XVe Congrès
de la Société Française
de Pharmacie Clinique

5, 6 et 7 février 2014
Grenoble
Centre de congrès WTC

Particules: incompatibilités physico-chimiques et filtres en ligne

Dre Caroline Fonzo-Christe
Pharmacie des HUG

Hôpitaux Universitaires de Genève

UNIVERSITÉ DE GENÈVE
FACULTÉ DES SCIENCES
Section des sciences pharmaceutiques

Conflits d'intérêt

Aucun à déclarer

Définition

Particules étrangères, non dissoutes et mobiles, autres que des bulles de gaz, involontairement introduites dans les préparations injectables.

Pharmacopée Européenne 7.1 (04/2011):3559-75

Pollution de l'air

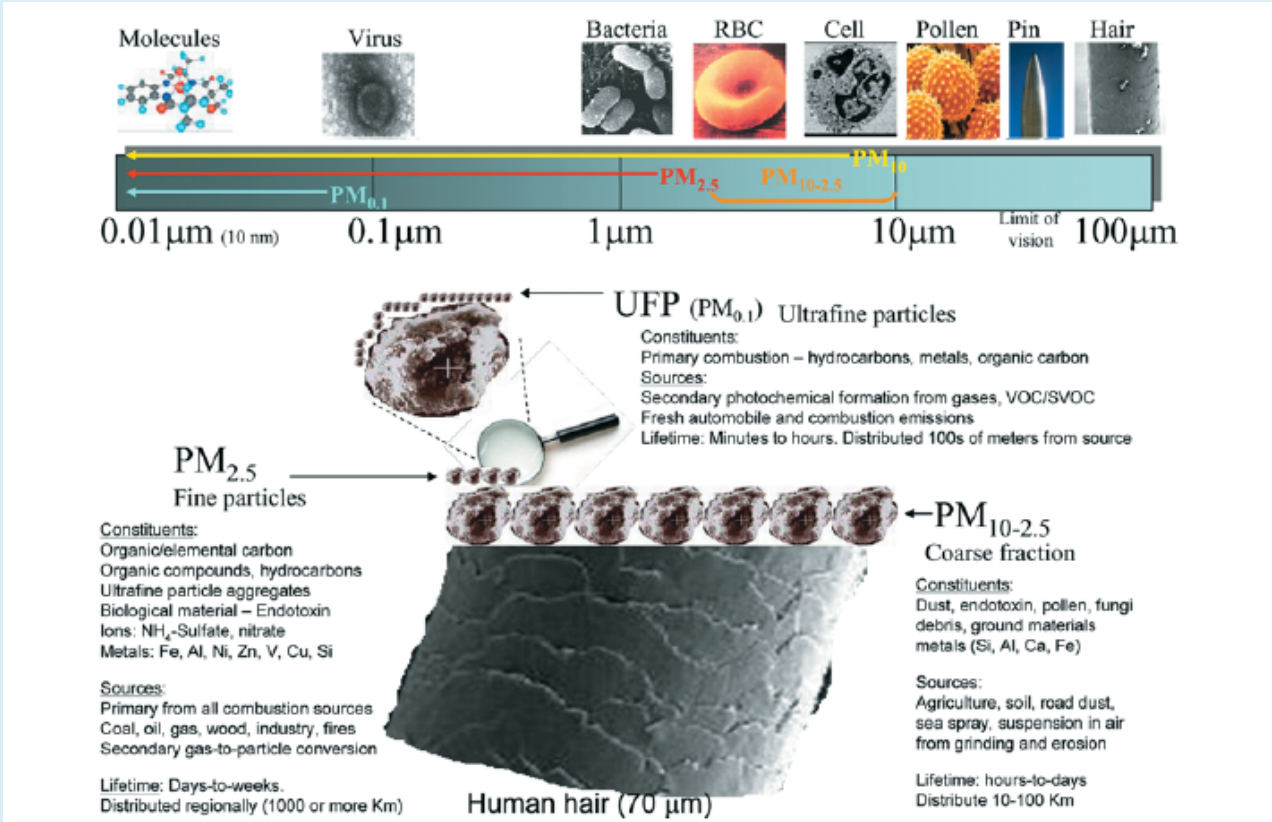


Figure 1 Size, sources and composition of PM air pollution
RBC, red blood cell; SVOC, semi-volatile organic carbons; UFP, ultra-fine particles; VOC, volatile organic carbons.

