Clinical implications of intravenous drug incompatibilities in critically ill patients

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Abstract

Objective: The aim of this review is to analyse the clinical consequences of intravenous drug incompatibilities in critically-ill patients, especially the incidence of organ dysfunctions and mortality.

Methods: A review of literature was conducted according to the PRISMA statement in June 2017, using Medline, ISI Web of Science and Clinicaltrials.gov.

Data extraction: Eligible studies were case reports and randomised controlled trials (RCTs) that evaluated the effects of drug incompatibilities in critically-ill patients on morbidity or mortality as primary or secondary outcomes, or adverse events. Two investigators independently reviewed the eligibility of the study from abstracts or manuscript data.

Data synthesis: Twelve articles met the selection criteria. The six articles reporting RCTs concern only four RCTs. RCTs were single-centre studies comparing infusion with or without filter. Two of them included adult patients. The others included pediatric and neonatal intensive care unit patients. Primary endpoints were SIRS, organ failure, overall complication rate, bacteremia, sepsis, phlebitis and length of stay. The results are mixed with one RCT reporting a reduction in SIRS, organ failure and overall complication rate, two studies in disagreement over the occurrence of sepsis and one study reporting no impact on length of hospital stay. The six articles on case reports show different drug incompatibility situations. They report pulmonary toxicity.

Conclusion: Little data is available on this topic. Infused particles may induce organ failure, in particular pulmonary toxicity and SIRS. Further studies are needed to establish a link between the level of exposure to drug incompatibilities and clinical implication.

Keywords

Parenteral nutrition; Intravenous; Infusion pumps; Filters; Drug incompatibility; Critical care

1. Introduction

In intensive care units (ICUs), patients require numerous intravenous (IV) drugs administered *via* a central venous catheter and this parenteral drug infusion is often complicated by the fact that the number of concurrently administered drugs exceeds the number of available venous lines. Drug incompatibility, particularly between two drugs is sometimes visible and recognisable through precipitate, especially in multidrug IV therapy [1]. The mechanisms of drug incompatibility were well described by Newton [2] who drew a distinction between physical and chemical reactions. Physical incompatibilities include visible (precipitation, turbidity and colour change) and sub-visible (pH change, sub-visible particles, decrease in drug concentration) reactions. Chemical drug incompatibilities are often sub-visible and lead to reactions such as redox, complexation or racemisation which reduce the effectiveness of the administered drug or create toxicity. The frequency of drug incompatibility has been evaluated in different studies. For example, one observational study, performed in two adult ICUs and a medical unit, showed that 3.7% of drug combinations used were incompatible [3]. Another showed that physicochemical incompatibilities represented 19 out of 102 (18.6%) recorded nursing acts during a 30-day period in an adult ICU [4].

Drug incompatibilities increase particle formation. In animal studies, this particulate contamination induces thrombogenesis, impairs microcirculation and modulates the immune response [5]. In addition to particles arising from drug incompatibilities, particulate contamination may be introduced into the patient from the IV solutions. X-ray analyses have shown that particulate matter consists mainly of glass from ampoules, rubber from stoppers of infusion bottles, and plastic from infusion sets [6]. To improve the detection of drug incompatibility, various decision-supporting tools are available such as Trissel's handbook, the King guide to parenteral admixtures, the cross-table on the compatibility of injectable Y-delivered drugs from the University Hospital of Geneva and some databases, the most essential being the French Stabilis database [7,8]. In ICUs, the use of a multi-lumen catheter improves efficacy in terms of drug delivery and safety by minimising the risk of incompatibility reactions. To decrease the particulate contamination generated by drug incompatibility, the use of filters and in-line filtration is recommended [9] particularly during parenteral nutrition, to reduce inflammatory response and microcirculation impairment [10]. The clinical impact of drug incompatibilities might be particularly deleterious in critically-ill patients. This indicates how important it is to clarify and synthesise the relative strengths and weaknesses of literature on this subject.

The objective of this review was to evaluate the clinical consequences of intravenous drug incompatibilities in critically-ill patients.

