of hospital stay and shorten mechanical ventilation use. Then, Boehne identified that in-line filters can be utilised to reduce haematologic, kidney, or respiratory dysfunction. However, no difference was demonstrated in the occurrence rates of cardiovascular, hepatic or neurologic dysfunction between filter and non-filter groups.

Authors	Methods	Results
Foster, Richards & Showel (2015)	Systematic review 4 trials (1 RCT van Lingen and 3 quasi Thomas, Bennion and van den Hoogen, In-line filter (van lingen, Bennion and van den Hoogen) End-line filter (Thomas) 704 neonates (Bennion 111, van Lingen 88, van den Hoogen 442, Thomas 63)	Necrotising, RR =0.2 (0.01–4.05) Mortality during hospitalisation, RR =0.87 (0.52, 1.47) Septicaemia, RR =0.86 (0.59, 1.27) Suspected septicaemia, RR=0.57 (0.18, 1.81) Localised phlebitis, RR =1.2 (-.40, 3.77) Thrombus and sepsis, RR =0.38 (0.19–0.77) In-line filters do not significantly affect any outcomes of septicaemia, phlebitis and mortality.
Sasse *et al*. (2015)	Randomised controlled trial on 305 children with cardiac symptoms with in-line filters (N:155) and no filter (N:150)	The rate of complication reduction: Systemic Inflammatory Response Syndrome (−11.3%; 95% CI −21.8 to −0.5%). Renal dysfunction (−10.0%; 95% CI −17.0 to −3.0%). Haematologic (−8.1%; 95% CI −14.2 to −0.2%) dysfunction significantly decreased within the filter group. Filter decreases systemic inflammatory response syndrome, renal disorder and haematologic disorder. No difference in risks is observed.
Tanaka *et al*., 2016	Observational study on 84 patients using a central venous catheter	Central-line-associated bloodstream infection (CLABSIs) Incidence of CLABSI rates of filter group vs. non-filter group: 2.5/1000 vs. 3.3/1000 (p<0.58). Filters do not significantly reduce CLABSIs.
Perez, 2018	In vitro study on multidrug infusion lines	Filters reduce the overall particulate matter in filter versus non-filter groups; 417 [208–880] versus 7.5 [1.99–11.29] p<0.001. In-line filters effectively prevent particles from entering patients' body.
Villa, 2018	Controlled trial on 268 surgical patients with in-line filtration compared with control group (no filter).	During 48 h, the incidence of phlebitis of the filter groups is lower than that of control group (odds ratio (OR) =0.05 [0.01–0.15], P < .001). Patients with in-line filters have longer patency than that of the control group (P = 0.01). In-line filtration significantly prolongs the patency and reduces the phlebitis event on postsurgical patients.
Virlouvet, 2020	Randomised controlled trial to assign filter (N; 73) and no filter (N:73) patients of very preterm neonates	The rates between control and filter group: Gastrointestinal perforation 0% [n=0] vs. 4.1% [n=3], p<0.08 Late onset sepsis 41% [n=30] vs. 41% [n=30], p<0.94 Death before discharge 1.4% [n=1] vs. 5.6% [n=4], p<0.3. No significant difference in reducing pro-inflammatory cytokines, morbidity and mortality is found.
Schmitt, 2019	Retrospective controlled cohort study In-line filter 0.2 or 1.2 micron (1506 critically ill adult patients) versus 5 microns (1506 critically ill adult patients)	The complication rates of fine filter vs. control filter cohort Respiratory dysfunction (Horowitz index 206 (119–290) vs. 191 (104.75–280); P = 0.04) Pneumonia event (11.4% vs. 14.4%; P = 0.02) Sepsis (9.6% vs. 12.2%; P = 0.03), Interleukin-6 (471.5 (258.8–1062.8) ng/l vs. 540.5 (284.5–1147.5) ng/l; P = 0.01), Length of ICU stay (1.2 (0.6–4.9) vs. 1.7 (0.8–6.9) days; P < 0.01) Reduced hospital stay (14.0 (9.2–22.2) vs. 14.8 (10.0–26.8) days; P = 0.01) Severe vasoplegia (21.0% vs. 19.6%; P > 0.20) Acute kidney injury (11.8% vs. 13.7%; P = 0.11). In-line filters markedly reduce pneumonia, sepsis, interleukin-6 levels and hospital stay.

