Patient Safety & Infusion Management
Rethinking the Role of Filtration
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Hannover Medical School

Disclosures
Honorarium
• Pall Corporation

Why Filtration?
...the Beginning
The Cholera Epidemic of 1831-1832
• Major cause of death: dehydration
• Dr. Thomas Latta pioneered the use of intravenous saline solution in the treatment of cholera: 1832
The Cholera Epidemic of 1831-1832

- First use of intravenous albumin 1834: Dr. John Mackintosh
- Mackintosh warned of the complications of injecting any solid particles into the circulation
- Recommended the solution be "carefully strained twice through leather" rather than linen or other materials which could allow "minute portions of flaky threads" to be injected


Intravenous Fluids and Medications

- Garvan (1964) was among the first to identify harmful effects of particles in intravenous solutions in humans
- IV solutions marketed at the time had as many as 500 to 2000 particles larger than 5 µm per liter of fluid
- Particles exceeding 7-12 µm may result in pulmonary arteritis, microemboli, thrombosis, foreign body granulomas, and pulmonary hypertension
- Particles found included glass, rubber, starch, crystals, spores, insects, and cellulose fibers, to name a few


Intravenous Fluids and Medications

- 1966: FDA holds national symposium on the safety of large volume parenterals (LVP)
- 1974: After finding microbial contamination of LVPs, USP publishes standards for (LVP) in collaboration with AMA, ASHP, and PMA
Regulations
FDA Safety Alert
- April 1994: Resulted from the death of 2 patients who received peripheral infusions of all-in-one
- Autopsies revealed diffuse microvascular pulmonary emboli containing calcium phosphate

Recommendations included
- Use a filter when infusing either central or peripheral parenteral nutrition
  - 1.2 micron air eliminating filter for lipid admixtures
  - 0.22 micron air eliminating for non-lipid admixtures

Why Filtration?
...Background

ASPPEN: 1997
Safe practices for Parenteral Nutrition Formulations
- A 0.2 micron filter should be used for 2-in-1 formulas
- A 1.2 to 5 micron filter should be used for TNAs
- A filter that clogs during administration of PN is indicative of a problem and may be replaced but should never be removed

ASPPEN: 2004
Task Force for Revision of Safe Practices for Parenteral Nutrition Formulations
- Recommendation unchanged

Why Filtration?
...Standards / Guidelines

Infusion Nursing Standards of Practice: 2011
- The use of bacteria-and particulate-retentive, air eliminating, and blood and blood component filters shall be established in organizational policies, procedures, and guidelines
Infusion Nursing Standards of Practice: 2011

- For lipid infusions or TNAs that require filtration, a 1.2 µm filter containing a membrane that is particulate retentive and air-eliminating shall be used.

- For non-lipid-containing solutions that require filtration, a 0.2 µm filter containing a membrane that is particulate retentive and air-eliminating shall be used.

What requires filtration?

MMWR. August 9, 2002. 51(RR10);1-26.

- 2002: Do not use filters routinely for infection control purposes (category IA)
- 2011: Guidelines do not address IV filtration
So why are we still talking about this?

What is there to rethink?

...Rethinking the Role of Filtration!

The Changing Healthcare Landscape

...Patient Safety

The Changing Healthcare Landscape

...2005 Deficit Reduction Act

October 1, 2008 hospitals no longer received additional payment for cases in which one of 10 selected conditions was not present on admission

- Foreign objects retained after surgery
- Air embolism
- Blood incompatibility
- Stage III and IV pressure ulcers
- Falls and trauma
- CAUTI
- Vascular catheter associated infection
- Manifestations of poor glycemic control
- SSI
- DVT

“Never” events list
The Changing Healthcare Landscape

2010 Affordable Care Act

The changing healthcare landscape

Regulatory requirements

- Reportable quality metrics
- Patient outcome measures
- Patient satisfaction reporting
- Use of evidence-based medicine
- Standards/guidelines/policies/procedures

Reimbursement penalties/rewards

- Healthcare acquired conditions reduction program: Non-payment/penalty
- Value-based purchasing: Reward/penalty
- Hospital readmissions: Penalty

Penalty

How are we doing?

Hospital Acquired Condition Reduction Program...

