Contamination Control in Hospital Aseptic Dispensing
What’s it about?

X-CONTAMINATION in the hospital pharmacy

• An intriguing mystery to solve

• A scary tale has become more scary
Aseptic Dispensing in hospitals

Manufacture of injections and infusions not commercially available:
• unstable in solution
• dose/volume patient specific
• components not heat stable in combination
• no parenteral form accessible

Laminar Air Flow Workstations

TERMINAL STERILISATION NOT POSSIBLE
Aseptic Dispensing

Meticulous ‘no-touch’ technique mandatory

Trained and validated operators

Cytotoxic Drug Safety Cabinet
Products dispensed

Mainly parenteral nutrition solutions for intravenous feeding patients with intestinal failure and low birth weight infants and Cytotoxic (anti-cancer) drugs

- some antibiotics, analgesics, etc.
- Monoclonal Antibodies
Parenteral Nutrition (PN) solutions

Amino acids, glucose, fat emulsion, multi-vitamins, trace elements ...
### Notable PN Aseptic Dispensing Disasters

<table>
<thead>
<tr>
<th>Year</th>
<th>City</th>
<th>Solution</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989</td>
<td>Johannesburg</td>
<td>PN</td>
<td>2 infants died</td>
</tr>
<tr>
<td>1993</td>
<td>Johannesburg</td>
<td>PN</td>
<td>8 infants died</td>
</tr>
<tr>
<td>1994</td>
<td>Manchester</td>
<td>PN</td>
<td>2 infants died</td>
</tr>
<tr>
<td>1998</td>
<td>Roraima, Brazil</td>
<td>PN</td>
<td>20 infants died</td>
</tr>
<tr>
<td>2000</td>
<td>Campinas, Brazil</td>
<td>PN</td>
<td>7 infants died</td>
</tr>
<tr>
<td>2005</td>
<td>Malaysia</td>
<td>PN</td>
<td>7 infants died</td>
</tr>
<tr>
<td>2007</td>
<td>Groningen, Neth</td>
<td>PN</td>
<td>3 infants died</td>
</tr>
<tr>
<td>2010</td>
<td>Mainz Univ, Ger</td>
<td>PN</td>
<td>3 infants died</td>
</tr>
<tr>
<td>2011</td>
<td>Alabama, USA</td>
<td>PN</td>
<td>9 adults died</td>
</tr>
</tbody>
</table>

*Enterobacter cloacae* (mostly), *Serratia* and *Klebsiella* sps. — the primary causative organisms in every case – all members of *Tribe Klebsielleae*

*Tribe Klebsielleae* organisms originate in the human GI tract

- no airborne organisms involved

All solutions were prepared by pharmacists or technicians in laminar air flow workstations or isolators

<table>
<thead>
<tr>
<th>Year</th>
<th>City</th>
<th>Solution</th>
<th>Outcome</th>
</tr>
</thead>
</table>
Many were prepared in cleanrooms
Purpose of cleanrooms

Control airborne particulates with limits established by relevant Standards

- maintain low pathogen environments in which pools of pathogens are eliminated or held within very low limits specified by Standards

So where do the contaminants come from?
People constantly shed skin cell debris

Operators wearing cleanroom garments:

<table>
<thead>
<tr>
<th>Activity</th>
<th>Particles per minute (&gt; 0.3mµ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting or standing still</td>
<td>100,000</td>
</tr>
<tr>
<td>Simple arm movement</td>
<td>500,000</td>
</tr>
<tr>
<td>Average arm, body movement</td>
<td>1,000,000</td>
</tr>
<tr>
<td>Walking slowly</td>
<td>5,000,000</td>
</tr>
<tr>
<td>Walking average pace</td>
<td>7,500,000</td>
</tr>
<tr>
<td>Walking fast pace</td>
<td>10,000,000</td>
</tr>
<tr>
<td>Boisterous activity</td>
<td>15 M - 30 M</td>
</tr>
</tbody>
</table>

Based on work by Dr. Phillip Austin ('Austin's Contamination Index')
Origin of cleanroom contaminants?

