Tragic incidence of sepsis caused by contaminated TPN solutions
Aseptic preparations of TPN admixtures

- Preparation centralized in the pharmacy department cleanrooms, aseptic conditions
  ~ 10,000 TPN admixtures/y for paediatric patients

- Patient individual admixtures
  1. aqueous admixture (amino acid solution, carbohydrate solution, electrolytes)
  2. admixture of fat emulsion, vitamins

- Infusion time: 24 h

Good Preparation Practice PIC/S PE10-03

- Dedicated cleanrooms, standardized process
  gloves changed every 20 min

- Environmental monitoring
  Basic monitoring/ routine monitoring (in operation)
  Particle counts (every 6 months)
  Active air samples (monthly)
  Settle plates (weekly)
  Contact plates (weekly)
  Glove finger dabs (weekly, twice weekly/employee)

- Trend analysis, warning levels, action levels
Good Preparation Practice

- Daily preparation of dummy solutions standardized composition (25% amino acid-solution 10%) at the end of the process
- Aliquots transferred to blood culture bottles (aerob, anaerob)
- Dummies stored over 14 d (max. incubation period) = reference samples
- Disadvantages (not) each bulk solution tested generation time of microbes

Good Preparation Practice

- Quality is to be ensured by the process

- Ph. Eur limits for aseptic preparation
  - Sterility
  - Microbiological contamination risk 1:1000
  - Endotoxins: < 0,1 I.U./ml
TPN admixture preparation at Friday 20.8.2010

- 11 paediatric patients (3 wards)
  11 aqueous admixtures prepared at LAF 1
  11 fat emulsion admixtures prepared at LAF 2

- 2 dummy solutions/reference samples
  Aliquots transferred into blood culture bottles
  aerob/anerob

- Infusion systems connected by nurses in LAF on ward
  0.2 µm in line filter with zeta potential (aqueous sol.)
  1.2 µm filter (fat emulsion)

Chronology of the Incidence

- Saturday morning
  Contamination of samples from dummy solutions
  reported by the Department of Microbiology to the pharmacy
  Pharmacist on duty called the director of pharmacy
  Wards were informed and TPN infusion stopped.
  Fresh admixtures were prepared in the pharmacy.

- Saturday afternoon
  Staff in the paediatric clinic refused to administer freshly prepared TPN admixtures.
Positive blood cultures from aqueous dummys

- Contaminated TPN admixtures?
  - Contamination during preparation process?
  - Contamination by devices used?
  - Contamination of bulk solutions?

Chronology of Sunday morning

- 9:00 a.m.
  Samples of the aqueous infusion solutions and samples taken by the pharmacists on Saturday evening from different items showed contamination

- 9:15 a.m.
  Chairman of the board of directors was informed

- 11:00 a.m.
  Meeting of a crisis management group in the childrens hospital
Setting the priorities

- Prevent further harm for patients
- Find out the origin of the contamination
- Inform family members
- Inform staff
- Inform and cooperate with police, state attorney, competent authorities
- Public information
- Minimize harm for the university medical center

Further Chronology

- 11:45 Physicians and nurses of the paediatric clinic called
- 12:00 Information of parents/family members
- 12:00 Information of manufacturers
- 12:30 Information local health authority, pharmacy authority, ministry
- 13:10 Information state attorney
- 14:00 Pharmacist and technicians involved were asked to come to the pharmacy department
- 15:00 Arrival of the investigative authorities
- 17:00 Press release
- 18:00 Press conference
- 19:00 Top information in the TV news
Newborns died
Negligent homicide?

Investigation of origin of contamination
Investigation of cause: Devices
<table>
<thead>
<tr>
<th>Bulk solution</th>
<th>Expiration Date</th>
<th>Lot Number</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aqua ad injectabilia Ecoflac 1000ml</td>
<td>31.3.2013</td>
<td>0147A251</td>
<td>B. Braun</td>
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<tr>
<td>Glucose 70 % 500 ml</td>
<td>31.2.2013</td>
<td>0125A164</td>
<td>B. Braun</td>
</tr>
<tr>
<td>* Aminopäd 10% 1000 ml</td>
<td></td>
<td></td>
<td>Baxter</td>
</tr>
<tr>
<td>Natriumchlorid 5,85% 250 ml</td>
<td>31.1.2014</td>
<td>221345</td>
<td>Serag Wiessner</td>
</tr>
<tr>
<td>Glycerophosphat-Natrium 100 ml</td>
<td>31.12.2011</td>
<td>221286</td>
<td>Serag Wiessner</td>
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<tr>
<td>Calciumgluconat 10 % 250 ml</td>
<td>31.3.2011</td>
<td>220747</td>
<td>Serag Wiessner</td>
</tr>
<tr>
<td>* Kaliumchlorid 7,45% 250 ml</td>
<td>31.3.2013</td>
<td>221446</td>
<td>Serag Wiessner</td>
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<tr>
<td>* Magnesiumaspartat 100ml</td>
<td>31.12.2012</td>
<td>S1007079</td>
<td>Eigenherstellung, Apotheke Uni-Mz</td>
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</tbody>
</table>

