

The risk of in-use microbial contamination of intravenous products



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MAINZ

Aseptic preparation of TPN admixtures

- Preparation centralized in the pharmacy department cleanrooms, aseptic conditions
~ 10.000 TPN admixtures/y for paediatric patients
- Patient individual **T**otal **P**arenteral **N**utrition 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
- Routine environmental monitoring (in operation)
Particle counts (every 6 months)
Active air samples (monthly)
Settle plates (weekly)
Surface contact plates (weekly)
Glove finger dabs (twice weekly/employee)
- Media fills (every 6 months)
- Trend analysis, warning levels, action levels

Good Preparation Practice

- In-process control
daily preparation of dummy solutions
standardized composition, at the end of the process
content: 25% amino acid-solution 10%
- Aliquots transferred to blood culture bottles
(aerob, anaerob)
- Dummies stored over 14 d (max. incubation period)
= reference samples

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**

Blood culture bottles of aqueous dummy solution positiv

Department of Microbiology informed pharmacy

Pharmacy informed wards, infusion stopped

Residual admixtures, devices send to microbiology

Origin of Positive Blood cultures

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

Bulk solution	Expiration Date	Lot Number	Manufacturer
Aqua ad injectabilia Ecoflac 1000ml	31.3.2013	0147A251	B. Braun
Glucose 70 % 500 ml	31.2.2013	0125A164	B. Braun
* Aminopäd 10% 1000 ml	800 ml gesamt	10C0292	Baxter
Natriumchlorid 5,85% 250 ml		31.1.2014	221345
Glycerophosphat-Natrium 100 ml	31.12.2011	221286	Serag Wiessner
Calciumgluconat 10 % 250 ml	31.3.2011	220747	Serag Wiessner
* Kaliumchlorid 7,45% 250 ml	31.3.2013	221446	Serag Wiessner
* Magnesiumaspartat 100ml	31.12.2012	S1007079	Eigenherstellung, Apotheke Uni-Mz