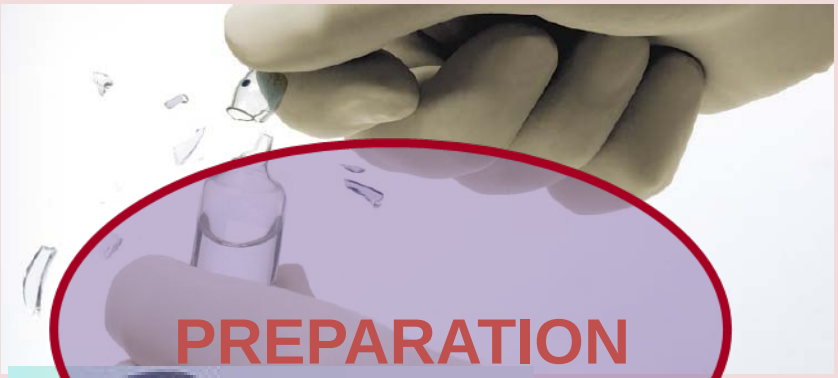
Visible:
env . 50 µm

Erythrocytes:
env. 7.5 µm

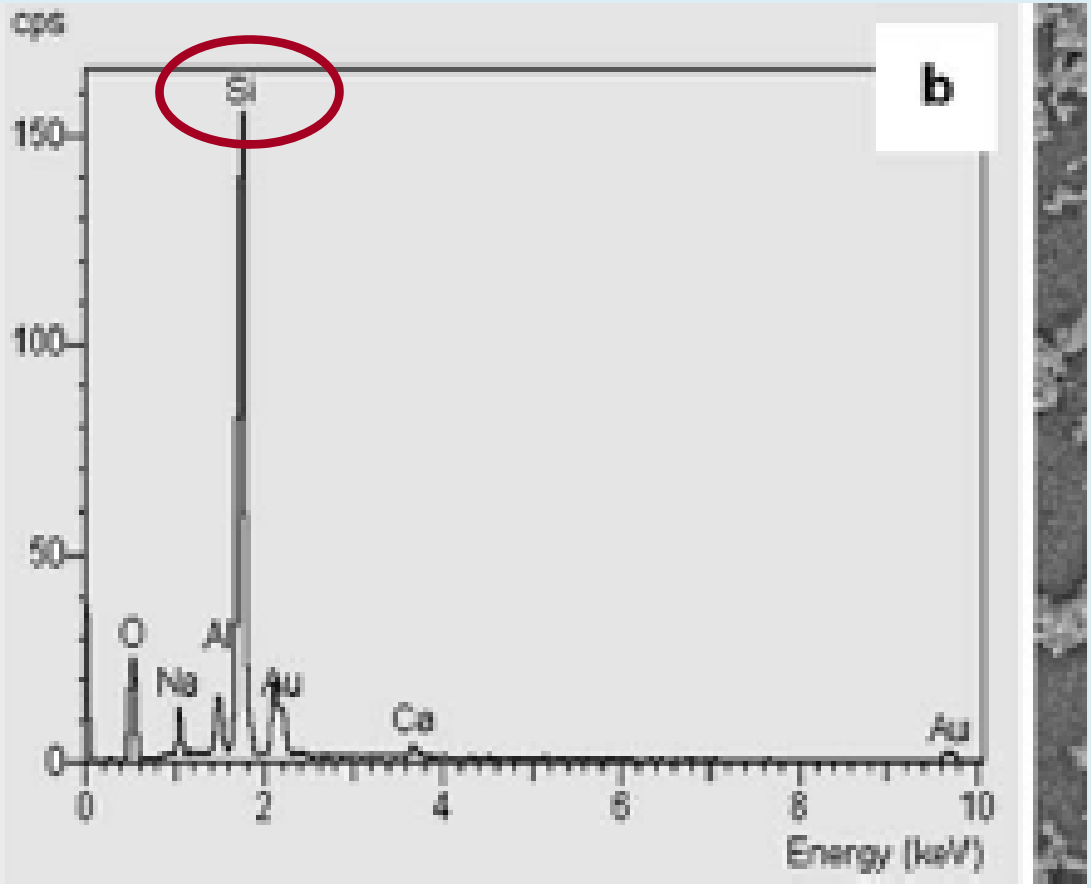
Capillaires:
8-10 µm

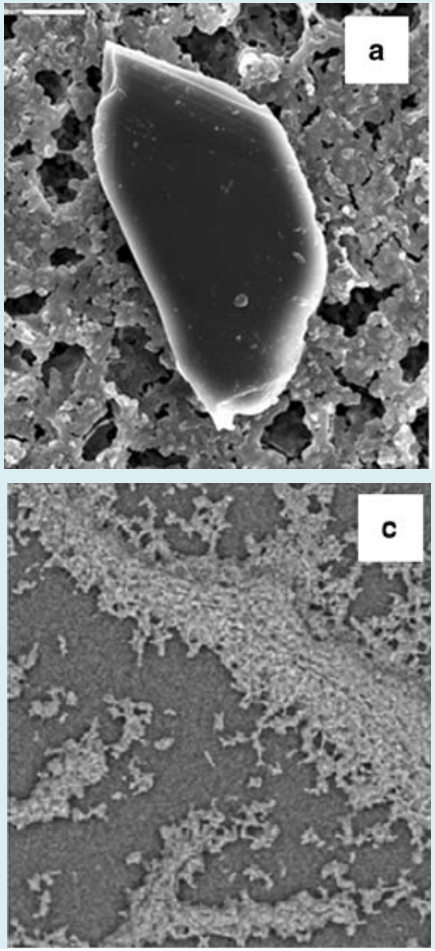
Brook RD. Clinical Science 2008;115:175–187

Sources à l'hôpital



Composition et taille





Jack T et al. Intensive Care Med 2010;36:707–711

Conséquences cliniques

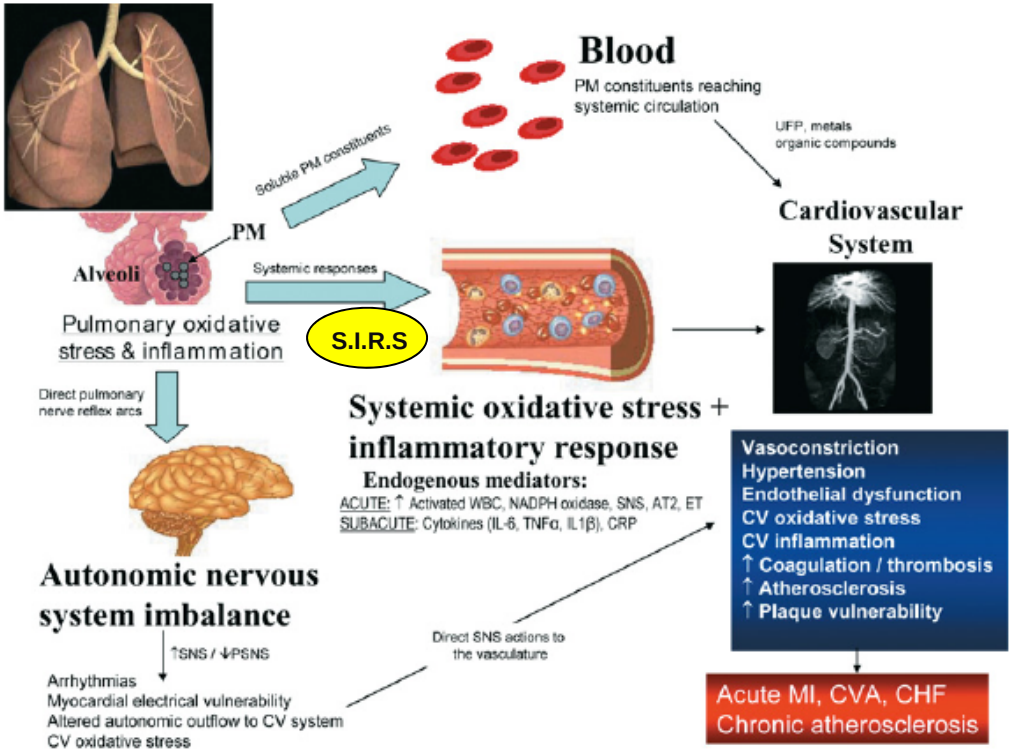
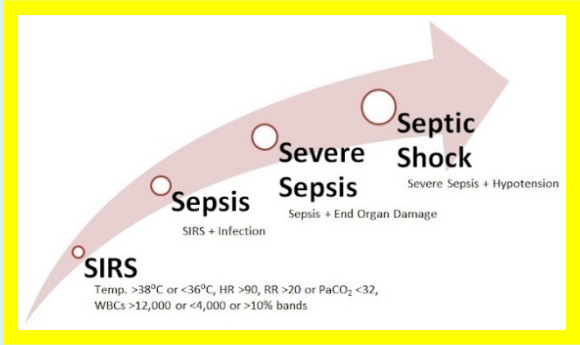


Figure 2 Broad biological pathways whereby PM may cause CV events

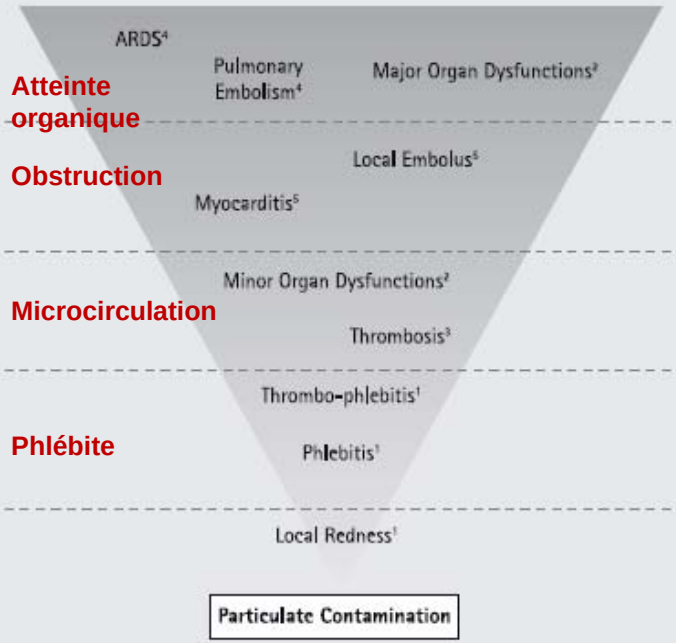
AT2, angiotensin II; CVA, cerebrovascular accident; CHF, congestive heart failure; ET, endothelins; MI, myocardial infarction; ROS, reactive oxygen species; UFP, ultra-fine particles; WBC, white blood cells.