HAC Reduction Program Framework Finalized for FY 2015

Total HAC Score

- Domain 1 (Weighted 25%)
- Domain 2 (Weighted 50%)

Measures

- PSI-90 Core Measure
- CLABSI and CAUTI Measures

Setting the Standard for Infusion Care®

Figure 4.1: Change in state-specific hospital rates for CLABSI in adults, 2010-2011
Patient safety issues addressed by IV filtration
- Infusion related air embolism
- Catheter-related bloodstream infection
- Endotoxin retention
- Infusion of particulate matter
- Infusion related phlebitis
- Respiratory compromise

Infusion Related Air Embolism
…How Does It Happen?

Passive air entry: Inspiration
- Insertion: Open needle, sheath, catheter
- Inadvertent tubing disconnection
- Hole or severed catheter or hub
- Catheter removal / patient position

Forced air entry: Infusion-related
- Unprimed administration tubing (25-30ml)
- IV bag run drys
- IV bag exchange / open roller clamp
- Small bubbles below pump sensor detection

Infusion Related Air Embolism
…How Much Air is Safe?

- 1 ml infused over 15 min is close to 1.4 ml dose for potentially fatal in coronary artery in adult
- Bubbles ~ 15µl can pass thru the lungs but can cause cerebral ischemia
- Bubbles as small as 0.004µl may create cerebral ischemia (these are significantly smaller than 50µl IEC standard)
- 10-35% population with potential patent foramen ovale

There is no demonstrable maximum safe dose of air infusion
Estimated incidence per catheterization events

- High estimate: 1:4
- Low estimate: 1:3000

**Mortality: ≥ 32%**

Infusion-related air embolism

- 100% non-reimbursement
- 100% preventable with an air-eliminating filter

CDC Guidelines 2002

Do not use filters routinely for infection control purposes - category IA

The evidence


**Effect of inline filtration on post-infusion phlebitis**


**Purpose**

- Evaluate the effect of an in-line 0.22 µm filter on
  - The incidence, severity, duration, and clinical characteristics of post infusion phlebitis
  - The bacterial colonization of indwelling iv catheters

**Study Design**

- Experimental, randomized, controlled
- **Control group:** Filter / no membrane
- **Test group:** Cellulose membrane filter (changed q 24h)
Methods (no IV team)

- **Subjects**: 195 males (general surgical patients)
- **Catheters**: Polyethylene
- **Skin prep**: Shave and cleanse 1% povidone iodine
- **Outcome measures**:
  - **Phlebitis**: Phlebitis scale (0 – 5+)
  - **Colonization**: Catheter cultures (SQ)

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### Results

<table>
<thead>
<tr>
<th>Time of onset</th>
<th>Control</th>
<th>Filter</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 hours</td>
<td>1 (100)</td>
<td>2 (95)</td>
</tr>
<tr>
<td>24 hours</td>
<td>8 (89)</td>
<td>7 (84)</td>
</tr>
<tr>
<td>36 hours</td>
<td>11 (68)</td>
<td>14 (63)</td>
</tr>
<tr>
<td>48 hours</td>
<td>13 (47)</td>
<td>7 (40)</td>
</tr>
<tr>
<td>60 hours</td>
<td>2 (27)</td>
<td>5 (31)</td>
</tr>
<tr>
<td>72 hours</td>
<td>3 (19)</td>
<td>2 (23)</td>
</tr>
<tr>
<td>84 hours</td>
<td>1 (5)</td>
<td>0 (9)</td>
</tr>
<tr>
<td>96 hours</td>
<td>0 (5)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

*Patients remaining in study at that time

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<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Filter</th>
</tr>
</thead>
<tbody>
<tr>
<td>16g Catheter</td>
<td>68</td>
<td>79</td>
</tr>
<tr>
<td>D5W / 0.45% NS</td>
<td>54</td>
<td>53</td>
</tr>
<tr>
<td>IV in forearm</td>
<td>40</td>
<td>53</td>
</tr>
<tr>
<td>Phlebogenic drugsa</td>
<td>61</td>
<td>53</td>
</tr>
<tr>
<td>Phlebitis of 3+ intensityb</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Positive catheter culture</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Rate of phlebitis</td>
<td>33%</td>
<td>40%</td>
</tr>
</tbody>
</table>

*aCephalosporin, penicillin, phenytoin, lidocaine

*bPainful site, erythema, swelling, induration, cord, no purulence

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Conclusion

- Inline filters did not affect the incidence of post infusion phlebitis (PIP) or bacterial colonization of IV catheters.
- While the use of inline filters to prevent infusion of microorganisms deserves consideration, their routine use as a mechanism for reducing PIP is warranted.