Table IV. Studies on the multi-lumen use for incompatibility prevention

Authors	Methods	Results
Bertsche, 2008, 2010	Three or four lumen infusions which were set to patients	Three or four lumens of the infusion set do not significantly reduce the incompatibility event (62% vs. 72%, p=0.28).
Foinard *et al.,* 2013	In vitro study assaying the infusion access of three lumens versus nine lumens	Triple-lumen infusion prevents the incompatibility of midazolam and furosemide at the lowest concentration. Nine-lumen infusion prevents the incompatibility of midazolam and furosemide at all concentrations.
Perez *et al,* 2015	In vitro study comparing the infusion set standard versus 8-lumen infusion	Eight-lumen infusion prevents 49% incompatibility compared with the standard set that prevents 80% incompatibility.
Perez *et al.,* 2015	In vitro study comparing the infusion set standard versus 3- or 4-lumen infusion	Multi-lumen infusion set reduces large precipitation from incompatibility approximately 60%.

Above findings concluded to recommend a filter for routine use. Critical care patients are at risk of particulate matter for which an in-line filter is needed because of the following reasons. Firstly, critically ill patients usually receive multiple infusions and IV medications, which can potentially produce more than a million particles per day; moreover, the complexity and quantity of medications increase the number of particles (Jack *et al*., 2010). Secondly, critical care patients are more susceptible to tissue damage after cases of trauma, surgery, and sepsis (Langille, 2013). In addition, the particulate matter seems to be more easily deposited when the body is in poor condition (Walpot *et al*., 1989). Thirdly, the age of patients may affect the risk level. Doessegger indicated that the smaller size and lower density of blood vessels and the lower number of alveoli in children pose a high risk of pulmonary embolism (Doessegger *et al*., 2012). Lastly, in developing countries, a glass ampoule that is prone to breakage and glass particle production is still commonly used, therefore an in-line or end-line filter should be applied.

MULTI-LUMEN CATHETER TO PREVENT DWELLING MEDICATION

To avoid a combination of the incompatible drugs meet in the y-site, multi-lumen catheter is promising. More consistent data regarding the benefit of multi-lumen devices, particularly with more than three lumens, are available. Even though two lumens reduce precipitation, they cannot thoroughly avoid the dwelling of medications; thus, precipitation still occurs (Collins *et al*., 1991). More lumens tend to achieve better prevention.

One scholar confirmed the benefit of three and four lumens compared with a one or two standard set (M. Perez, Décaudin, Abou Chahla, *et al*., 2015). Foinard (Foinard *et al*., 2013) used the prototype of incompatible drugs, namely, midazolam and furosemide, to examine the advantage of multi-lumens. A study on three lumens has shown that they prevented incompatibility at low concentrations but failed to do so at high concentrations. Furthermore, the concentration of drugs and the saline flushing rate amongst the drugs become the determinants of incompatibility (Foinard *et al*., 2013). Then another study identified the capacity of eight devices connected to nine multi-lumens in a single tube to reduce the physical incompatibility between the combinations of several incompatible drugs (furosemide–midazolam, midazolam–amoxicillin/clavulanate, furosemide–amiodarone and furosemide–pantoprazole–amiodarone–midazolam) with considerably different pH levels at the fastest flow (M. Perez, Décaudin, Foinard, *et al*., 2015). Compared with the standard set, this new multi-lumen device avoids 49% of incompatibility, whereas the single lumen evokes precipitation of approximately 80% of the drug combinations tested. Even though this device

cannot entirely deny the incompatibility, it provides a valuable result regarding the concomitant infusion of the combination of two or four incompatible drugs.

The sophisticated technology in infusion devices has become a new challenge when it faces incompatibility problems. Such devices allow drugs or solutions to be shared in different administration accesses. This separated flow seems meaningful in terms of incompatibility. Other consideration to reduce incompatibility are the length and the diameter of cannula. A shorter extension tubing reduces the production of precipitation. Therefore, a smaller cannula with less dead stock volume are chosen to reduce the delay of the fluid flow of multi-lumens (Décaudin *et al*., 2009).