* 800 ml gesamt

**Investigation of cause: Bulk solutions**
Microbiological Results

- Enterobacter cloacae, Escherichia hermannii
  - in 11 TPN admixtures prepared at 20.8.2010
  - in bulk solutions of amino acid solution, Ca-gluconate solution,
    in some tubes (also connecting tube to empty containers)
- Concentration of bacteria
  - reference sample: 30.000 (3 * 10^4) bacteria/ml
  - Ca-gluconate solution: 9000 bacteria/ml
- Concentration of endotoxin
  - reference sample: 1111 I.U. endotoxin/ml

Potentially contaminated bulk solution
measured bacteria concentration: 1,2*10^5/ml
Endotoxin concentration: 4*1100 I.U./ml = 4 µg/ml
= calculated bacteria concentration: 2-4*10^6/ml
Clinical Results

- Only 3 patients (n=11) with positive blood cultures
- Only 2 patients (n=11) with Enterobacter cloacae/E. hermannii
- In 7 patients (n=11) symptoms of sepsis/endotoxin exposition
- In 7 patients (n=11) CRP elevation Immediate CRP decrease when infusions were stopped

Microbiological Results

- Specific strains of Enterobacter cloacae and E. hermannii were not identified in the cleanroom area or pharmacy staff
- Up to 10^7 bacteria/ml no turbidity
- Simulation tests in 10% amino acid solution with Enterobacter cloacae
  - High concentrations of bacteria and endotoxins not measured only after 24 hours
  - Low level contamination = long lag time
  - High concentrations of bacteria remain over months
- Conclusion: Contamination occurred weeks or months earlier
Good Transportation Practice?

- Quality of primary package
- Adequate secondary packages
  thickness of cardboard boxes
  paperboard between glass bottles
- Safe transport conditions
- Trained, responsible transport staff
Fractography at Fa. Schott, Mainz in March 2011
Origin of breakage: inclusion of a foreign particle

Checking of Bulk Solutions

- Visual inspection of containers

- Possible In-process-tests
  - Raman-Spectroscopy
  - Endotoxin test
  - Under pressure
Changes in the Preparation Process

- Used bottles of bulk solutions collected per daily production stored over 1 week

- Discussion about administration of TPN admixtures via 0.2 µm filter with zeta potential experimental testing
Storage of Waste

Endotoxin retaining capacity
0.2 µm filter with positive charged nylon membrane

<table>
<thead>
<tr>
<th>Filterleerwerte</th>
<th>Ampuwe® Infl Air 120 EE/ml</th>
<th>NaCl Infl Air 120 EE/ml</th>
<th>Glucostat® Infl Air 120 EE/ml</th>
<th>AKE Infl Air 120 EE/ml</th>
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<td>100 ml LRW 1</td>
<td>&lt; 0.002</td>
<td>&lt; 0.002</td>
<td>&lt; 0.002</td>
<td>&lt; 0.002</td>
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<td>1 100 ml</td>
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<td>&lt; 0.002</td>
<td>4.90</td>
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<tr>
<td>2 100 ml</td>
<td>&lt; 0.002</td>
<td>2.25</td>
<td>&lt; 0.002</td>
<td>5.10</td>
</tr>
<tr>
<td>3 100 ml</td>
<td>&lt; 0.002</td>
<td>0.42</td>
<td>&lt; 0.002</td>
<td>5.20</td>
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<tr>
<td>4 100 ml</td>
<td>&lt; 0.002</td>
<td>0.43</td>
<td>&lt; 0.002</td>
<td>5.50</td>
</tr>
<tr>
<td>5 100 ml</td>
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<td>0.42</td>
<td>&lt; 0.002</td>
<td>5.10</td>
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<tr>
<td>6 100 ml</td>
<td>&lt; 0.002</td>
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<td>&lt; 0.002</td>
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<td>7 100 ml</td>
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<td>0.45</td>
<td>&lt; 0.002</td>
<td>5.30</td>
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<tr>
<td>8 100 ml</td>
<td>&lt; 0.002</td>
<td>0.53</td>
<td>&lt; 0.002</td>
<td>5.20</td>
</tr>
<tr>
<td>9 100 ml</td>
<td>&lt; 0.002</td>
<td>0.52</td>
<td>&lt; 0.002</td>
<td>5.30</td>
</tr>
<tr>
<td>10 100 ml</td>
<td>&lt; 0.002</td>
<td>0.60</td>
<td>&lt; 0.002</td>
<td>5.40</td>
</tr>
</tbody>
</table>

Infusion solutions loaded with 5 IU Endotoxin/ml
Observation time: 120 h
Endotoxin measured in 100 ml filtrate
One week later

- Press conference organized by the state attorney

Result
- Staff of the university medical center is not guilty

How did we manage the crisis?

- Investigation of the origin of contamination taken over by the head of microbiology
- Rapid detection of the contamination source by close cooperation of internal and external experts and investigational authorities
- Faithful, mutual respect, acceptance
- Reliability of skills of the staff and QMS ↔ Mistakes can never be totally excluded
+++++ Mainz ++++++

4. August 2011
Contaminated infusion solutions: state attorney informed that investigations were stopped. According to the results of the investigations a contaminated infusion solution bottle was delivered and used.

Medical director of the University medical center. We are happy about the results, but at the same we are sad because 3 children died....