2. Method

Data Sources and search strategy

A review of literature was conducted according to the PRISMA statement in June 2017, using Medline, ISI Web of Science and Clinicaltrials.gov.

The following keywords were used: “parenteral nutrition” OR “parenteral nutrition, total” AND ”crystallisation” OR “granuloma, foreign body”; “parenteral nutrition” OR “parenteral nutrition, total” AND “calcium phosphates”; “critical care” OR “care, critical” OR “critical ill*” OR “intensive care units” OR “intensive care units, neonatal” OR “intensive care units, pediatric” AND infusion, intravenous” AND “particulate matter” AND “filtration”; “drug incompatibility” AND “particulate matter”; “*phlebitis” AND “filtration” AND “infusion intravenous”; “drug contamination*” AND “infusion, intravenous” AND “filtration; “parenteral nutrition” OR “parenteral nutrition, total” AND “infusion intravenous” AND “drug therapy, combination”.

Study selection

Included studies were human case reports and randomised controlled trials (RCTs) published after 1990 that evaluated the effects of drug incompatibility in critically-ill patients on morbidity or mortality as primary or secondary outcomes, or adverse events. Adult and pediatric populations were concerned. We included studies investigating the effects of IV in-line filtration on organ functions in intensive care patients. Animal and *in vitro* studies were not included. Reviewed articles were restricted to those in English and French, and published as full-text articles. Reference lists of all included studies were also scanned. Two investigators (MB and MP) independently reviewed the identified abstracts or manuscripts to determine which studies were eligible. Discrepancies were resolved through the intervention of two other authors (BD and GL).

3. Results

A total of 187 studies were screened for eligibility (Fig. 1). Twelve publications (six case reports and six RCT) met the selection criteria.

Fig 1. Flow chart.

Case reports

The six articles on case reports show different drug incompatibility situations (i.e. total parenteral nutrition (TPN), ceftriaxone with calcium gluconate and various medications) (Table 1). These articles report pulmonary toxicity (diffuse interstitial pneumonitis, occlusions in pulmonary artery branches and pulmonary granulomata).

Table 1. Data from case reports.

Total parenteral nutrition

Four articles concern drug incompatibilities involving TPN [9-12]. All of them highlight vascular crystal precipitation in the lung. Three articles contain clinical data on adults [9-11].

Hill SE *et al*. reported sudden cardio-respiratory arrest in two previously healthy young women receiving peripheral vein parenteral nutrition [11]. Autopsies documented amorphous material containing calcium and obstructing the pulmonary microvasculature of each patient. Mc Nearney T *et al.* reported the history of a young woman with Crohn's disease who, six weeks after starting TPN, developed fever, shortness of breath, a dry cough, diffuse crackles in all pulmonary fields and miliary nodules visible on a high-resolution computed tomography (HRCT)-scan [12]. Reedy JS *et al.* reported the case of a surgical patient who developed chest tightness, shortness of breath and fever while receiving TPN [13]. Investigations undertaken by the authors of clinical cases focused mainly on lung biopsy and chest HRCT-scan. The clinical symptoms presented by these patients ranged from respiratory failure including shortness of breath, chest tightness, and dry cough with or without fever to sudden death or cardio-respiratory arrest. The persistence of severe respiratory status or persistent hypoxemia resulted in a high-resolution CT scan being taken which showed either pulmonary miliary nodules or something resembling ground glass. Trans-bronchial or open-lung biopsies were needed to document TPN-associated pulmonary complications i.e. thrombi or granulomas containing crystalline precipitates. The last case reported post-mortem examinations of 41 parenterally-fed infants [14].

Other drugs

Bradley JS *et al*.[15] reported the deaths of seven neonates from cardio-respiratory arrest after receiving the concomitant IV infusion of ceftriaxone and calcium. This data was drawn from the Food and Drug Administration adverse event reporting system database [15]. The autopsy findings in four of the five infants for whom information was available revealed the presence of crystalline material or white precipitates in vascular beds and most often in the lungs. Precipitate formation occurred when both ceftriaxone and calcium were infused simultaneously, as well as when given at different time intervals. These observations suggest that for some infants the serum concentration of ceftriaxone may be sufficiently high for hours after infusion to interact with subsequently administered IV calcium.