Skin squames shed from all body surfaces

- GI tract cells rapidly turn over because of digestive processes

* Perineal fallout or shedding – OR Infection Control terminology
The need for “Packaging people"

- cleanroom garments well-designed
- effective cuff closures at ankles

A Possible Cause

- Few if any operators in the hospital pharmacy cleanrooms appear to have been wearing particle trapping garments
- Too heavy reliance on laminar flow cabinets for sterility?
But why so predominantly *Tribe Klebsielleae* micro-organisms?

The Enterobacter species are ubiquitous.

*E cloacae* infection is associated with the highest mortality rate of all Enterobacter infections.

MedScape Reference: Enterobacter Infections
Author: Susan L Fraser, MD; Chief Editor: Burke A Cunha, MD
But why so predominantly *Tribe Klebsielleae* micro-organisms?

Nosocomial infections surveyed 1995-2002:

- *Enterobacter* species the second-most-common gram-negative organism behind *Pseudomonas aeruginosa*
- both represented 4.7% of bloodstream infections in ICU settings
So where are the Pseudomonads, Coliforms, the Staphs, Candida etc.?
Growth characteristics of bacteria in 5% Glucose (Dextrose)

*No strains tested

** Mean normalized concentration of all strains in group

Redrawn from:
Growth curves of 106 microbial strains in D5%W at 25°C - Maki and Martin
(\textit{J Infect Dis} 1975;131:267)
Sad Facts

*Tribe Klebsielleae* organisms appear to proliferate more rapidly in parenteral solutions than other micro-organisms that may be present and are often implicated in death of compromised patients

- *Tribe Klebsielleae* organisms are endotoxin producers that may precipitate septic shock
- Antibiotics used to treat infection may accelerate release of endotoxin
Sad Facts

*Tribe Klebsielleae* organisms are opportunistic – cause infections only in certain circumstances or in certain patients.

e.g.
- aqueous solutions
- blood
- urinary tract
Not only PN solutions contaminated by Tribe Klebsielleae organisms

- albumin
- fat emulsions
- cardioplegic (electrolyte) solutions
- sodium chloride 0.9% catheter flush solutions
### Analysis

In 3 cases, extrinsic contamination occurred because incoming solutions in vials or ampoules from external manufacturers were identified as the source.

In 2 cases, bottles of amino acids or lipid emulsion became cracked during shipping and contaminated by *Enterobacter cloacae* prior to introduction into cleanrooms.
Question
Do mixed GI micro-organisms (including the Enterobacter species) colonising perineal skin squames circulate freely in uncontrolled environments?

And in at least some cleanroom environments?
Question 2
Why don’t we detect *Enterobacter* et al. when performing routine airborne microbial monitoring in cleanrooms and surrounding controlled environments?

- swamped by normal airborne organisms?
- numbers below level of detection?
- requires fluid medium?
- any ideas?
Go figure!
Cytotoxic drugs dispensing

A scary tale has become more scary
Cytotoxic drugs

Many supplied as lyophilised powders requiring reconstitution with saline or Water for Injections
1/15,000th second
Fluid Aerosols: particle size distribution

<table>
<thead>
<tr>
<th>No. of Particles</th>
<th>0.01*</th>
<th>1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>micrometres</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* not to scale

From the Stanford Research Institute Chart
Stoke's Law: Time taken for small spherical particles to fall in **still** air

<table>
<thead>
<tr>
<th>Diameter of Particle (micrometres)</th>
<th>Calculated time to fall 1 metre</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>339 hrs</td>
</tr>
<tr>
<td>0.4</td>
<td>42 hrs</td>
</tr>
<tr>
<td>1.0</td>
<td>7.8 hrs</td>
</tr>
<tr>
<td>2.0</td>
<td>2.2 hrs</td>
</tr>
<tr>
<td>4.0</td>
<td>34 mins</td>
</tr>
<tr>
<td>8.0</td>
<td>8 mins</td>
</tr>
<tr>
<td>10.0</td>
<td>5.3 mins</td>
</tr>
</tbody>
</table>