- **Agression mécanique**
- **Action inflammatoire et thrombotique**

Brook RD. Clinical Science 2008;115:175–187

Conséquences économiques



	Complications resulting from Particle Contamination	Severity	Clinical Treatment	Length of Stay	Additional Cost[6]
Atteinte organique	ARDS[4], Pulmonary Embolism[4], Major Organ Dysfunctions[2]	High	Full ICU treatment (Treating/Monitoring/Feeding etc.)	4–30d ICU + 4–30d Normal Ward	7,556 € – 56,670 €
Obstruction	Local Embolus[5], Myocarditis[5]	Medium High	ICU/Intermediate care treatment (Observation/Monitoring/Treatment)	1–7d RICU + 1–7d Normal Ward	1,136 € – 7,952 €
Microcirculation	Minor Organ Dysfunctions[2], Thrombosis[3]	Medium	Extension of clinical treatment (Observation/Monitoring)	0d RICU + 1–3d Normal Ward	382 € – 1,146 €
Phlébite	Thrombo-phlebitis[1], Phlebitis[1]	Medium Low	Local treatment (No additional Monitoring)	0d ICU + 0–1d Normal Ward	0 € – 382 €
	Local Redness[1]	Low	No complication for patient	0d ICU 0d Normal Ward	0 €

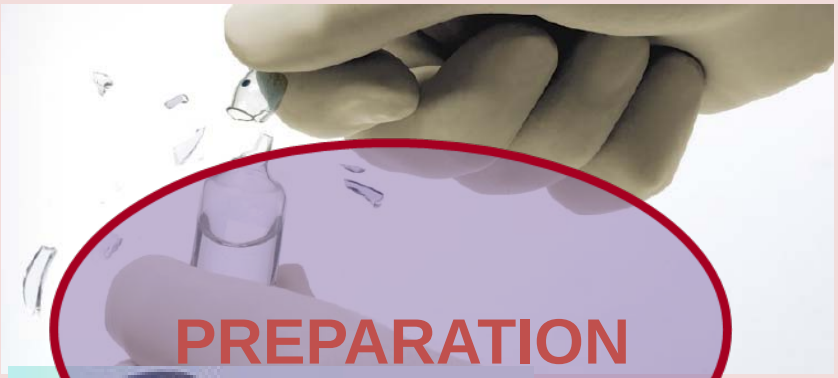
References
[1] Yorioka et al. 2006, Grünewald et al. 2004, Ellenbogen et al. 1975
[2] Yorioka et al. 2006, Lye 2003, Puntis et al. 1992, Walpot et al. 1989, Turco et al. 1971
[3] Lehr et al. 2002, Panknin 2007, Walpot et al. 1989
[4] Walpot et al. 1989, Garvan 1971, Gross et al 1966
[5] Kossovsky et al. 1995, Lehr et al 2002, Douglas et al 2001
[6] Gianino et al. 2007, Bertolini et al. 2005

BBraun. Particulate contamination, 03/2011

Constat

→ Réduire le nombre de particules!

Sources à l'hôpital



PREPARATION

ADMINISTRATION

CIVAS (prêt à l'emploi)

- Haut risque d'erreurs lors de la préparation (dilution)
- Haut risque de particules

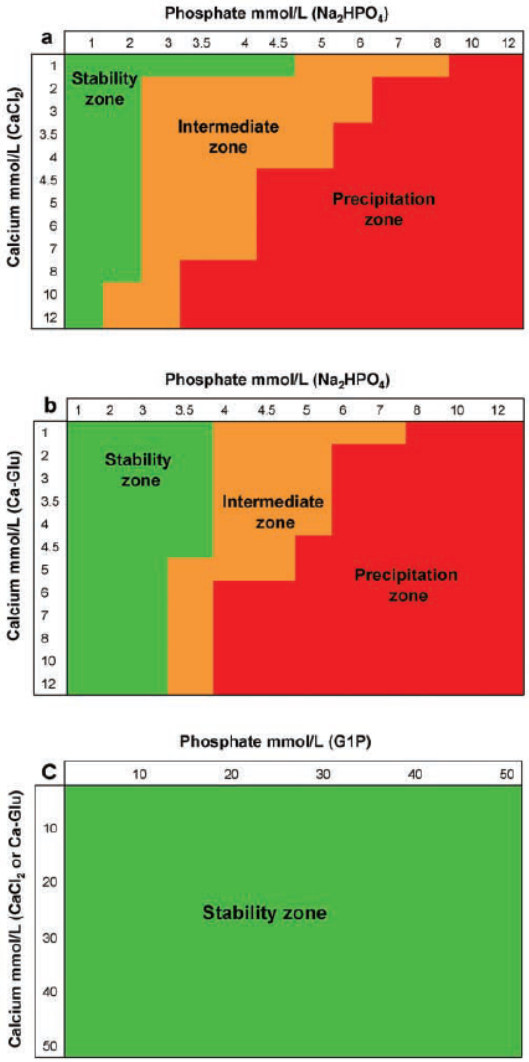
Fabrication GMP (environnement dédié, filtration finale 0.2 µm)

- Seringue 5mg/mL, 10 mL
- Particules / mL: - 10 µm: 3
  - 25 µm: 1

TPN et calcium / phosphate

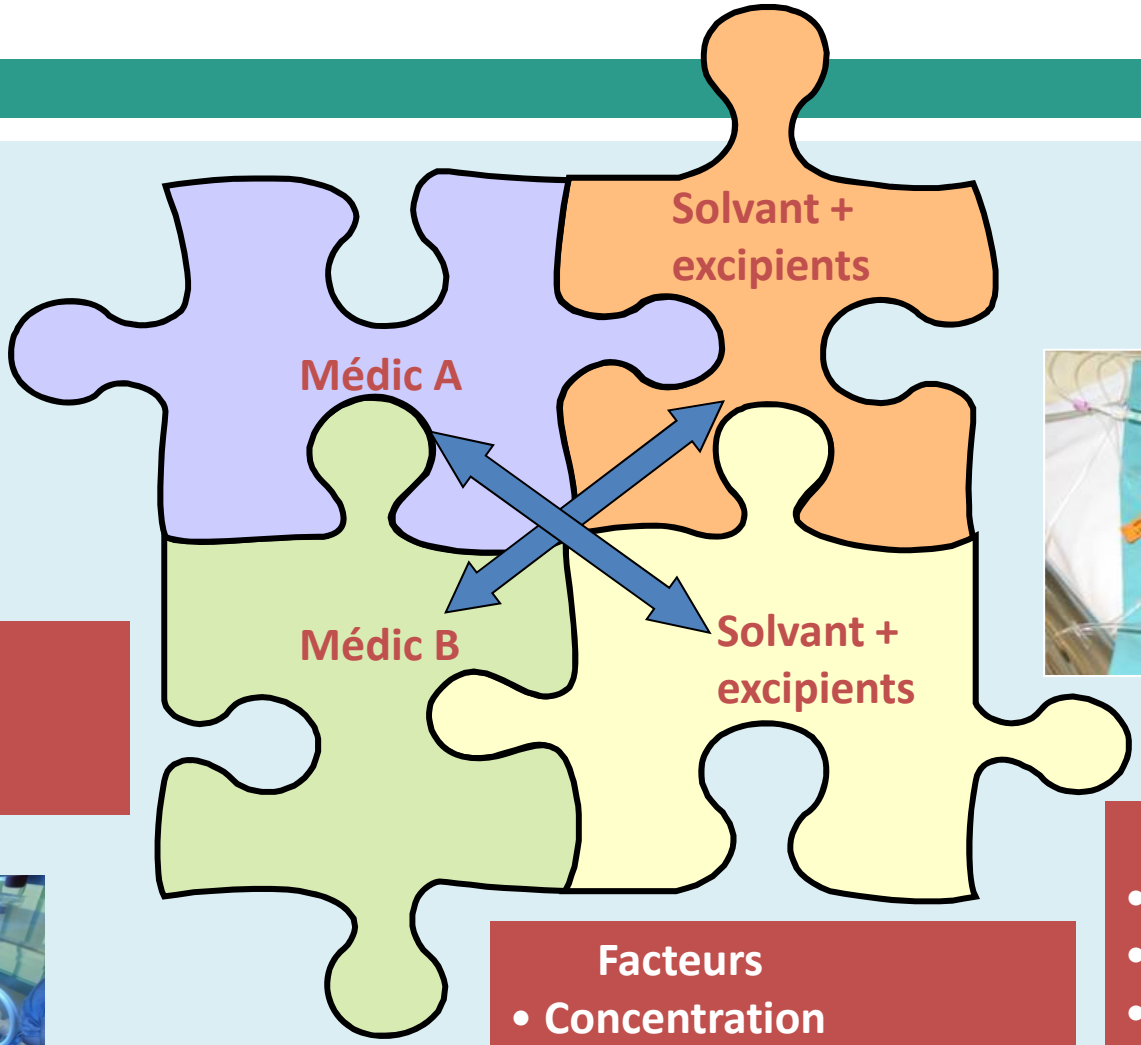
Maximizing Calcium and Phosphate Content in Neonatal Parenteral Nutrition Solutions Using Organic Calcium and Phosphate Salts