Felton TW *et al.* observed life-threatening pulmonary hypertension and right ventricular failure in a 43 year-old man, a complication due to calcium and phosphate replacement in an ICU [16].

Randomised controlled trials

The six articles reporting RCTs concern four RCTs (different aspects of one RCT reported in three articles) (Table 2). The RCTs, concerning 1906 patients, were single-centre studies comparing infusion with or without filter. Two of them included adult patients. The others included pediatric ICU and neonatal ICU patients. Primary endpoints were systemic inflammatory response syndrome (SIRS), organ failure, overall complication rate, bacteremia, sepsis, phlebitis and length of stay. The results (Table 3) are heterogeneous with one RCT showing a reduction in SIRS, organ failure and overall complication rate, two studies in contradiction over the occurrence of sepsis and one reporting no consequence on length of stay.

Table 2. RCT study design.

Table 3. RCT main results.

One RCT was conducted in a PICU. This randomised single-centre, prospective trial, including 807 patients, aimed to assess the effects of in-line filtration on reducing the incidence of overall complications (sepsis, organ failure and thrombosis) and particularly SIRS, in critically-ill children. Jack T *et al.* reported a reduction in the incidence of SIRS and overall complication rate in the filter group [17]. The duration of mechanical ventilation was also reduced as were both PICU and length of hospital stay. Boehne M *et al.* evaluated the influence of in-line filtration on different organ functions on the same cohort of patients [18]. The incidence of respiratory, renal and hematological dysfunction was lower in the filter group. No difference was observed for cardiovascular, hepatic or neurological morbidities

between groups. Sasse M *et al.* performed a sub-group analysis on 305 critically-ill cardiac children [19]. The risk of SIRS, renal and hematological dysfunction was significantly lower within the filter group.

Two RCTs were conducted in a NICU. Van Lingen RA *et al*. reported a significant reduction in major complications through a composite criterion including the occurrence of thrombosis, sepsis and necrotising enterocolitis (NEC) [20]. Van den Hoogen A *et al*. evaluated the incidence of nosocomial sepsis and did not find any statistical difference between infants infused with or without filters [21].

One RCT was performed on adult ICU patients. Gradwolh-Matis I *et al.* carried out a prospective randomised, controlled, open-label study that evaluated the influence of in-line filters on systemic immune activation in critically-ill adults [22]. The author observed that the number of ICU days with SIRS, the incidence of SIRS, acute lung injury, the number of new infections and thromboembolic complications and the duration of mechanical ventilation were no different between filter and control group.

4. Discussion

This review of literature shows the potentially deleterious clinical effects of intravenous drug incompatibilities, which may induce or aggravate organ dysfunctions in critically-ill patients. Pulmonary morbidities seem to be the main complications observed. These have been reported by authors cited above and are mainly caused by the micro-emboli of crystal precipitates obstructing pulmonary vessels and generating granulomatous pulmonary arteritis and granulomatous interstitial pneumonitis. Severe arterial pulmonary hypertension associated with cardiac arrest can occur during a diffuse and multiple emboli procedure. One of the first clinical complications was described by the FDA who reported that the ceftriaxone-calcium complexation formed during the concomitant IV administration of ceftriaxone and calcium led to the cardiac arrest and death of seven neonates due to pulmonary emboli of white precipitate [15]. This report is one of the best examples of pulmonary complication induced by drug incompatibility in a pediatric population. In contrast, Dalton BR *et al*. [23] showed that, in critically-ill adult patients, the simultaneous IV administration of high concentrations of calcium and ceftriaxone was not significantly associated with greater mortality or adverse events compared to matched unexposed patients. Although Dalton's study is limited by its low-powered capacity for detecting effects i.e. only severe cardiorespiratory events or death, discrepancies in results may be explained by differences in calcium concentration and infusion method, ceftriaxone dose and respiratory function.