Investigation of cause: Bulk solutions



Microbiological Results

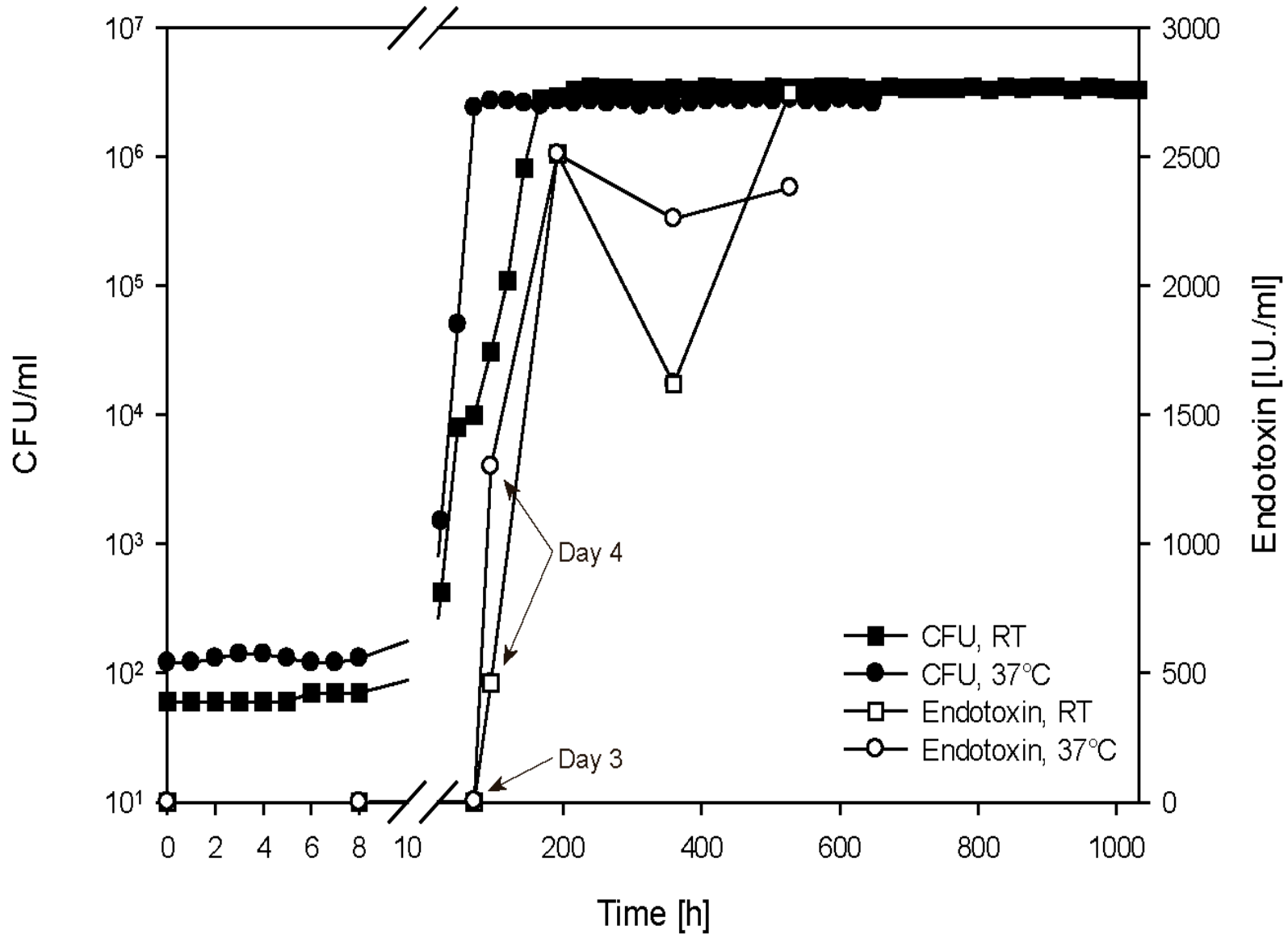
- Enterobacter cloacae, Escherichia hermannii
 - in 11 TPN admixtures prepared at 20.8.2010
 - in bulk solutions of amino acid solution/in bulk solution of Ca-gluconate solution
- Concentration of bacteria
 - Dummy solution: 30.000 ($3 \cdot 10^4$) bacteria/ml
 - Potentially contaminated amino acid solution $1,2 \cdot 10^5/\text{ml}$
- Concentration of endotoxin
 - Dummy solution: 1111 I.U. endotoxin/ml
 - Potentially contaminated amino acid solution:
 $4 \cdot 1100 \text{ I.U./ml} = 4 \mu\text{g/ml}$
= calculated bacteria concentration: $2-4 \cdot 10^6/\text{ml}$