Bouchoud L et al. JPEN J Parenter Enteral Nutr. 2010;4:542-5



Sources à l'hôpital

Incompatibilités



Environnement
- Température
- Lumière

Facteurs
- Concentration
- Temps de contact

Matériel
- PVC (DEHP)
- Silicone
- …

Incidents cliniques et incompatibilités

0148-6071/89/1302-0209$02.00/0
JOURNAL OF PARENTERAL AND ENTERAL NUTRITION
Vol. 13, No. 2
Printed in U.S.A.
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Pulmonary Deposition of Calcium Phosphate Crystals as a Complication of Home Total Parenteral Nutrition

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From the Nutrition Support Service and Clinical Nutrition Research Unit, Department of Medicine, University of Chicago, Chicago, Illinois

0148-0671/96/2001-0081$03.00/0
JOURNAL OF PARENTERAL AND ENTERAL NUTRITION
Vol. 20, No. 1
Printed in U.S.A.

Case Report

Fatal Microvascular Pulmonary Emboli From Precipitation of a Tot Nutrient Admixture Solution*

STEVEN E. HILL, MD†; LESLIE S. HELDMAN, MD‡; ELWIN D. H. GOO, PHARMD§; PAUL E. WHIPPO, DVM‖; AND JOSEPH C. PERKINSON, MD†

From the Departments of †Surgery, ‡Pathology, §Pharmacy, and ‖Clinical Investigation, Tripler Army Medical Center, Honolulu, Haw

ABSTRACT. *Background:* Paroxysmal respiratory failure and death occurred in two young adult females with pelvic infections. Autopsy revealed an amorphous material containing calcium obstructing the pulmonary microvasculature of each patient. Both patients received an identical total nutrient admixture (TNA) solution before their deaths. *Methods:* Infusion of TNA into an animal model was undertaken in an effort to reproduce the clinical effect. Laboratory investigation was also performed to isolate a precipitate and identify the factors contributing to precipitation. *Results:* A nonvisible precipitate containing calcium, phosphorus, and organic material was isolated from the TNA solution. Infusion of the formulation into healthy pigs re sudden death within 4 hours. Alteration of the amino a ponent, mix sequence, agitation technique, and mixing c influenced precipitate formation. *Conclusion:* Pul embolization of a precipitate containing calcium phosp sulted in the death of two patients. The pH of the am component, transient elevation of calcium and phosph centrations during mixing, and the lack of agitation dur mated preparation of the formulation were identified as logic factors producing the fatal precipitate. (*Journal of P and Enteral Nutrition* **20**:81–87, 1996)

Knowles JB et al. JPEN 1989;13:209-13

Hill SE et al. JPEN 1996;20:81-87

ization. The effects of duration of
tion, solution temperature, pH, and
on calcium phosphate precipitation

McNearney T et al. Dig Dis Sci 2003;48:1352-4

Digestive Diseases and Sciences, Vol. 48, No. 7 (July 2003), pp. 1352–1354 (© 2003)

CASE REPORT

Total Parenteral Nutrition Associated Crystalline Precipitates Resulting in Pulmonary Artery Occlusions and Alveolar Granulomas

TERRY McNEARNEY, MD,*†‡ CHRISTOPHER BAJAJ, DO,* MICHAEL BOYARS, MD,* JOHN COTTINGHAM, MS IV,§ and ABIDA HAQUE, MD§

KEY WORDS: parenteral nutrition; crystalline precipitates; pulmonary artery occlusion; alveolar granulomas.

Crystal precipitation from total parental nutrition (TPN) and systemic embolization has been described in patients on TPN, including in the lung (1–4). This is a rare and

sequence as recommended by American Society for Parenteral and Enteral Nutrition and American Journal of Health System Pharmacy guidelines was as follows: Automix: intralipid 20%, 177 ml; Travesol 10%, 815 ml; dextrose 70%, 457 ml.; sterile wa-

Complexation et calcium

Intravenous Ceftriaxone and Calcium in the Neonate: Assessing the Risk for Cardiopulmonary Adverse Events

John S. Bradley, MD[a], Ronald T. Wassel, PharmD[b], Lucia Lee, MD[c], Sumathi Nambiar, MD, MPH[d]

[a]Rady Children's Hospital San Diego, San Diego, California; [b]Office of Surveillance and Epidemiology and [d]Office of New Drugs, Office of Antimicrobial Products, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland; [c]Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, US Food and Drug Administration, Rockville, Maryland

The authors have indicated they have no financial relationships relevant to this article to disclose.

What's Known on This Subject

The package label for ceftriaxone was changed in August 2007 to contraindicate the co-administration of ceftriaxone with calcium-containing intravenous solution.

What This Study Adds

The cases reported to the FDA and the FDA AERS database search are provided and discussed to provide clinicians the basis for these new precautions.

ABSTRACT

OBJECTIVES. Unsolicited reports regarding potentially serious adverse drug reactions in neonates and young infants were reported to the Food and Drug Administration, leading to changes in the package label for ceftriaxone. This report describes and summarizes the reported cases that led to safety concerns regarding the concurrent administration of intravenous ceftriaxone and calcium in this age group.

METHODS. Nine reported cases were assessed. The Food and Drug Administration Adverse Event Reporting System database was searched for potential drug interactions in patients who were receiving concomitant ceftriaxone and calcium therapy.

RESULTS. Eight of the reported 9 cases (7 were ≤2 months of age) represented possible or probable adverse drug events. There were 7 deaths. None of the cases were reported from the United States. The dosage of ceftriaxone that was administered to 4 of 6 infants for whom this information was available was between 150 and 200 mg/kg per day. The rate of occurrence of these serious adverse drug reactions cannot be accurately determined from available data.

CONCLUSIONS. The concurrent use of intravenous ceftriaxone and calcium-containing solutions in the newborn and young infant may result in a life-threatening adverse drug reaction. Contributing factors for infants in this report may include the use of ceftriaxone at dosages higher than those approved by the Food and Drug Administration, intravenous "push" administration, and administration of the total daily dosage as a single infusion. *Pediatrics* 2009;123:e609–e613

www.pediatrics.org/cgi/doi/10.1542/peds.2008-3080

doi:10.1542/peds.2008-3080

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Food and Drug Administration.

Key Words

ceftriaxone, calcium, newborn, drug therapy/adverse event, cardiopulmonary arrest

Abbreviations

FDA—Food and Drug Administration
AERS—Adverse Event Reporting System

Accepted for publication Dec 17, 2008

Address correspondence to John S. Bradley, MD, 3020 Children's Way, Mail Code 5041, San Diego, CA 92123. E-mail: jbradley@rchsd.org.