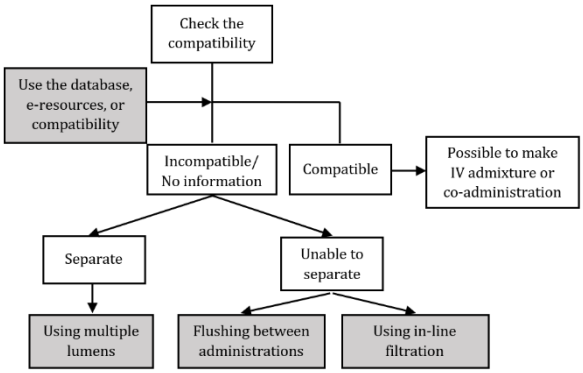

Figure 2. Managing the incompatibility of IV drug administration

This review reveals that multi-lumens are promising to overcome incompatibility problems. However, making an appropriate technology with a sufficient number of medications needed in ICUs is challenging. Therefore, the combination of procedures to manage incompatibility is recommended (Figure 2).

CONCLUSION

A typical study on compatibility prevention is limited on provision compatibility information, flushing, in-line filter, and multi-lumen catheter. The compatibility information provided in a chart is comparable with the gold standard data base and preferred rather than pH-colour code. Flushing has a significant benefit to prolong IV-line patency. The effectiveness of NS is comparable with heparin. Normal saline is recommended over heparin regarding heparin-induced thrombocytopenia. A recent study proved the benefit of an in-line filter to reduce particulate matter also the inflammation, infection, and complication. Three or more lumen infusion has a positive impact to reduce incompatibility events. More number lumen seems to become solution of incompatibility prevention.

REFERENCES

Ali, M., Gorji, H., Rezaei, ; Fatemeh, Jafari, H., Jamshid, ;, & Cherati, Y. (2015). Comparison of the effects of heparin and 0.9% sodium chloride solutions in maintenance of patency of central venous catheters. *Anesthesiology Pain Medicine*, *5*(2), 22595. https://doi.org/10.5812/aapm.22595

Bertsche, T., Mayer, Y., Stahl, R., Hoppe-Tichy, T., Encke, J., & Haefeli, W. E. (2008). Prevention of intravenous drug incompatibilities in an intensive care unit. *American Journal of Health-System Pharmacy*, *65*(19), 1834–1840. https://doi.org/10.2146/ajhp070633

Bertsche, T., Veith, C., & Stahl, A. (2010). A purging procedure for pantoprazole and 4-lumen catheters to prevent IV drug incompatibilities. *Pharmacy World & Science*, 32, 663–669. https://doi.org/10.1007/s11096-010-9422-9

Boehne, M., Jack, T., Köditz, H., Seidemann, K., Schmidt, F., Abura, M., Bertram, H., & Sasse, M. (2013). In-line filtration minimizes organ dysfunction: New aspects from a prospective, randomized, controlled trial, *BMC Pediatrics,* 13(1), 1-8, https://doi.org/10.1186/1471-2431-13-21

Bradley, J. S., Wassel, R. T., Lee, L., & Nambiar, S. (2009). Intravenous ceftriaxone and calcium in the neonate: assessing the risk for cardiopulmonary adverse events. *Pediatrics*, 123(4). https://doi.org/10.1542/peds.2008-3080

Collden, H., Teimori, K., & Asadian, R. (2015). Compatibility of intravenous medications needs attention. Catheter occlusion, treatment failure and embolisms can be prevented. *Lakartidningen*, 112.

Collins, J., Care, R. L.-H. & lung: the journal of critical, & 1991, U. (1991). In vitro study of simultaneous infusion of incompatible drugs in multilumen catheters. *Heart & Lung: The Journal of Critical Care*, 20(3), 271–277.

Dal Molin A, Clerico M, Baccini M, Guerretta L, & Sartorello B, R. L. (2015). Normal saline versus heparin solution to lock totally implanted venous access devices: Results from a multicenter randomized trial.

European Journal of Oncology Nursing, 19(6), 683–684. https://doi.org/doi:10.1016/j.ejon.2015.04.001

De Giorgi, I., Guignard, B., Fonzo-Christe, C., & Bonnabry, P. (2010). Evaluation of tools to prevent drug incompatibilities in paediatric and neonatal intensive care units. *Pharmacy World and Science*, 32(4), 520–529. https://doi.org/10.1007/s11096-010-9403-z

Décaudin, B., Dewulf, S., Lannoy, D., Simon, N., Secq, A., Barthélémy, C., Debaene, B., & Odou, P. (2009). Impact of multiaccess infusion devices on in vitro drug delivery during multi-infusion therapy. *Anesthesia and Analgesia*, 109(4), 1147–1155. https://doi.org/10.1213/ane.0b013e3181ae06e3