Purpose

- Determine the frequency of the occurrence of infusion-phlebitis;
- Its underlying cause(s) in the absence of infection;
- The most appropriate means of treatment / prevention

Study design

- Experimental, double blinded
  - Control group: Filter / no membrane (264)
  - Test group: Cellulose membrane filter (277) (changed q 24h)

Methods (no IV team)

- Subjects: 541 (males-296 females-255)
- Catheters: pvi: teflon midline: pvc intracaths
- Frequency of change: 72 h
- Outcome measures:
  - Phlebitis: Two or more symptoms
    - Pain, erythema, swelling, induration, palpable cord
### Results

<table>
<thead>
<tr>
<th>Time of onset</th>
<th>No. patients with phlebitis</th>
<th>Control</th>
<th>Filter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>% Phlebitis</td>
<td>% Phlebitis (Cumulative)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>14.3</td>
<td>6.9</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>31.4 (41.3)</td>
<td>9.7 (16)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>27 (57.2)</td>
<td>11.3 (25.5)</td>
<td></td>
</tr>
</tbody>
</table>

**Chance of being free of phlebitis at 72 h**

| 42% | 75% | p < 0.001 |


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### Conclusion

- Infusion-related phlebitis is a pervasive problem in hospitalized patients; it is usually caused by microparticulate components that are present in the infusion fluids and can be removed by in-line filtration.


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### Microorganism Retention

**...Prevent Catheter-Related Bloodstream Infection?**

Pathogenesis... microbial access to the catheter and bloodstream.

- The skin
- The hub
- Which one is the greater risk?
Purpose
• To determine whether an institution should focus resources on a specific phase of CVC life to prevent CRBSI (insertion vs maintenance)

Methods
• Analysis of the PA NHSN database for 2011-2012 to determine the date of primary BSI event from time of insertion

Sample size
• 1,890 events

Conclusion: This data implicates maintenance as the phase in which CLABSI most likely is developed


Table 5.—Risk Factors Predictive of Local Catheter-Related Infection as Determined by Stepwise Multivariate Logistic Regression

<table>
<thead>
<tr>
<th>Prognostic Risk Factor</th>
<th>Frequency to Infection (%)</th>
<th>Logistic Regression Coefficient</th>
<th>Relative Risk</th>
<th>95% Confidence Interval</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheter site</td>
<td>74 (46)</td>
<td>1.35</td>
<td>2.46-6.05</td>
<td>&lt;.00</td>
<td></td>
</tr>
<tr>
<td>Monitored catheter</td>
<td>46 (46)</td>
<td>1.33</td>
<td>2.45-5.82</td>
<td>&lt;.00</td>
<td></td>
</tr>
<tr>
<td>Duration of catheter</td>
<td>63 (66)</td>
<td>1.64</td>
<td>1.03-3.79</td>
<td>.00</td>
<td></td>
</tr>
<tr>
<td>Duration of catheter</td>
<td>12 (57)</td>
<td>1.22</td>
<td>0.22-4.84</td>
<td>.61</td>
<td></td>
</tr>
<tr>
<td>Systemic antibiotics</td>
<td>61 (61)</td>
<td>1.22</td>
<td>0.22-4.74</td>
<td>.68</td>
<td></td>
</tr>
</tbody>
</table>

Maki DG, Ringer M. JAMA. 1987;258:2396-2403
### Intraluminal bacterial transfer...how does it happen?