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2009 by the American Academy of Pediatrics

complexe insoluble calcium-ceftriaxone

Bradley JS et al. Pediatrics 2009;123:609-13

Types de réactions

Physico- chimiques

- Acide-base (pH)
- Solubilité
- Rupture émulsion
- Oxydo-réduction
- …

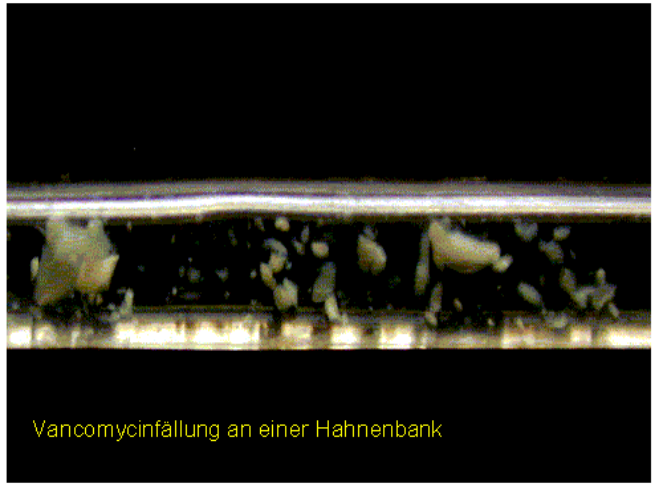
Conséquences

- Précipitation (visible)
- Coloration (visible)
- Formation gaz (visible)
- Changement pH (invisible)
- ↓ concentration (invisible)

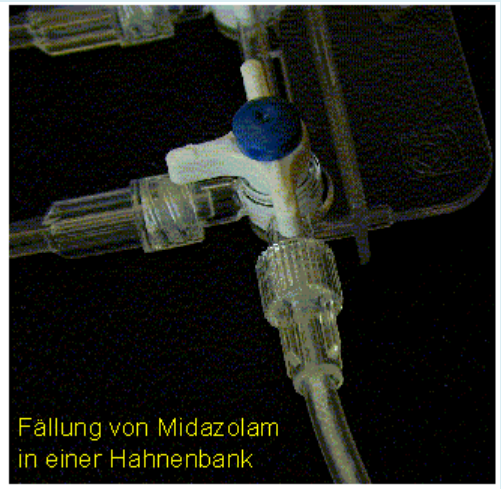
- Occlusion cathéter
- Embolies (particules au niveau rénal, pulmonaire)
- ↓ effet thérapeutique
- Effet toxique (ex. peroxides)

patient

Médicaments acides et basiques



furosémide sodique (pH 9) + vancomycine HCl (pH 3)



furosémide sodique (pH 9) + midazolam HCl (pH 4)

From: KIK 2.1, BBraun, 2002

Solvant de dilution

Solvant	pH	Adapté pour
Glucose 5%-20%	pH = 3.5 - 6.5	amiodarone, amphotéricine B
NaCl 0.9%	pH = 5.0 - 7.0	aciclovir, phénytoine

From: KIK 2.1, BBraun, 2002

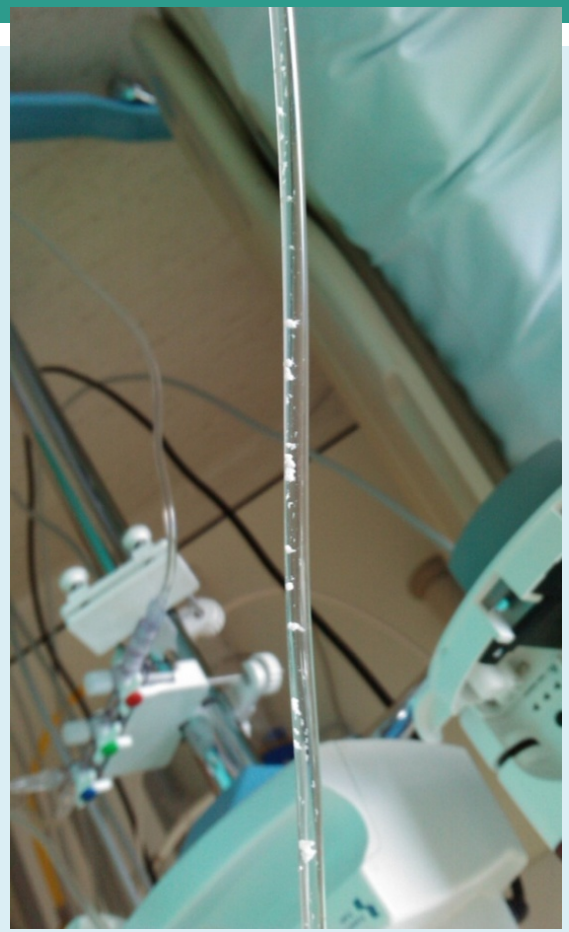
Flush d'héparine

Perfusion de base:

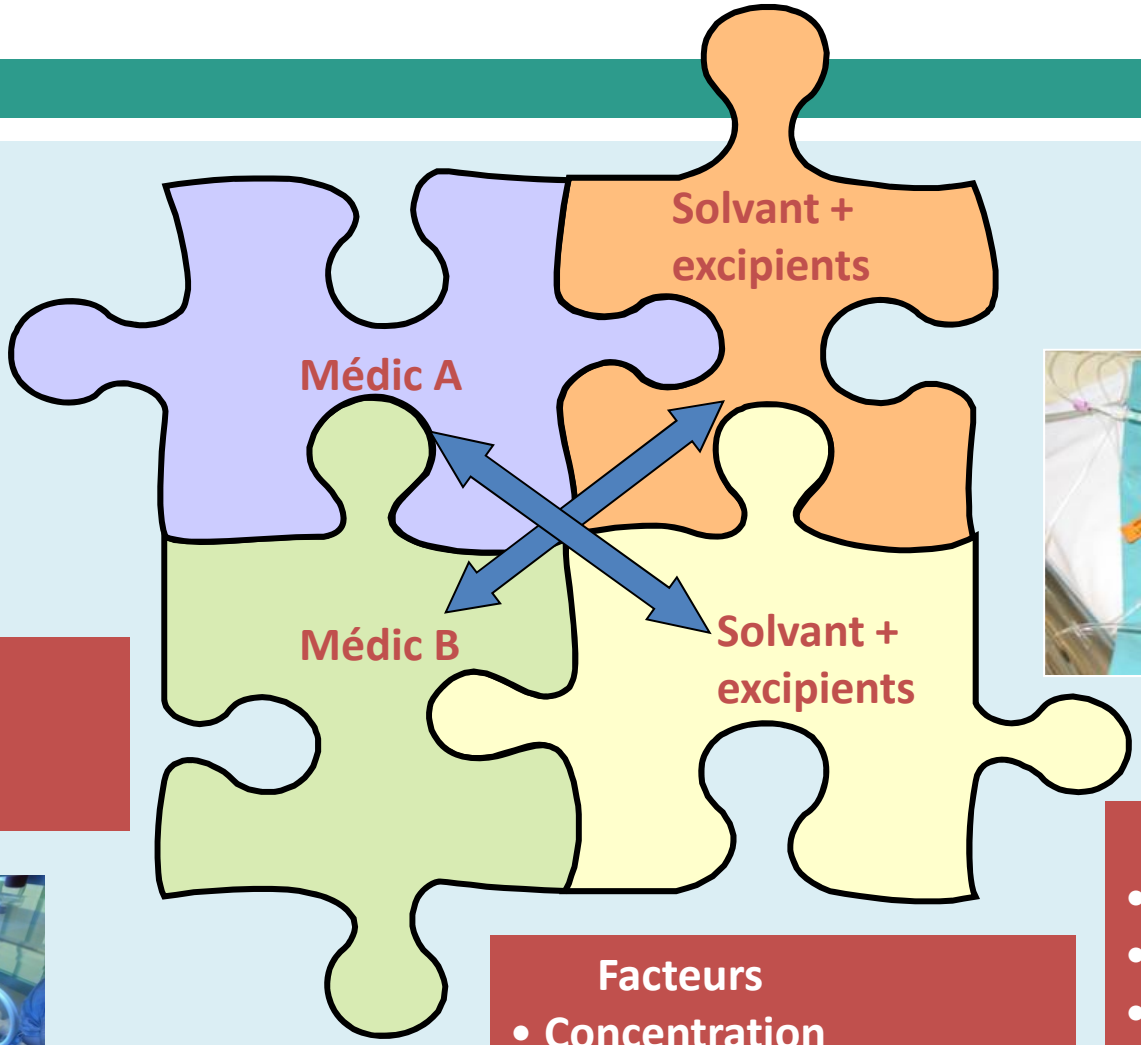
NaCl 0,9% + héparine 20 UI/mL !