Similar pulmonary complications have been observed with TPN [10,12-14]. The origin of precipitation remains to be elucidated. One of the mechanisms could be related to the proportion or mixing sequence of electrolytes in the solution and exposure to extremes of temperature in storage or transfer. Such pulmonary complications occur frequently from a few days up to six weeks after the start of TPN. Vascular occlusion by precipitates should be hypothesised in patients on TPN who experience unexplainable fever, cough and shortness of breath. Diagnosis may require a CT scan showing diffuse pulmonary nodular opacities or even a lung biopsy in search of micro-emboli precipitates. In this context, Mc Nearney *et al.* suggested a prompt discontinuation of parenteral nutrition [12].

There are many arguments suggesting that the proportion of electrolytes in the TPN solution may be the cause of certain pulmonary complications. The high concentration of di- or trivalent cations lead to the degradation of lipid emulsions and the aggregation of lipid particles. High concentrations of calcium, phosphate and magnesium in the TPN solution contribute to the formation of calcium phosphate crystals.

As a result of drug incompatibilities, particles can activate the immune system and lead to the development of SIRS, one of the major risks for organ failure and death in

critically-ill patients. The incidence of SIRS, studied by Jack T *et al.* in a randomised controlled trial evaluating the effect of in-line filtration, was significantly lower in the group of critically-ill children using in-line filter [17]. Based on this data, in-line filtration seems effective and represents a potent strategy for preventing SIRS but is in contrast to the negative results in adults shown by Gradwolh-Matis I *et al*. [22].

The effects of drug incompatibility on organ dysfunction constitute the essential part of this review. Mechanisms of particle-induced organ damage are probably accounted for by a mechanical blockage of micro-vessels, an activation of platelets and neutrophil granulocytes with the generation of occlusive micro-thrombi and the formation of foreign-body granulomas [8,23-25]. To elucidate the pathophysiological effects of particle infusion, Boehne M *et al*. [18] and Sasse M *et al*. [19] evaluated, in critically ill children, the influence of in-line filtration on different organ functions and observed a significant reduction in the incidence of SIRS, respiratory, renal and hematological dysfunction in the filter group. However, the absence of any difference between groups concerning other organ dysfunctions is questionable.

This raises the problem of the effectiveness of in-line filtration and reliability of different studies, particularly a meta-analysis of four randomised trials performed by Forster JP *et al*., including 704 neonates, which did not demonstrate any difference in mortality or morbidity between filtration group and control group [24]. Nevertheless, the positive effects of filtration on organ function need to be considered. Renal and respiratory dysfunctions induced by particles are probably due to microcirculation impairment. Lehr *et al.* underlined the important role of microcirculation [10]. They investigated in an animal model whether particles from different antibiotic solutions might affect the blood supply in a microvascular bed that has been compromised by prior injury induced experimentally by exposure of muscle tissue to ischemia and reperfusion. The loss of capillary perfusion due to particle infusion was dependent on the extent of ischemia-induced muscle injury with more capillaries lost in the more severely compromised muscle areas. These findings suggest that particles may severely compromise tissue perfusion in patients with prior microvascular compromise of vital organs (i.e. sepsis, trauma) and thus predispose to complications such as acute respiratory distress syndrome, acute renal failure and multi-organ failure. Therefore, prior microcirculation impairment in pathological conditions such as sepsis can induce or worsen organ dysfunction**.** Arima H *et a*l. investigated whether the injection of polystyrene beads as an artificial contaminant of intravenous fluids after lipopolysaccharide (LPS) administration affected mortality and organ damage in mice [25]. The mice were divided into four groups and received injections of: polystyrene beads only, LPS only, polystyrene beads 30mn after LPS or saline. The survival rate after LPS injection associated with polystyrene bead injection was significantly lower than that of the other three groups. In kidney sections,

injured glomeruli were significantly higher with LPS and polystyrene bead injection than in the other three groups. LPS and polystyrene bead injection decreased the glomerular filtration rate and led to renal failure. Orbegozo D *et al.* observed that microvascular reactivity is soon affected in patients with ARDS and this impairment is directly related to the severity of the disease. We can therefore easily understand that particles may aggravate this pathology [26]. Robinson LA *et al*. used an isolated rat heart model to assess whether unfiltered direct intra-arterial administration of cardioplegic solutions, as in open-heart surgery, could be damaging to the myocardium [27]. This led to a significant reduction in coronary blood flow which could be largely prevented by filtration.