Clinical Results

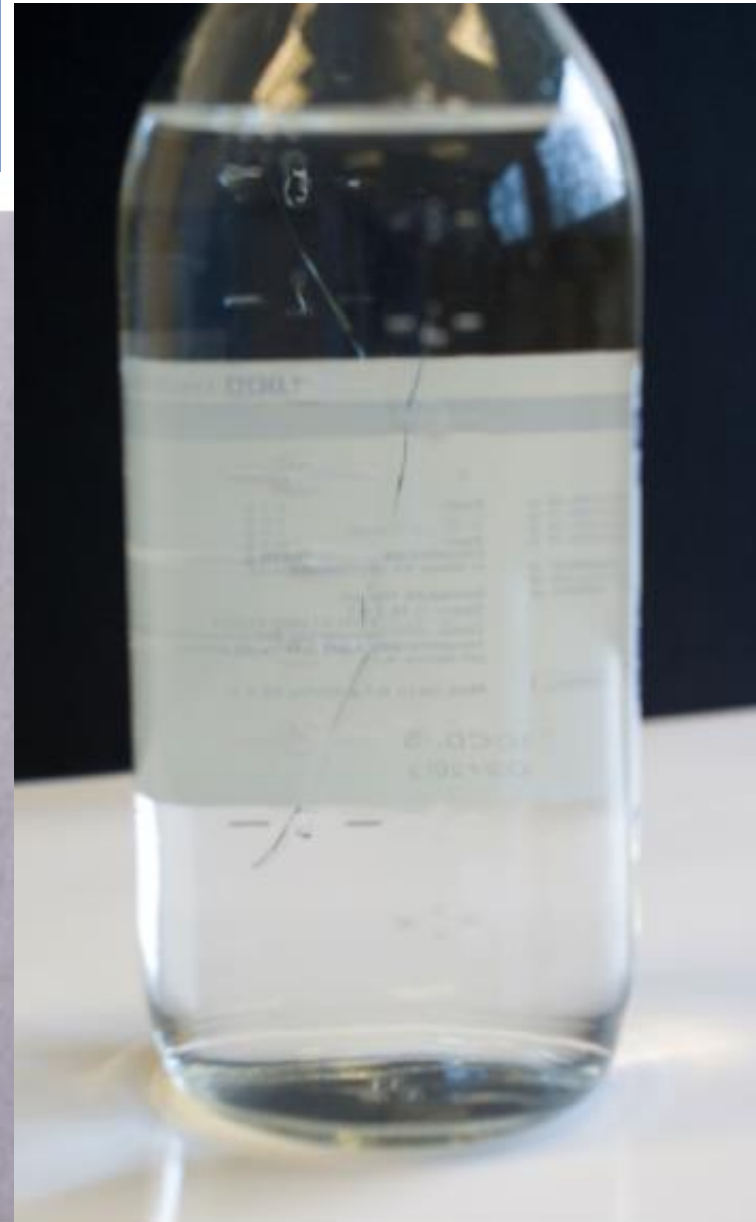
- Only 3 patients (n= 11) with positive blood cultures
- Only 2 patients (n=11) with *Enterobacter cloacae*/E. *hermannii*
- In 7 patients (n=11) symptoms of sepsis/endotoxin exposition
- In 7 patients (n=11) CRP elevation
Immediate CRP decrease when infusions were stopped