héparine + caspofungine

➔ précipitation



Gestion des incompatibilités

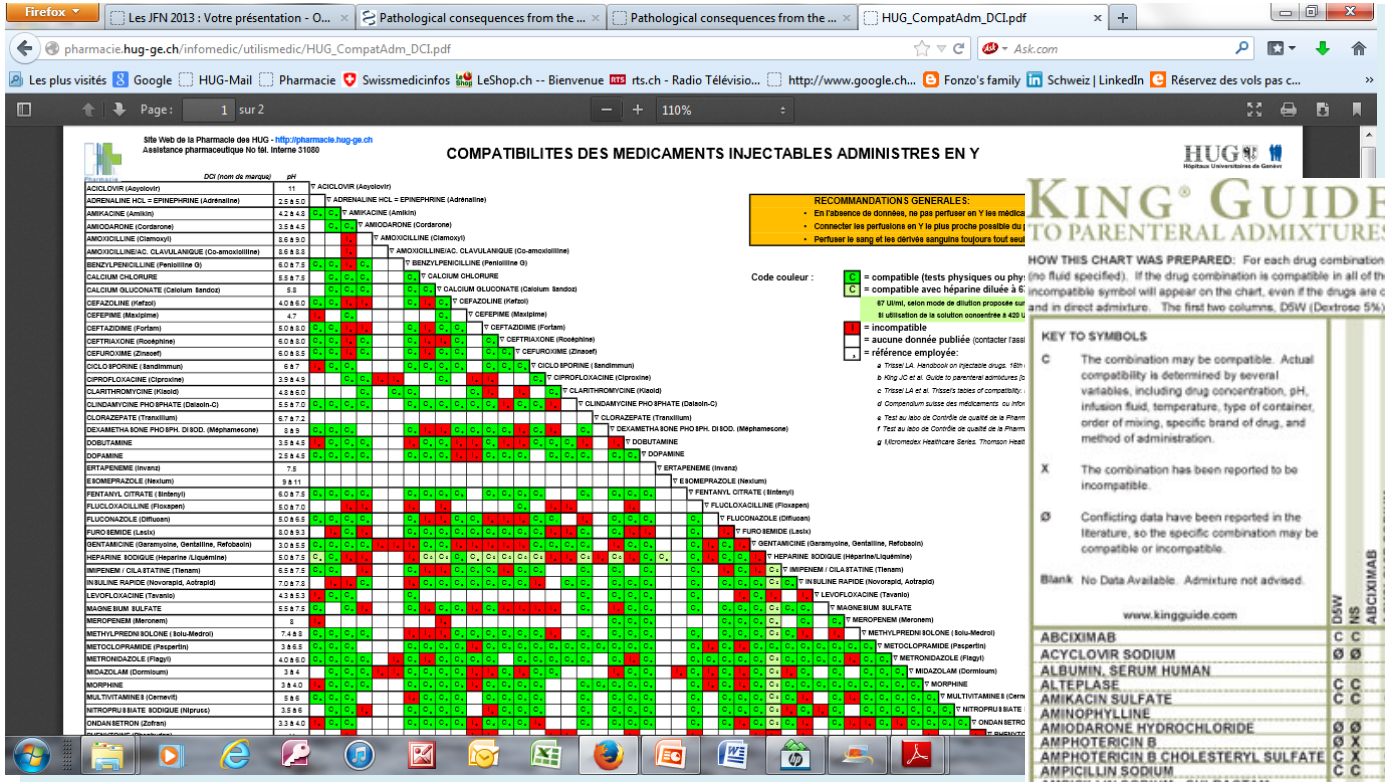


Environnement
- Température
- Lumière

Facteurs
- Concentration
- Temps de contact

Matériel
- PVC (DEHP)
- Silicone
- …

Cross-tables



http://pharmacie.hug-ge.ch/infomedic/utilismedic/HUG_CompatAdm_DCI.pdf

Test in vitro

Compatibility of Intravenous Medications With Parenteral Nutrition: In Vitro Evaluation

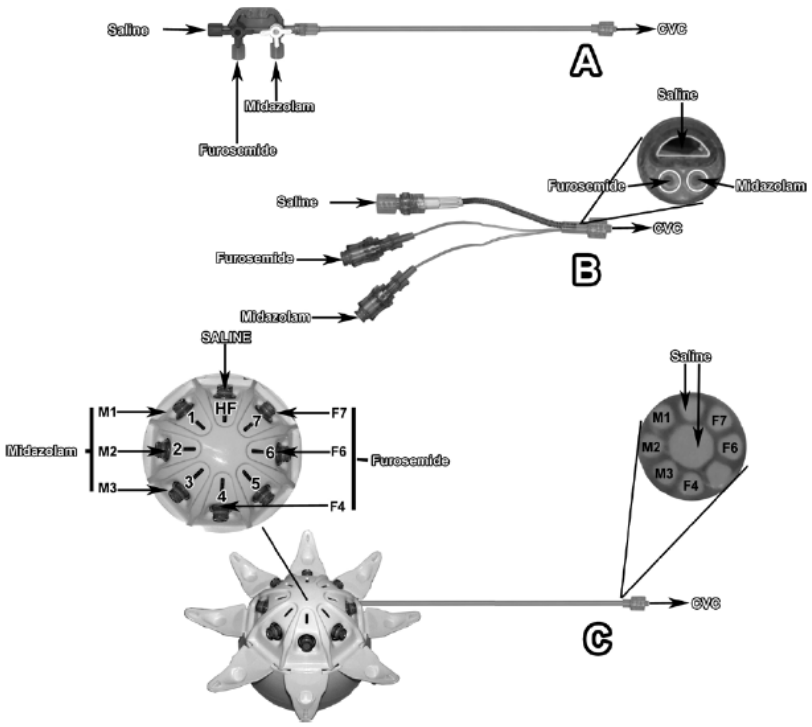
Table 8. Overall Physicochemical Compatibility Data of the 25 Tested Admixtures

Medication	Tested Concentrations	Contact 1:1 Compatibility With PN After 1 h	Contact 1:1 Compatibility With PN After 4 h
Albumin	**200 mg/mL**	**I**	**I**
Amoxicillin/Ac. clav.	50 mg/mL (amoxicillin) 10 mg/mL (Ac. clav.)	C	I
Calcium chloride	0.13 mmol/mL Ca	C	C
Cefepime	100 mg/mL	C	I
Cyclosporine	2.5 mg/mL	C	C
Esomeprazole	**0.8 mg/mL**	**I**	**I**
Fentanyl	0.05 mg/mL	C	C
Fluorouracil	**25 and 50 mg/mL**	**I**	**I**
Fluorouracil	≤12.5 mg/mL	C	C

Bouchoud L et al. JPEN J Parenter Enteral Nutr. 2013;37:416-24

Choix du matériel de perfusion

The Impact of Multilumen Infusion Devices on the Occurrence of Known Physical Drug Incompatibility: A Controlled In Vitro Study



Foinard A et al. Anesth Analg 2013;116:101-6

Constat

→ Réduire le nombre de particules!