1965-1978

- >93% of intravascular device-related bacteremic epidemics were traced to contaminated infusates
- 25% from contamination during manufacture (intrinsic)
- 75% from organisms introduced during preparation and administration (extrinsic)

### Are intravenous admixtures still a threat for contamination?

**Pathogenesis**

**...Preventing Catheter-Related Bloodstream Infection**

**Microorganism Retention**

**...Preventing Catheter-Related Bloodstream Infection**
Intraluminal bacterial transfer...how does it happen?

Access site contamination

Pathogenesis
...Preventing Catheter-Related Bloodstream Infection

Bacterial transfer...intraluminal biofilm

0.22 micron filters retain all bacteria, fungi and protozoa

Pathogenesis
...Preventing Catheter-Related Bloodstream Infection

Bacterial Retentive Filter
...Patient Safety Strategy
British Pharmaceutical Nutrition Group Position Paper and Guidelines: Use of filters during preparation and administration of parenteral nutrition

- When used, on-line filters should be placed as close to the patient as possible

Infusion Nursing Standards of Practice: 2011

- Add-on bacteria- and particulate-retainive and air eliminating filters should be located as close to the catheter insertion site as possible

Lipopolysaccharide (LPS) molecules found as part of the cell wall of gram negative bacteria released primarily upon cell lysis of bacteria in the bloodstream or within biofilms

Effects of endotoxin
- Fever
- Hypotension
- Shock
- Acidosis
- DIC
- Respiratory failure
- Multiple organ failure
- Sepsis/septic shock
- Death

**What is Endotoxin?**

Sievert DM, et al. ICHE. 2013;34:1-14

**What is the Risk of Gram Negative CRBSI?**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>No. (%) of pathogens</th>
<th>Acute (1-48 h)</th>
<th>Subacute (48-7 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter</td>
<td>1,294 (1.1)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Enterobacter aerogenes</td>
<td>1,294 (1.1)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>2,979 (27.5)</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>2,979 (27.5)</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>2,979 (27.5)</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>2,979 (27.5)</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>2,979 (27.5)</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>2,979 (27.5)</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>2,979 (27.5)</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>2,979 (27.5)</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>
**Endotoxin Retentive Filter**

*Patient Safety Strategy*

**Infusion Nursing Standards of Practice: 2011**

- Add-on bacteria- and particulate-retentive and air eliminating filters should be located as close to the catheter insertion site as possible

**Particulate Matter**

*What Is It?*

"Mobile, undisolved substances unintentionally present in parenterals"

- Drug incompatibility reactions
- Incomplete reconstitution of drugs
- Lipid macro micelles
- Components of the infusion systems
- Entrapped air emboli

**Particulate Matter**

*Current Regulations*

<table>
<thead>
<tr>
<th>General Chapter</th>
<th>≥10 μm</th>
<th>≥25 μm</th>
<th>≥50 μm</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥78B- Test 2.A. Large-Volume injections (more than 100 mL)</td>
<td>12 per mL</td>
<td>2 per mL</td>
<td>Not applicable</td>
</tr>
<tr>
<td>≥78B- Test 2.B. Small-Volume injections (less than and equal to 100 mL)</td>
<td>3000 per container</td>
<td>300 per container</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

Over the years, manufacturers have made great efforts to produce high quality products, but these efforts may be negated by manipulating the products before their infusion.
Particulate Matter

...Is It Still a Problem?

The number of small particles of 2–10 µm in diameter was 30 times higher in antibiotics B and C, as compared with antibiotic A.

Comparison of Claforan admixture with two generic cefotaxime products

- The number of small particles of 2–10 µm in diameter was 30 times higher in antibiotics B and C, as compared with antibiotic A.

Routine resite of peripheral intravenous devices every 3 days did not reduce complications compared with clinically indicated resite: a randomised controlled trial

**Purpose**

- Compare the impact of 3-day routine resite with clinically indicated resite on peripheral IVD in a general hospital without an IV team.

**Study design**

- Multicenter, randomized, nonblinded equivalence trial
Particulate Matter

...Catheter Failure

Table 3: Effect of Intervention on primary and secondary outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>3-Day Intensive Change Group (n = 32)</th>
<th>Clinically Indicated Change Group (n = 30)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary complications per patient</td>
<td>64 (14)</td>
<td>36 (14)</td>
<td>0.06</td>
</tr>
<tr>
<td>Secondary complications per patient</td>
<td>99 (46)</td>
<td>106 (55)</td>
<td>0.28</td>
</tr>
<tr>
<td>DVT complications per 1000 catheter day</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.99</td>
</tr>
<tr>
<td>Infection rate per 1000 catheter day</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Catheter-related infection</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Microbiologically infected catheter</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Mean dwell time (SD)                    70 h (14)       89 (24)       P = 0.014
Median dwell time (IQR)                 70 h (57-77)    84 (54-115)  P = 0.003

Particulate Matter

...Phlebitis

Phlebitis
An inflammatory “process”

Particulate Matter

...What is the Harm?