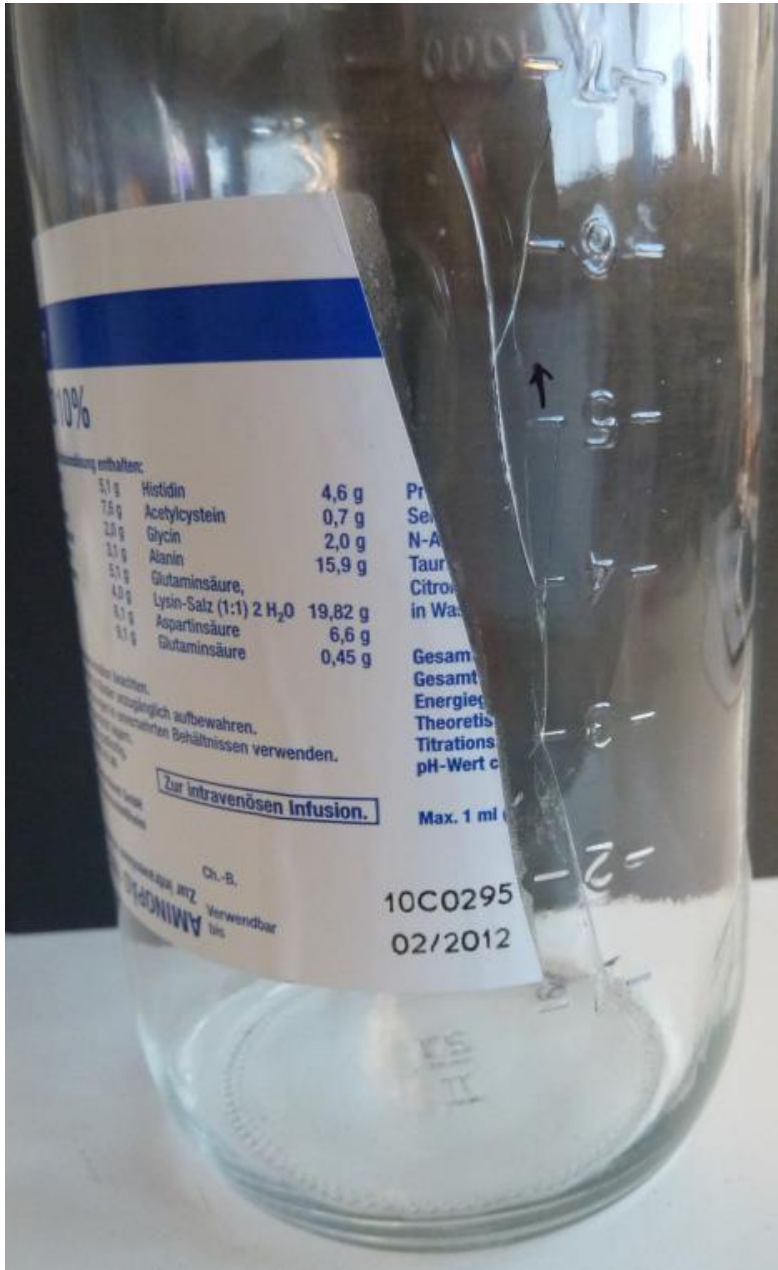
Microbiological Results

- Specific strains of *Enterobacter cloacae*, *E. hermanni* not identified in the cleanroom area or pharmacy staff
- 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
 - Up to 10^7 bacteria/ml no turbidity
- **Conclusion:**
Contamination occurred weeks or months earlier

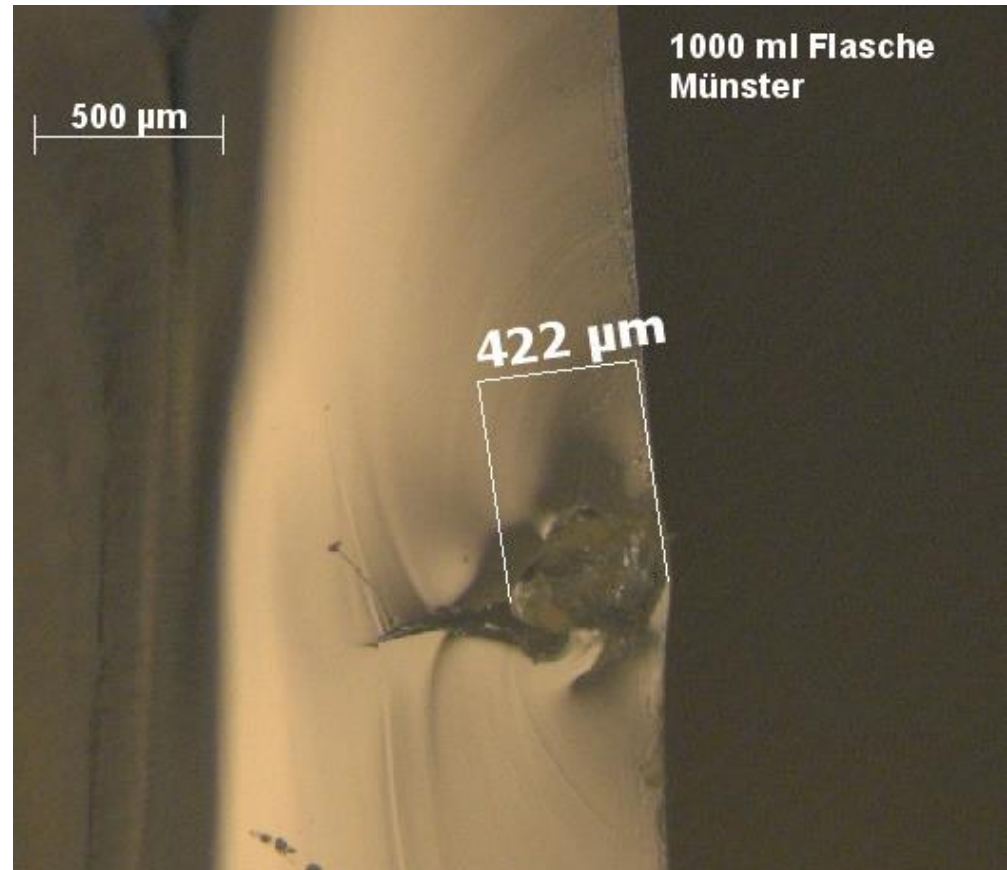


Good Transportation Practice ?





Fractography at Fa. Schott, Mainz in March 2011 Origin of breakage: inclusion of a foreign particle



+++++ 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.

Staff of the university medical center is not guilty

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