Filtres en ligne

Evidence

Pas d'évidence sur morbidité ni mortalité

THE COCHRANE COLLABORATION®

Intravenous in-line filters for preventing morbidity and mortality in neonates

Main results

There were four eligible studies that recruited a total of 704 neonates. This review found no significant effect of in-line filters in any of the reported outcomes of overall mortality, proven and suspect septicaemia, local phlebitis and thrombus, necrotizing enterocolitis, duration of cannula patency, length of stay in hospital, number of catheters inserted and financial costs.

Authors' conclusions

There is insufficient evidence to recommend the use of intravenous in-line filters to prevent morbidity and mortality in neonates.

Foster JP et al. Cochrane Database of Systematic Reviews 2006 (review June 2011), Issue 2. Art. No.: CD005248. DOI: 10.1002/14651858.CD005248.pub2

Quid?

Intravenous in-line filters: filtering the evidence

Patrick A. Ball

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.

Introduction

It is generally held that the medical community was made aware of the issue of particulate contamination in the 1960s [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

Current Opinion in Clinical Nutrition and Metabolic Care 2003, 6:319–325

TPN: recommandation

1. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR)

Recommendations

- Sodium chloride 0.9% should be used to flush the CVC between all therapies and heparin should be instilled at least weekly when the CVC is not in use. **GOR D**
- Terminal in-line filters should be used for all PN fluids. **GOR D**
- Occlusion of in-line filters should be investigated. **GOR D**

Koletzko B et al. JPGN 2005;41:S1-S4

Thrombophlébites

Acta Pædiatr 93: 658–662. 2004

Taylor&Francis healthsciences

The use of in-line intravenous filters in sick newborn infants

RA van Lingen[1], W Baerts[1], ACM Marquering[1] and GJHM Ruijs[2]

Department of Paediatrics Princess Amalia[1], Division of Neonatology Diseases, Isala Clinics, Zwolle, The Netherlands

Thrombophlébites
Réduction coûts

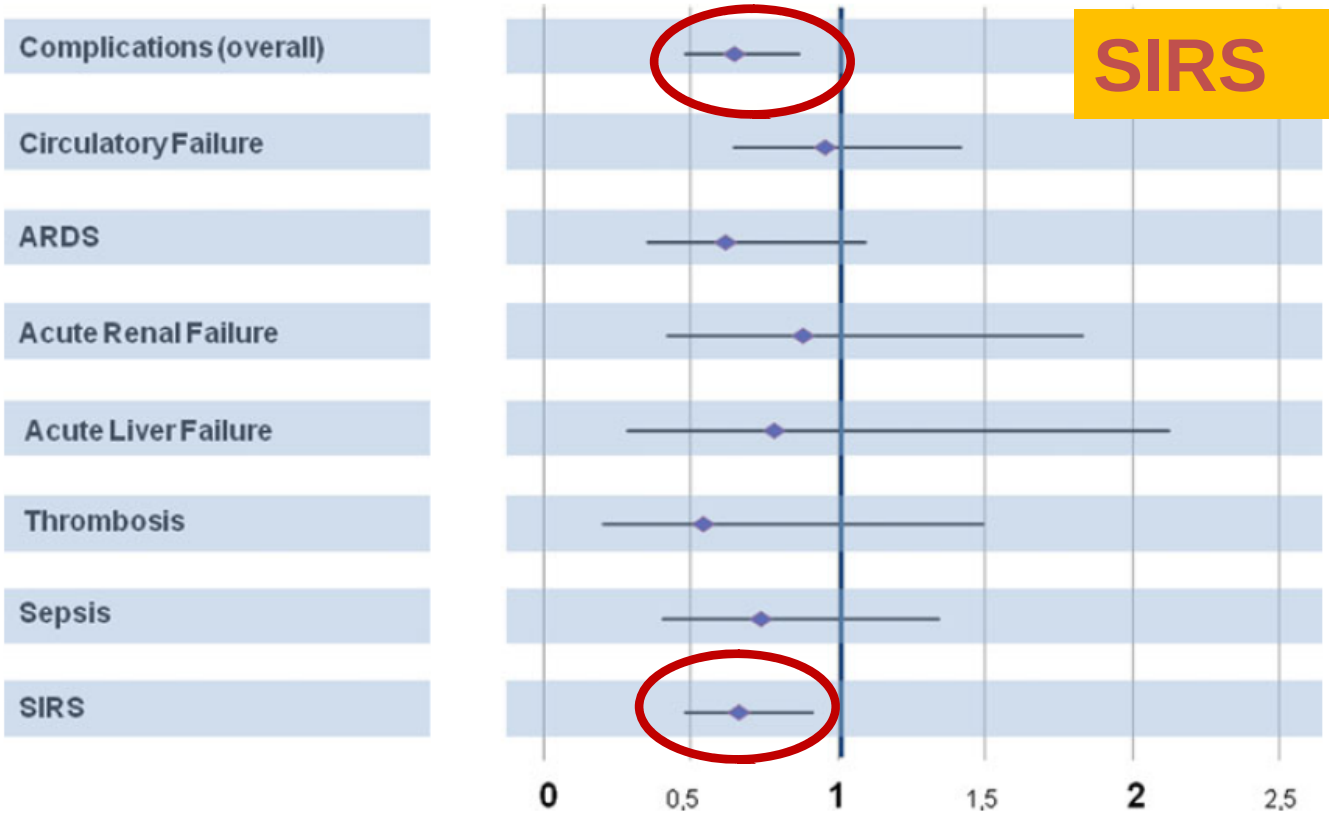
Van Lingen RA, Baerts W, Marquering ACM, Ruijs GJHM. The use of in-line intravenous filters in sick newborn infants. Acta Pædiatr 2004; 93: 658–662. Stockholm. ISSN 0803-5253

Aim: This study assesses the improvement in outcome for newborn infants by decreasing major complications associated with intravenous fluid therapy by using an in-line filter, and evaluates the economical impact this might have in relation to daily changing of i.v. lines. *Methods:* In a prospective controlled study, 88 infants were randomly assigned to receive either filtered (except for lipids, blood and blood products) or non-filtered infusions via a central catheter. Main outcome measures such as bacteraemia, phlebitis, extravasation, thrombosis, septicaemia and necrosis were all scored. The costs attributable to patients during a standard 8-day stay were also recorded. *Results:* Significant reductions were found in major complications such as thrombi and clinical sepsis (control group (21), filter group (8); $p < 0.05$). Bacterial cultures of the filters showed a contamination rate on the upstream surface of 15/109 filters (14%). The mean costs of disposables were less in the filter group, showing a reduction from €31.17 to €23.79.

Conclusions. The use of this in-line filter leads to a significant decrease in major complications and substantial cost savings.