Other studies have also shown the benefit of a multi-lumen strategy to prevent particle contamination. Perez M *et al.* underlined the advantage of a multi-lumen infusion set in reducing particulate contamination [28]. In an *in vitro* study, the authors reproduced the parenteral multidrug infusion used in a pediatric hematology unit. With a multi-lumen infusion set, particulate contamination was significantly reduced by 68% compared to the standard infusion set. The same team, in a controlled *in vitro* study, tested the compatibility of medications during multi-infusion therapy and confirmed the impact of a new multi-lumen infusion access device on the occurrence and prevention of known physical drug incompatibilities [29]. Foinard A *et al.* evaluated *in vitro* the impact of multi-lumen infusion devices on the occurrence of known physical drug incompatibilities [30]. They observed that physical incompatibilities between two drugs could lead to a significant reduction in drug delivery to the patient, even in the absence of visible particles. Indeed, furosemide precipitation resulting in the formation of visible and/or sub-visible particles led to a drug loss to the patient estimated at between 10% and 15% in the presence of midazolam. This experimental data requires to be confirmed in clinical practice so as to determine to what extent the choice of device affects the efficiency and safety of IV therapeutics administered to the patient.

Our analysis focused mainly on the clinical implications of the administration to patient of particles resulting from intravenous drug incompatibilities. This is a limitation to our study as other consequences of drug incompatibilities are not included. Chemical incompatibilities induce drug degradation that may lead to a decrease in drug delivery and/or the formation of toxic substances. For example, diluting epinephrine in a sodium bicarbonate solution induces its oxidation and decreases its concentration in solution [31]. The clinical relevance of such incompatibility depends on the contact time between the two chemically incompatible drugs [1,31,32]. It is therefore important to read carefully the results of drug stability studies to know how long the contact time is between mixed drugs in the same container [1].

5. Conclusion

This review shows that drug incompatibilities *via* particulate contamination may increase the risk of severe complications and damage to different organs. Drug incompatibilities can increase morbidity in critically-ill patients particularly during prolonged TPN. Prevention of drug incompatibilities therefore appears to be a safety procedure to be implemented for critically-ill patients by using multi-lumen infusion lines and catheters and/or in-line filtration. In critically-ill neonates and children, in-line filtration reduces and even prevents some organ dysfunctions with no effect on mortality. Randomised controlled trials with a larger patient population are required to confirm the deleterious prognosis of particle contamination and to evaluate the preventive effect of in-line filtration and/or a multi-lumen strategy on morbidity.