Doessegger L, Mahler HC, Szczesny P, Rockstroh H, Kallmeyer G, Langenkamp A, Herrmann J, Famulare J.. (2012). The potential clinical relevance of visible particles in parenteral drugs. *Journal of Pharmaceutical Sciences*, 101(8), 2635–2644. https://doi.org/10.1002/jps.23217

Foinard, A., Bertrand, D., Barthélémy, C., Bertrand, D., & Pascal, O. (2013). The impact of multilumen infusion devices on the occurrence of known physical drug incompatibility: a controlled in vitro study. *Anesthesia & Analgesia*, 116(1), 101–106. http://doi.org/10.1213/ANE.0b013e31826f5e02

Foster, J., Richards, R., & Showell, M. (2015). Intravenous in-line filters for preventing morbidity and mortality in neonates. *Cochrane Database of Systematic Reviews*, *8*. https://doi.org/10.1002/14651858.CD005248.pub3

Franco Sereno, M. T., Pérez Serrano, R., Ortiz Díaz-Miguel, R., Espinosa González, M. C., Abdel-Hadi Álvarez, H., Ambrós Checa, A., & Rodríguez Martínez, M. (2018). Pharmacist adscription to intensive care: generating synergies. *Medicina Intensiva*, 42(9), 534–540.https://doi.org/10.1016/j.medin.2018.02.006

Gunes, A., & Bramhagen, A. C., (2018). Heparin or sodium chloride for prolonging peripheral intravenous catheter use in children–A systematic review. *Journal of Pediatric Nursing*, *43*, E92–E99. https://doi.org/10.1016/j.pedn.2018.08.001

Han, S. S., Park, J. E., Kim, N. E., & Kang, H. J. (2012). Effects of normal saline for maintenance of arterial lines of surgical patients. *Journal of Korean Academy of Nursing*, 42(6), 791. https://doi.org/10.4040/jkan.2012.42.6.791

Hanifah, S. (2016). *The Compatibility of multiple intravenoys intravenoys (IV) drugs administered simultaneously*. Charles Sturt Unviersity.

Hanifah, S., Ball, P., & Kennedy, R. (2018). Medication incompatibility in intravenous lines in a paediatric intensive care unit (PICU) of Indonesian hospital. *Critical Care and Shock*, *21*(3), 118–127.

Hanifah, S., Kennedy, R. A., & Ball, P. A. (2018). Extended compatibility of fentanyl and ketamine in dextrose 5%. *Anaesthesiology Intensive Therapy*. https://doi.org/10.5603/ait.a2018.0022

Hanifah, S., Putri NS, Hadi NS, Sari CP, Nafiah, Z. (2022). Intravenous drugs use and potency of incompatibility in a neonatal intensive care unit (NICU), *European Journal of Clinical Pharmacy*, 24(2), 79-83

Hoff, R., Vervisch, K., De Coen, K., & Smets, K. (2019). Continuous infusion vs. intermittent flushing of peripheral cannulas in neonates using a needleless connector: A prospective cohort study. *Journal of Perinatal Medicine*, *47*(4), 464–469. https://doi.org/10.1515/jpm-2018-0285

Husna, M., Munawiroh, S. Z., Ekawati, R. P., & Hanifah, S. (2021). Systematic review of the stability and compatibility of propofol injection. In *Anaesthesiology Intensive Therapy*, 53(1),79–88. https://doi.org/10.5114/ait.2021.103542

Jack, T., Boehne, M., Brent, B. E., Hoy, L., Köditz, H., Wessel, A., & Sasse, M. (2012). In-line filtration reduces severe complications and length of stay on pediatric intensive care unit: A prospective, randomized, controlled trial. *Intensive Care Medicine*, 38(6), 1008–1016. https://doi.org/10.1007/s00134-012-2539-7

Jack, T., Brent, B. E., Boehne, M., Müller, M., Sewald, K., Braun, A., Wessel, A., & Sasse, M. (2010). Analysis of particulate contaminations of infusion solutions in a pediatric intensive care unit. *Intensive Care Medicine*, 36(4), 707–711. https://doi.org/10.1007/s00134-010-1775-y

Kanji, S., Lam, J., Johanson, C., Singh, A., Goddard, R., Fairbairn, J., Lloyd, T., Monsour, D., Kakal, J.