- Endothelium
- Tunica media
- Valves
- Mechanical injury
- Chemical / particulate injury
- Microorganisms

Particulate Matter

...Infusion Phlebitis – How?
Endothelial injury
Expose subendothelium

Infusion Failure
.....Pathogenesis

Expose tissue factor (Transmembrane protein)
Stabilizes platelet plus
Thrombin generation
Platelet activation
Thrombin burst
Conversion of fibrinogen to fibrin

Bind to P-selectin Ligand and Activate Platelets

Vascular Space
Circulating TF-Bearing Microvesicles
Monocyte / Macrophage Membrane TF

TF-bearing microvesicles
Activated Plueter
PSGL-1
Monocyte
Lympocyte
PSGL: P-Selectin Glycoprotein Ligand
Venous Stasis Results in Local Desaturation of Hemoglobin

Venous Blood Supply
Endothelium Primarily Oxygenated by Blood in Vessel Lumen

Venous Valves
- Stasis in valves creates hypoxia

Hypoxia Results in Endothelial Injury
Ischemia Rapidly Activates Endothelium to Express P-Selectin

• Stasis in valves creates hypoxia
Purpose
• Assess the relative importance of independent risk factors for peripheral intravenous catheter (PIVC) failure.

Study design
• Secondary analysis from a randomized controlled trial of PIVC dwell time.

<table>
<thead>
<tr>
<th>TABLE 1. Independent Risk Factors for Phlebitis</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>1.64</td>
<td>1.28-2.09</td>
<td>.001</td>
</tr>
<tr>
<td>Size 18 gauge or larger compared with size 20 gauge</td>
<td>1.48</td>
<td>1.08-1.93</td>
<td>.014</td>
</tr>
<tr>
<td>Current infection</td>
<td>1.41</td>
<td>1.05-1.89</td>
<td>.022</td>
</tr>
<tr>
<td>Age</td>
<td>0.99</td>
<td>0.98-1.00</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other drugs infused through IV</td>
<td>0.72</td>
<td>0.56-0.92</td>
<td>.009</td>
</tr>
</tbody>
</table>
**Occlusion**

**Risk Factors**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand compared with forearm</td>
<td>1.47</td>
<td>1.28–1.68</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.44</td>
<td>1.30–1.61</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Antibiotics infused through IV</td>
<td>1.41</td>
<td>1.25–1.59</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hydrocortisone infused through IV</td>
<td>1.36</td>
<td>1.05–1.80</td>
<td>0.02</td>
</tr>
<tr>
<td>Current infection</td>
<td>1.27</td>
<td>1.15–1.44</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Intravenous lines compared with forearm</td>
<td>1.27</td>
<td>1.08–1.49</td>
<td>0.00</td>
</tr>
<tr>
<td>Upper arm compared with forearm</td>
<td>1.15</td>
<td>1.04–1.30</td>
<td>0.01</td>
</tr>
<tr>
<td>Second through fifth cannula compared with first cannula</td>
<td>1.17</td>
<td>1.01–1.35</td>
<td>0.03</td>
</tr>
<tr>
<td>Inserted in OR/ICU compared with ward</td>
<td>0.80</td>
<td>0.67–0.94</td>
<td>0.00</td>
</tr>
<tr>
<td>Antibiotics infused through IV</td>
<td>0.76</td>
<td>0.59–0.97</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**Particulate Matter**

**Local Injury**

**Chemical phlebitis:**
- Due to injury of the veins by chemical agents dissolve completely in infusion fluid remain partly dissolved as particles 1 – 25 μm in size (abx)
- pH
- Osmolarity

**Particulate Matter**

**Antibiotics**

**Prevalence of Antimicrobial Use in US Acute Care Hospitals, May-September 2011**

**Purpose**
- Determine the prevalence of and describe the rationale for antimicrobial use in participating hospitals

**Study design**
- One day point prevalence survey in acute care hospitals in 10 states between May and September 2011
Results

- 90 unique antimicrobial drugs
- Patients receiving antimicrobial drugs: 5635
- Patients receiving one drug: 2811 (49.9%)
- Patients receiving two drugs: 1840 (32.7%)
- Patients receiving three drugs: 682 (12.1%)
- Patients receiving four or more drugs: 302 (5.4%)


Particulate Matter

Local injury

- Infectious phlebitis caused by infectious agents present in the infusion fluid, in the skin around the puncture site or catheter tip, or in a thrombus in the vein
Particulate Matter

...What is the Harm?