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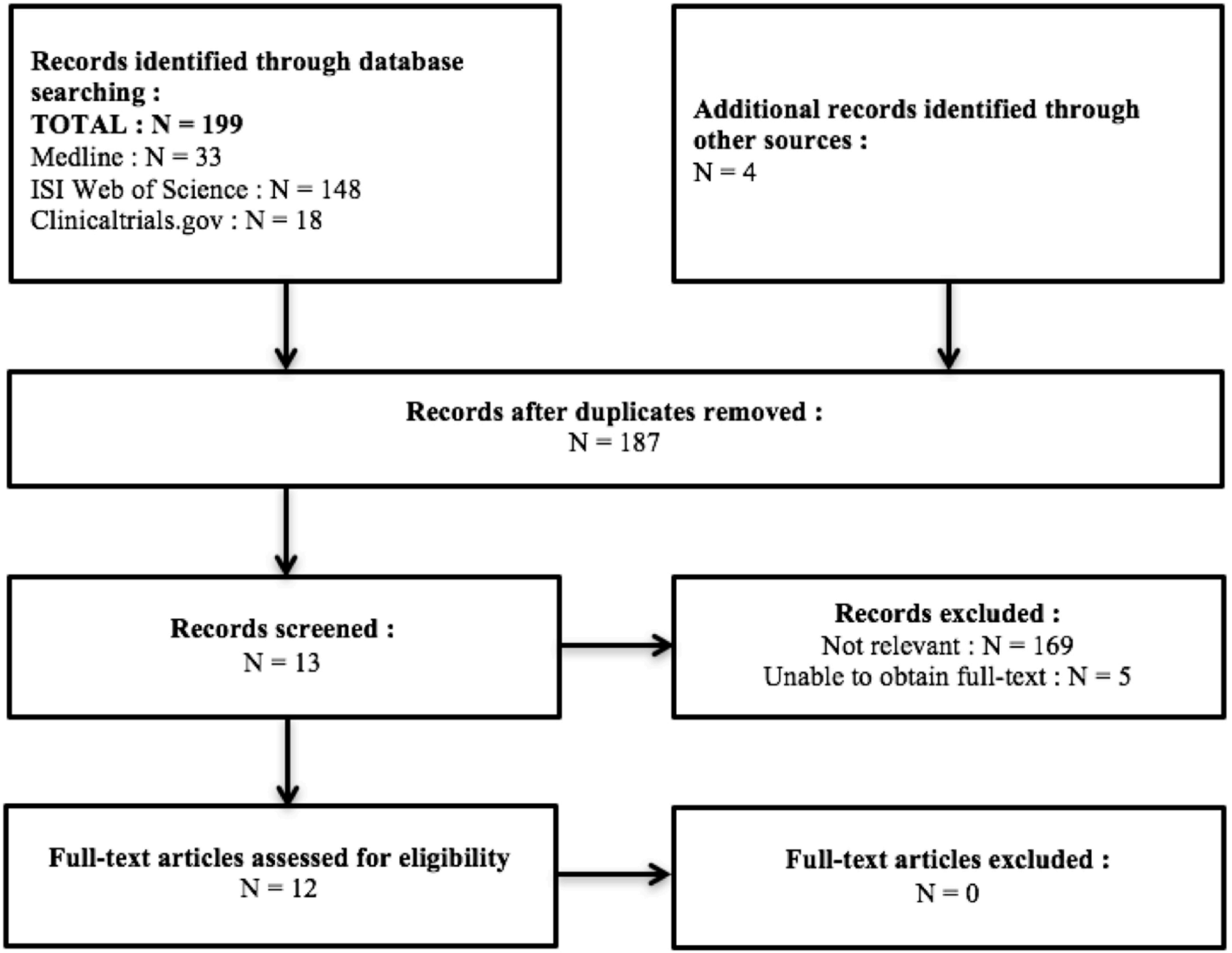
Records identified through database searching :
TOTAL : N = 199
Medline : N = 33
ISI Web of Science : N = 148
Clinicaltrials.gov : N = 18
Additional records identified through other sources :
N = 4
Records after duplicates removed :
N = 187
Records screened :
N = 13
Records excluded :
Not relevant : N = 169
Unable to obtain full-text : N = 5
Full-text articles assessed for eligibility
N = 12
Full-text articles excluded :
N = 0

Reference	Patient(s)	Treatment involved	Detectability (biospsy, autopsy, clinical observation)	Treatment undertaken	Time between treatment and occurrence	Context of care	Clinical data reported
Bradley JS et al, 2009 [15]	Nine neonates and young infants, mostly younger than 2 months	Ceftriaxone + calcium gluconate with concurrent IV drugs (metronidazole, midazolam, furosemide, etc.)	Autopsy findings	-	From a few minutes after ceftriaxone infusion to around 2 hours	-	Presence of crystalline material or white precipitate in vascular beds (in the lungs) for 4 infants
Felton TW et al, 2006 [16]	43-year-old man	5L of crystalloid fluids, furosemide 10 mg, calcium gluconate 10% 10 mL and potassium phosphate 20 mmol/14 mmol	Electrocardiogram, transthoracic echocardiography white precipitate in the drip chamber	Anesthesia with fentanyl, propofol and succinylcholine, intubation and mechanical ventilation	90 minutes	Ischiorectal abscess.	Acute severe deterioration by flooding pulmonary oedema, severe pulmonary hypertension and right heart failure
Hill S et al, 1996 [11]	Two young women with pelvic infections	TPN	Autopsy	-	-	-	Death of the two patients. Amorphous material containing calcium obstructing the pulmonary microvasculature revealed by the autopsy