(2010). Systematic review of physical and chemical compatibility of commonly used medications administered by continuous infusion in intensive care units. *Critical Care Medicine*, *38*(9), 1890–1898. https://doi.org/10.1097/CCM.0b013e3181e8adcc

Ku, H. M., Kim, J. Y., Kang, S. H., & Lee, E. K. (2010). Meta-analysis of in-line filtration effects on post-infusion phlebitis caused by particulate contamination of intravenous administration. *Journal of Pharmaceutical Investigation*, 40(4), 225-230.https://doi.org/10.4333/kps.2010.40.4.225

Kumar, M., Vandermeer, B., Bassler, D., & Mansoor, N. (2013). Low-dose heparin use and the patency of peripheral IV catheters in children: A systematic review. *Pediatrics*, 131(3), e864–e872). https://doi.org/10.1542/peds.2012-2403

Langille, S. E. (2013). Particulate matter in injectable drug products. *PDA Journal of Pharmaceutical Science and Technology*, 67, 186–200. https://doi.org/10.5731/pdajpst.2013.00922

Lao, G. C., Reyes, M. R., Turet, J. R., Dot, M. P., Muner, D. S., & Cabezas, C. L. (2019). Compatibility of drugs administered as Y-site infusion in intensive care units : A systematic review. *Medicina Intensiva*, 44(2), 80-87.https://doi.org/10.1016/j.medine.2018.08.008

Maison, O., Tardy, C., Cabelguenne, D., Parat, S., Ducastelle, S., Piriou, V., Lepape, A., & Lalande, L. (2019). Drug incompatibilities in intravenous therapy: evaluation and proposition of preventive tools in intensive care and hematology units. In *European Journal of Clinical Pharmacology*, 75(2), 179–187. https://doi.org/10.1007/s00228-018-2602-6

Manrique-rodríguez, S., Sánchez-galindo, A., Mora-garcía, T., Fernandez-llamazares, C. M., Echarri-martínez, L., López-herce, J., Rodríguez-gómez, M., Bellón-cano, J. M., & Sanjuro-sáez, M. (2012). Development of a compatibility chart for intravenous y-site drug administration in a Pediatric Intensive Care Unit. *Journal of Infusion Nursing*, *35*(2), 109-114. https://doi.org/10.1097/NAN.0b013e3182425b34

McNulty, I., Katz, E., Kim, K. Y. (2005). Thrombocytopenia following heparin flush. *Progress in Cardiovascular Nursing*, *20*(4), 143–147. https://doi.org/10.1111/j.0889-7204.2005.04693.x

Nemec, K., Kopelent-Frank, H., & Greif, R. (2008). Standardization of infusion solutions to reduce the risk of incompatibility. *American Journal of Health-System Pharmacy*, *65*(17), 1648-1654. https://doi.org/10.1093/ajhp/zxac256

Niël-Weise, B. S., Stijnen, T., & van den Broek, P. J. (2010). Should in-line filters be used in peripheral intravenous catheters to prevent infusion-related phlebitis? A systematic review of randomized controlled trials. *Anesthesia & Analgesia*, *110*(6), 1624-1629. http://doi: 10.1213/ANE.0b013e3181da8342

Perez, A., Feuz, I., Brotschi, B., & Bernet, V. (2012). Intermittent flushing improves cannula patency compared to continuous infusion for peripherally inserted venous catheters in newborns: Results from a prospective observational study. *Journal of Perinatal Medicine*, *40*(3), 311–314. https://doi.org/10.1515/jpm-2011-1000

Perez, M., Décaudin, B., Abou Chahla, W., Nelken, B., Barthélémy, C., Lebuffe, G., & Odou, P. (2015). In vitro analysis of overall particulate contamination exposure during multidrug IV therapy: Impact of infusion sets. *Pediatric Blood and Cancer*, *62*(6), 1042–1047. https://doi.org/10.1002/pbc.25442

Perez, M., Décaudin, B., Foinard, A., Barthélémy, C., Debaene, B., Lebuffe, G., & Odou, P. (2015). Compatibility of medications during multi-infusion therapy: A controlled in vitro study on a multilumen infusion device. *Anaesthesia Critical Care and Pain Medicine*, *34*(2), 83–88. https://doi.org/10.1016/j.accpm.2014.06.003

Sasse, M., Dziuba, F., Jack, T., Köditz, H., Kaussen, T., Bertram, H., Beerbaum, P., & Boehne, M. (2015). In-line filtration fecreases systemic inflammatory response syndrome, renal and hematologic dysfunction in pediatric cardiac intensive care patients. *Pediatric Cardiology*, *36*(6), 1270–1278. https://doi.org/10.1007/s00246-015-1157-x

Schmitt, E., Meybohm, P., Herrmann, E., Ammersbach, K., Endres, R., Lindau, S., Helmer, P., Zacharowski, K., & Neb, H. (2019).