Septic thrombophlebitis

Setting the Standard for Infusion Care®

Particulate Matter

...What is the Harm?

Clinical epidemiology and outcomes of peripheral venous catheter-related bloodstream infections at a university-affiliated hospital

A. Pujo*a, A. Harms, W. Safdar, M.J. Murphy, K. M. Atituaron, A. Asiné, F. Balfe

Peripheral Vena Cava-Related Staphylococcus aureus Bacteremia

Time to CRBSI

3.9 days

4 days

3.5 days

Peripheral intravenous catheter-associated Staphylococcus aureus bacteremia: more than 5 years of prospective data from two tertiary health services

Purpose

• To determine the primary bloodstream infection rate in the Pennsylvania NHSN database for the years of 2011 and 2012

Methods

• Analysis of the PA NHSN database for 2011-2012 to determine the date of primary BSI event from time of admission

Sample size

• 1,890 events

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Purpose

- Assess the effect of in-line filters on infusion-related phlebitis with peripheral IV catheters

Study design

- Systematic review and meta-analysis

Table: Top 10 Pathogens Causing Primary BSIs in Pennsylvania, 2011 to 2012

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>No. of Infections</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>169</td>
<td>19.9</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>120</td>
<td>14.5</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>120</td>
<td>14.5</td>
</tr>
<tr>
<td>Coagulase-positive staphylococci</td>
<td>97</td>
<td>11.4</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>52</td>
<td>6.3</td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>52</td>
<td>6.3</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>52</td>
<td>6.3</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>52</td>
<td>6.3</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>46</td>
<td>5.5</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>45</td>
<td>5.3</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>45</td>
<td>5.3</td>
</tr>
</tbody>
</table>


![Graph](image)
Results
• Meta-analysis of all trials showed that in-line filters reduced the risk of infusion-related phlebitis
• This benefit, however, is very uncertain, because the trials had serious methodological shortcomings and unexplained statistical heterogeneity

Conclusion
• In-line filters in peripheral IV catheters cannot be recommended routinely, because evidence of their benefit is uncertain

Purpose
• Identify the measures used in infusion phlebitis assessment and evaluate evidence regarding their reliability, validity, responsiveness and feasibility

Conclusion
• Many scales exist, but none has been thoroughly validated for use in clinical practice
• A lack of consensus on phlebitis measures has likely contributed to disparities in reported phlebitis incidence, precluding meaningful comparison of phlebitis rates

Systemic injury
• Impairment of the microcirculation
Rethinking IV Filtration

...Patient Safety

The use of filters that are air eliminating, and bacteria, endotoxin, and particulate retentive

- Reduce the risk of infusion-related air embolism
- Reduce the risk of systemic effects of endotoxin
- Reduce the risk of bacterial transfer
- May reduce the risk of catheter failure
- Reduce the risk of microcirculatory compromise

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In-line Filtration Reduces Complications and Increases Patient Safety in the ICU

Do we still filter the evidence or is it time to change infusion standards?

Thomas Jack, MD
Department of Pediatric Cardiology and Intensive Care Medicine
Hannover Medical School

Setting the Standard for Infusion Care®

Disclosures

- Pall Corporation*: Dreieich, Germany
- BBraun Corporation*: Melsungen; Germany

*Presented data. Internal use only. Information from NCT00209768 was funded by a research grant from Hannover Medical School and partially by an unrestricted free grant by the two abovementioned companies.

Setting the Standard for Infusion Care®
Background: Particles and Intravenous Therapy

- Since the 1960s, particulate contamination during intravenous therapy and the potential risk for our patients have been reported.¹
- In an intensive care setting, it has been estimated that up to one million particles per patient per day may be infused².

Experimental and clinical studies have proven the following effects³,⁴,⁵:
- Embolization
- Thrombogenic effects
- Immunomodulation
- Impairment of microcirculation


Data About the Influence of Intravenous Particles

- Deleterious effects of particles on microperfusion in different organ systems after ischemia and reperfusion
- Reduction of thrombophlebitis after elimination of particles with infusion filters
- Increase of typical neonatal complications like inflammation, sepsis and enterocolitis
- Immunomodulation by infused particles leading to in vitro changes of secretion of IL 1-beta, IL6, IL8, TNFalpha.