McNearney T et al, 2003 [12]	26-year-old woman	Home TPN + manual addition of selenium 40 µg/mL 1.05 mL. No phosphorus salt in the TPN.	Chest CT scan, bronchoscopy, BAL, open lung biopsy of the lingula (crystalline precipitates visible in energy dispersive X-Ray analysis)	Reintroduction of TPN on hospital day 2. Well tolerated until day 8 (spike fevers). IV antibiotherapies. Discontinuous TPN on day 11 with oral intake. Supplemental oxygen.	Fever, shortness of breath and exercise intolerance 2 weeks after TPN. Hospitalisation of dehydration secondary to decreased oral intake, abdominal pain and fistulae 3 weeks after	Crohn's disease receiving home TPN	Vascular pulmonary precipitates with occlusions in pulmonary artery branches containing crystalline precipitates visible with X-RAY analysis. Alveolar foreign body giant cell granulomas containing crystalline precipitates.
Puntis JW et al, 1992 [14]	Postmortem material from 41 parenterally fed infants from ICU	Parenteral nutrition for prematurity, according to a standard protocol with a fluid intake of 150 mL/kg.	Necropsy findings of tissue sections from each lobe of each lung	-	-	Prematurity and association with respiratory distress requiring ventilatory support (N = 38) or necrositing or ischaemic enterocolitis (N = 3)	2 cases of pulmonary granulomata in the pulmonary arterial system. No identification of specific foreign material, but occasionally fragments and visible cotton fibers.
Reedy JS et al, 1999 [13]	21-year-old man	Home TPN + hydrocortisone,	Chest X-ray and CT scan. Biopsy	Reduction in calcium	Patient received regimens of	Complex medical history	Amorphous material

		trimethoprim-sulfamethoxazole and ganciclovir during hospitalisation	during hospitalisation and autopsy of the lungs	gluconate from 30 to 20 mEq, and magnesium from 45 to 35 mEq per bag	TPN from the age of 6 weeks	notable for short gut secondary to mesenteric ischemia (intestinal malrotation)	obstructing the pulmonary microvasculature revealed by transbronchial biopsy

Reference	Design	Participants *n*	Treatment (n)	Study period (months)	Inclusion criteria	Exclusion criteria	Primary Endpoints	Secondary Endpoints
Van Lingen RA et al, 2004 [20]	Single-centre, prospective, randomised, controlled study	88	Control (44) / Filter (44)	-	Premature infants > 26 weeks and < 37 weeks of gestation with respiratory distress syndrome, asphyxia or pneumonia/septicaemia, and patients on antibiotic therapy	Patients with congenital malformations, preterm infants < 26 weeks	Bacteraemia, phlebitis, extravasation, thrombosis, septicaemia and necrosis	Costs attributable to patients
Van den Hoogen A et al, 2006 [21]	Single-centre, randomised trial	507	Control (214) / Filter group (228)	12	All infants admitted in NICU who needed a CVC	-	CVC insertion site, number of catheter days, occurrence of sepsis or phlebitis, costs for disposable materials and nursing time	-
Jack T et al, 2012 [17]	Single-centre, prospective, randomised, controlled trial	807	Control (406) / Filter group (401)	43	Patients < 18 years	Expected death within 48 h of admission, absence of IV infusion therapy	Overall complication rate of major events (SIRS, sepsis, organ failure and thrombosis)	Length of stay on PICU and overall hospital stay
Boehne et al, 2013 [18]	Single-centre, prospective,	807	Control (406) / Filter group	43	Patients < 18 years	Expected death	Overall complication rate of major events	-