In-line filtration of intravenous infusion may reduce organ dysfunction of adult critical patients. *Critical Care*, *23*(373), 1–14. https://doi.org/10.1186/s13054-019-2618-z

Sharma, S. K., Mudgal, S. K., Gaur, R., Sharma, R., Sharma, M., Thakur, K. (2019). Heparin flush vs. normal saline flush to maintain the patency of central venous catheter among adult patients: A systematic review and meta-analysis. *Journal of Family Medicine*, 8(9), 2779–2792.

Sotnikova, C., Fasoi, G., Efstathiou, F., Kaba, E., Bourazani, M., & Kelesi, M. (2020). The Efficacy of Normal Saline (N/S 0.9%) Versus heparin solution in maintaining patency of peripheral venous catheter and avoiding complications: a systematic review. *Materia Socio Medica*, *32*(1), 29. https://doi.org/10.5455/msm.2020.32.29-34

Stok, D., & Wieringa, J. W. (2016). Continuous infusion versus intermittent flushing: Maintaining peripheral intravenous access in newborn infants. *Journal of Perinatology*, *36*(10), 870–873. https://doi.org/10.1038/jp.2016.94

Tanaka, H., Ambiru, S., Kawaguchi, T., Sugita, Y., Kawajiri, C., Nagao, Y., & Shimura, T. (2016). Cessation of in-line filters in central venous catheters does not significantly influence the incidence of bloodstream infections and mortality in a hospital hematological ward. *Internal Med*, 55, 1287–1292. https://doi.org/10.2169/internalmedicine.55.6207

Tissot, E., Cornette, C., Demoly, P., Jacquet, M., Barale, F., & Capellier, G. (1999). Medication errors at the administration stage in an intensive care unit. *Intensive Care Medicine*, 25(4), 353–359. https://doi.org/10.1007/s001340050857

Tully, R. P., McGrath, B. A., Moore, J. A., Rigg, J., & Alexander, P. (2014). Observational study of the effect of heparin-containing flush solutions on the incidence of arterial catheter occlusion. *Journal of the Intensive Care Society*, 15(3), 213–215. https://doi.org/10.1177/1751143714015003 07

Villa, G., Chelazzi, C., Giua, R., Tofani, L., Zagli, G., Boninsegni, P., Pinelli, F., Gaudio, A. R. De, & Romagnoli, S. (2018). In-line filtration reduces postoperative venous peripheral phlebitis associated with cannulation: a randomized clinical trial. *Anesthesia & Analgesia.* 127(6), 1367–1374. https://doi.org/10.1213/ANE.0000000000003393

Virlouvet, A., Pansiot, J., Toumazi, A., Reports, M. C.-S., & 2020, U. (2020). In-line filtration in very preterm neonates: a randomized controlled trial. *Scientific Report: nature reseacrh*, 10(5003), 1–8.https://doi.org/10.1038/s41598-020-61815-4

Vogel Kahmann, I., Bürki, R., Denzler, U., Höfler, A., Schmid, B., & Splisgardt, H. (2003). Inkompatibilitätsreaktionen auf der intensivstation. Fünf jahre nach einführung einer einfachen farbkodierung (Incompatibility reactions in the intensive care unit. Five years after the mplementation of a pH-color code). *Anaesthesist*, *52*(5), 409–412. https://doi.org/10.1007/s00101-003-0481-3

Walpot, H., Franke, R. P., Burchard, W. G., Agternkamp, C., Müller, F. G., Mittermayer, C., & Kalff, G. (1989). Particulate contamination of infusion solutions and drug additives within the scope of long-term intensive therapy. 1. Energy dispersion electron images in the scanning electron microscope-REM/EDX. *Der Anaesthesist*, *38*(10), 544-548.

You, T., Jiang, J., Chen, J., Xu, W., Xiang, L., & Jiao, Y. (2017). Necessity of heparin for maintaining peripheral venous catheters: a systematic review and meta-analysis. *Experimental and Therapeutic Medicine*, 14(2), 1675-1684.https://doi.org/10.3892/etm.2017.4706