Study Design: Prospective, Randomized Clinical Trial for the Use of In-line Filtration in Critically Ill Children

- Prior to the study: optimization of infusion regimen to prevent precipitation and incompatibilities of drugs and solutions
- Randomization of pediatric intensive care patients to either control or interventional group
- Interventional group receiving in-line infusion filters throughout complete infusion therapy (all solutions and medications)
- Primary endpoints: reduction in incidence of severe defined complications (sepsis, SIRS, organ failure, thrombosis)
- Secondary endpoints: Reduction of LOS and Mortality

Prospective, Randomized Clinical Trial for the Use of In-line Filtration in Critically Ill Children

- Gaussian distribution of patients to both groups (406 non-filter vs. 401 filter)
- No differences in PIM II score, median age, weight or gender distribution
- Heterogeneous background of disease with no significant differences in filter vs. control group


Prospective, Randomized Clinical Trial for the Use of In-line Filtration in Critically Ill Children

Results of the Primary Outcome Measures

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>CONTROL GROUP</th>
<th>FILTER GROUP</th>
<th>P VALUE</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoints</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complications (overall)</td>
<td>166</td>
<td>124</td>
<td>0.833</td>
<td>0.450 - 0.805</td>
</tr>
<tr>
<td>adjusted to PIM II</td>
<td>123</td>
<td>90</td>
<td>0.611</td>
<td>0.462 - 0.643</td>
</tr>
<tr>
<td>SIRS adjusted to PIM II</td>
<td>16</td>
<td>10</td>
<td>0.818</td>
<td>0.506 - 0.930</td>
</tr>
<tr>
<td>Septis</td>
<td>27</td>
<td>20</td>
<td>0.513</td>
<td>0.360 - 0.667</td>
</tr>
<tr>
<td>Cardiovascular Failure</td>
<td>49</td>
<td>47</td>
<td>0.903</td>
<td>0.464 - 1.344</td>
</tr>
<tr>
<td>ARDS</td>
<td>25</td>
<td>22</td>
<td>0.882</td>
<td>0.504 - 1.068</td>
</tr>
<tr>
<td>Acute Renal Failure</td>
<td>14</td>
<td>14</td>
<td>0.756</td>
<td>0.425 - 1.083</td>
</tr>
<tr>
<td>Acute Liver Failure</td>
<td>9</td>
<td>7</td>
<td>0.851</td>
<td>0.290 - 2.125</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>11</td>
<td>6</td>
<td>0.250</td>
<td>0.058 - 0.428</td>
</tr>
</tbody>
</table>
Results: Hazard Ratios of Primary Endpoints and Mortality

- Overall Complication rate
- Circulatory Failure
- Lung Failure
- Renal Failure
- Liver Failure
- Thrombosis
- Infection
- SIRS
- Mortality

Results: Log-rank Analysis of SIRS (Filter vs. Non-Filter Group)

- Significant reduction in incidence of SIRS in filter group (123 non-filter group vs. 90 filter group; 95% CI, p=0.01)

Results: Secondary Outcome Measures

- Length of Stay on PICU and length of mechanical ventilation in minutes. Filter vs non-Filter group
Additional Results

- Significant reduction of respiratory, renal and hematologic dysfunction in the filter group (according to the definitions of the International Pediatric Sepsis Consensus Conference (IPSCC))

Boehne & Jack et al, BMC Pediatrics 2013

Additional non-published data:

- No significant difference of the demonstrated effects of in-line filtration depending on the different age groups*

- Patients in the age group of 12-18 years have the same favorable outcome as the ones between 0-1 year, 1-5 years and 6-12 years*

*Non-published data

Prospective, Randomized Clinical Trial for the Use of In-line Filtration in Critically Ill Children

But Why is the In-line Filter Effective?