	randomised, controlled trial		(401)			within 48 h of admission, recruitment for other trials, absence of IV infusion therapy, discharge from PICU within 6 h, discontinuation of intervention	(incidence of SIRS, sepsis, thrombosis, acute liver failure, ARDS, acute renal and circulatory failure)	
Sasse M et al, 2015 [19]	Single-centre, prospective, randomised, controlled trial	305	Control (150) / Filter group (155)	43	Patients < 18 years, Patients with cardiac diseases	Expected death within 48 h of admission, recruitment for other trials, absence of IV infusion therapy, discharge from PICU within 6 h, discontinuation of intervention	SIRS, sepsis, mortality, organ failure (circulation, lung, liver and kidney) or organ dysfunction (cardiovascular, respiratory, neurological, hematological)	Mortality rates, length of stay on PICU and duration of mechanical ventilation
Gradwohl-Matis I et al, 2015 [22]	Single-centre, prospective, randomised, controlled,	504	Control (252) / Filter group (252)	16	All critically ill patients > 18 years, expected length of stay > 24 h and a CVC in place	Age < 18 years, pregnancy, neutropenia (< 1,5 G/L) or known	Number of ICU days with SIRS	Incidence of SIRS, number of SIRS criteria per day with the syndrome, the duration

	open-label trial.					immunosuppression, limited intensive care		of invasive mechanical ventilation, length of stay in the ICU, incidence of acute lung injury/acute respiratory distress syndrome, maximum C-reactive protein serum concentration, maximum white blood cell count, incidence of new candida and/or central-line-associated bloodstream infections, incidence of new thromboembolic complications, cumulative insulin requirements and presence of hyper- or hypoglycemia

Reference	Study selection	Study characteristics	Primary endpoints (control vs filter group)	Secondary Endpoints
Van Lingen RA et al, 2004 [20]	Exclusion: 4 in control group (death)	Age 30.7 weeks	Reduction in major complications [21 vs. 8; P < 0.05)	Reduction in costs/infant for the study group with filter, but no statistical data
Van den Hoogen A et al, 2006 [21]	Exclusion: 39 in control group, 25 in filter group	Age 33 weeks, Male 57%	No significant difference in the incidence of sepsis (also sepsis per 1000 catheter days), on catheter days. No phlebitis during the study	
Jack T et al, 2012 [17]	-	Age 5.8 years old, Male 57%	Reduction of the overall complication rate [40.9% vs. 30.9%; 95% CI 0.484 to 0.865], SIRS [30.3% vs. 22.4%; 95% 0.485 to 0.913]	Reduction in length of stay [3.89 (2.96 to 4.81) vs. 2.98 (2.33 to 3.63)] and duration of mechanical ventilation [14.0 (5.6 to 22.4) vs. 11.0 (7.1 to 14.9)]
Boehne et al, 2013 [18]	-	Age 5.8 years old, Male 57%	Reduction in respiratory [14.5% vs. 9.5%; CI -9.52 to -0.59%], renal [9.9% vs. 6.0%; CI -7.58 to -0.15%] and hematological dysfunction [8.4% vs. 4.5%; CI -7.26 to -0.51%]	-

Sasse M et al, 2015 [17]	Exclusion: 32 in control group, 35 in filter group	Age 3.4 years old, Male 63%	Reduction in SIRS [36.0% vs. 25.2%; 95% CI -21.8 to -0.5%], renal dysfunction [10.3% vs. 19.3%; CI -17.0 to -3.0%] and hematological dysfunction [5.8% vs. 12.7%; CI -14.2 to -0.2%]	No significant reduction
Gradwohl-Matis I et al, 2015 [20]	No exclusion	Age 67.3 years old, Male 59%	No significant difference	Higher incidence of SIRS in in-line microfilter group [96.8% vs. 99.6%]