SIRS

Fig. 2 Hazard ratios of primary objectives for the treatment effect of in-line filtration. The incidence of overall complications and systemic inflammatory response syndrome (*SIRS*) were significantly reduced in the filter group. A trend towards a reduction in acute respiratory distress syndrome (*ARDS*) was evident for the filter group ($P = 0.08$). No significant differences were found for the incidence of sepsis, circulatory failure, acute renal failure, acute liver failure and thrombosis. *Filled rhombi* Hazard ratios, *horizontal lines* 95 % confidence intervals



Jack T et al. Intensive Care Med 2012;38:1008–1016

Complications

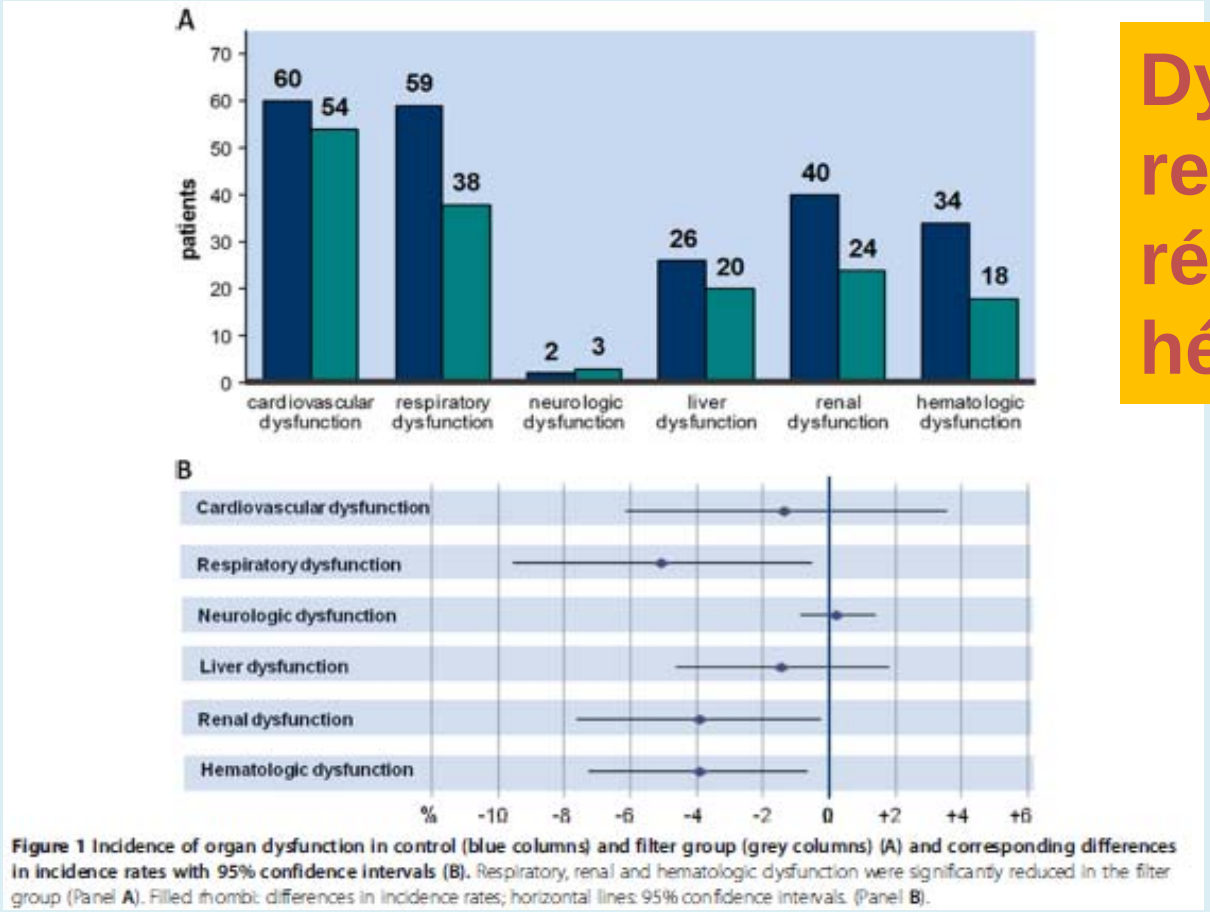


Figure 1 Incidence of organ dysfunction in control (blue columns) and filter group (grey columns) (A) and corresponding differences in incidence rates with 95% confidence intervals (B). Respiratory, renal and hematologic dysfunction were significantly reduced in the filter group (Panel **A**). Filled rhombi: differences in incidence rates; horizontal lines: 95% confidence intervals. (Panel **B**).

Dysfonction respiratoire, rénale et hématologique

Boehne et al. BMC Pediatrics 2013;13:21

Coûts

Coûts

Table 2 Morbidity outcomes

Characteristics	Control group ($n = 406$)	Filter group ($n = 401$)	P value[a]	95 % Confidence interval
Primary objectives (n)				
Complications (overall)	166	124	0.003	0.484–0.865
Adjusted to PIM II			0.011	0.502–0.914
SIRS	123	90	0.011	0.485–0.913
Adjusted to PIM II			0.026	0.500–0.958
Sepsis	27	20	0.313	0.406–1.337
Circulatory failure	60	57	0.593	0.604–1.334
ARDS	35	22	0.082	0.354–1.069
Acute renal failure	16	14	0.736	0.425–1.831
Acute liver failure	9	7	0.631	0.289–2.125
Thrombosis	11	6	0.230	0.200–1.489
Secondary objectives				
Mortality (n)	27	16	0.093	0.309–1.100
Length of stay (days)[b]	3.89 (2.96–4.81)	2.98 (2.33–3.63)	0.025	
Duration of mechanical ventilation (h)[b]	14.0 (5.6–22.4)	11.0 (7.1–14.9)	0.028	

Comparison of primary and secondary outcomes between control and filter group

ARDS Acute respiratory distress syndrome, *SIRS* systemic inflammatory response syndrome

[a] P values were calculated using Pearson's Chi-Square test, Fisher's exact test or log-rank test as indicated

[b] Data are presented as the median with the range given in parenthesis

Jack T. et al Intensive Care Med 2012;38:1008–1016

Filtres en ligne

TABLEAU RECAPITULATIF				
Photo Filtre				
Type filtre	**NEO96**	**ELD96**	**NLF2**	**TNA1E**
Membrane	**0,2 µm**	**0,2 µm**	**1,2 µm**	**1,2 µm**
Volume	**0,4 ml**	**2ml**	**0,8 ml**	**2,3 ml**
Débits	**inférieur ou égal à 75ml/h**	**supérieur à 75ml/h**	**débit maximum 75 ml/h**	**débit supérieur à 75 ml/h**
Solution	**solutions aqueuses**	**solutions aqueuses**	**émulsions lipidiques et autres** - Lipides : Lipofundin MCT/LCT®, Omegaven - Nutrition parentérale (APT StructoKabiven®, Nutriflex Lipid spécial®, PeriOlimel® - Propofol®, Disoprivan® - Etomidate Lipuro® - Vitalipid® - Cernevit®	
Changement du filtre	**96 heures**	**96 heures**	**24 heures**	**24 heures**
Médicaments non filtrables	○ **sang et dérivés sanguins** (PFC,CE, thrombaphérèse) ○ **facteurs de coagulation :** *Novoseven®, Haemate P®, Kogenate SF®, Prothromplex NF®, Immunine STIM plus®, Fibrogammin P®, Advate®, Hélixate®* ○ **Albumine 20%** ○ **Konakion MM® (phytoménadion, vitamine K)** ○ **Ambisome® (amphotéricine B liposomale)** ○ **Gardénal® (phénobarbital)** ○ **Privigen®, Kiovig®**			

http://pharmacie.hug-ge.ch/infomedic/utilismedic/filtres_USI.pdf

Conclusion

➔ Particules: effets délétères!

➔ Réduction de la charge particulaire à tous les niveaux pour les patients les plus à risques

- Utilisation adéquate du matériel
- Préparation et filtration
- Réduction du risque d'incompatibilités
- Filtres en ligne