Risks of Infusion Therapy

- Infection
- Wrong dosage
- Particles
- Incompatibilities of drugs
- Phlebitis
- Thrombosis
- Extravasation
- Air-Embolism
- Allergy
- Mistakes in application rate
- Device defects
- Flow irregularities during catecholamine therapy

The in-filter eliminates / or minimizes several risks of infusion therapy
Errors in administration of parenteral drugs in intensive care units: multinational prospective study

Table 3: Observed rates of parenteral medication errors

<table>
<thead>
<tr>
<th>No of errors</th>
<th>Events/100 patient days* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>861</td>
</tr>
<tr>
<td>Wrong time</td>
<td>386</td>
</tr>
<tr>
<td>Wrong med</td>
<td>239</td>
</tr>
<tr>
<td>Wrong dose</td>
<td>318</td>
</tr>
<tr>
<td>Wrong route</td>
<td>63</td>
</tr>
<tr>
<td>Wrong route</td>
<td>37</td>
</tr>
</tbody>
</table>

*Patient days calculated as total time (hours) of observation for all patients divided by 24.

Origin of Particles... Sometimes the Risks are Delivered by the Manufacturer!

FDA U.S. Food and Drug Administration

Dexamethasone Sodium Phosphate Injection, 4 mg/mL, 30 mL Multiple Dose Vial

Recall due to Particulates in Product (Posted 12/24/2010)

AUDIENCE: Risk Managers, Pharmacists

ISSUE: American Regent and FDA notified healthcare professionals of the nationwide recall of specific lots of Dexamethasone Sodium Phosphate Injection, USP 4 mg/mL, 30 mL Multiple Dose Vial because some vials of these lots either contain particulates or have the potential to form particulates prior to their respective expiration dates.

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

- 8 children are resuscitated after simultaneous application of Ceftriaxon and Calciumgluconate
- 5/8 died
- In 4/5 of the children who died severe pulmonary embolism could be proved as reason for the circulatory arrest
- Embolism was caused by calcium/ceftriaxon precipitations
1. Drug incompatibility reactions
- Account for 20% of all medication errors and up to 90% of administration errors
- Impair efficacy of administered drugs or increase risk of side effects, even formation of toxic compounds
- In ICU, coinfusion of two drugs is uncertain in up to 45% of instances in which the compatibility of drug combination is unknown

Kähny-Simonius J. Schweiz Rundsch Med Prax. 1993; 82:1320- 7

2. Incomplete reconstitution of drugs or particles inherent to drug formulation
- Generic formulations of antibiotics have been found to be heavily contaminated with particles
- Parenteral nutrition admixtures: Enlarged lipid droplets arise from emulsion instability and calcium phosphate precipitates occur

Driscoll DF et al Clinical Nutrition. 2006; 25(5): 842-5 0

3. Particle contamination from components and infusion systems
- IV lines (e.g. in conjunction with roller pumps)
- 3-way taps (abrasion by turning)
- Glass fragments from ampoules
- Rubber septa from injection sites and vial caps
Electron Microscopy of In-Line Filters Used in Our PICU

Particles from a filter membrane after 72 hours use in a 17 year old girl after aortic valve replacement

1. Brent B, Jack T, Sasse M; In-line filtration prevents intravascular infusion of “knife blades” and “spearheads” after open heart surgery. Eur Heart J. 2007 May; 28(10)

Origin of Particles

Aggravating Factors for Particle Formation

- Quantity of administered drugs and complexity of infusion regimen
- Lack of available intravenous lines
- Lack of incompatibility information for administered drugs or their formulation


Particulate Contamination Retained on Filter Membranes Precipitation Leads to Blockage

Analysis by electron microscopy of an in-line filter after 72 hours use on our PICU: Parenteral nutrition with high osmolarity and low infusion rate from a patient after neonatal liver transplantation

Prevention of Infusion Therapy Associated Risks
What is a Rational Strategy?

A multimodal infusion management concept
1. Standard operating procedure (SOP) of lumen arrangement at the CVC
2. Adaptation of infusion therapy to morbidity of patient
3. Maximum prevention of incompatibilities
4. Application of in-line filters
5. Training of medical staff
6. Reevaluation of entire process by team members

Summary
• Particulate contamination during intravenous therapy pose a potential risk for our patients
• Particle generation is a mandatory complication of our infusion therapy and is partially preventable by the optimization of the infusion management
• In-line filters retain air, endotoxins and particles and lead to a reduction of severe complications on the PICU and NICU
• In-line filters implemented in a multimodel infusion management concept ensure quality during infusion therapy and potentially increase patient's safety in the ICU