Particle SG=1/Temperature=21 deg C
Emerging consensus

- Certain cytotoxic drugs, particularly alkylating agents, are carcinogenic in humans.
- Many cytotoxic drugs are genotoxic, causing excretion of mutagens.
- Some cytotoxic drugs are teratogenic, capable of causing birth defects in offspring of exposed pregnant females.
- All cytotoxic drugs exhibit some, several, or all of these effects.
Leukemia risk following cancer chemotherapy, radiotherapy for Hodgkin’s Disease

Blayney DW et al.  
Mechanisms of occupational exposure

- inhalation of CTX drug aerosols
- inhalation of CTX drug vapour
- absorption through the skin
- mucosal absorption
- needlestick injuries ?
Engineering controls

Cytotoxic Drug Safety Cabinet
AS2567

Pharmaceutical Isolators
Cytotoxic drug contamination of vials and packaging

Another source of contamination external to CDSCs and isolators

# Inhalation of Drug Vapour

Several CTX drugs vapourise at 23 and 37°C

<table>
<thead>
<tr>
<th>Drug</th>
<th>23°C</th>
<th>Drug</th>
<th>37°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carmustine</td>
<td>++</td>
<td>Carmustine</td>
<td>++</td>
</tr>
<tr>
<td>Nitrogen mustard</td>
<td>++</td>
<td>Cyclophosphamide</td>
<td>++</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>+</td>
<td>Ifosfamide</td>
<td>++</td>
</tr>
<tr>
<td>Thiotepa</td>
<td></td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Nitrogen mustard</td>
<td></td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>?</td>
<td>Fluorouracil</td>
<td>?</td>
</tr>
</tbody>
</table>


**BOLD** – Class 1 human carcinogens
Deposition of Vapourised Drug Residue

Can settle on all surfaces within the area

- occupational exposure can occur in operators not actively involved in aseptic preparation of drugs
- chromosomal changes have been observed

Davis J, MacLauchlan R, Connor T. Exposure to hazardous drugs in Healthcare: An issue that will not go away. *JOPP* 2011;17(1):9-13

After 36 years ...

No scientifically proven case of hospital pharmacy or medical stores staff suffering neoplastic disease from handling cytotoxic drugs

- current safety practices are better than at any time in the past
Objective: To determine the frequency of "signature" chromosomal abnormalities in oncology workers handling anticancer drugs. Methods: Peripheral blood from healthcare personnel (N = 100) was examined with probes for targets on chromosomes 5, 7, and 11. The effect of drug-handling frequency on chromosome abnormalities was assessed. Results: An excess of structural (0.18 vs 0.02; P = 0.04) and total abnormalities (0.29 vs 0.04; P = 0.01) of chromosome 5 was observed in the high-exposure group compared with the unexposed. Increased incidence rate ratios (IRR5) for abnormalities of chromosome 5 (IRR5 = 1.24; P = 0.01) and for either chromosome 5 or 7 (IRR5 = 1.20; P = 0.01) were obtained at 100 handling events. Effect sizes were augmented 2- to 4-fold when alkylating agent handling alone was considered. Conclusions: Biologically important exposure to genotoxic drugs is apparently occurring in oncology work settings despite reported use of safety practices. When a vertical-flow class II biological safety cabinet (BSC) was used, which captures and vents contaminated air through a high efficiency particulate air filter and away from the operator.5-8

Scores of such monitoring studies of affected healthcare workers (HCWs) examining various measures of genotoxic exposure have accrued over the past three decades, with most documenting excess genotoxic activity.9-12 Some of these studies, however, reflected workplace conditions before the Occupational Safety and Health Administration guidance and consensus professional practice changes, which recommended but did not require the use of special handling and BSCs in the preparation of infusions, injections, and patient-ready drug products. These "safe-handling" policies were first promulgated in the mid-to-late 1980s and were updated subsequently.16-18 Importantly, however, these early studies documented the plausibility of biologically relevant genotoxic outcomes occurring as a result of workplace exposure.
X-Contamination in the hospital pharmacy

Two major areas of concern

Neither are addressed adequately by Code of Good Manufacturing Practice

Many practitioners inadequately informed

As a whole the profession is just waiting ...
DISCUSSION