Annals of Work Exposures and Health, 2019, 1–9
doi: 10.1093/annweh/wxz010
Original Article

Original Article

Reduction of Contamination with Antibiotics on Surfaces and in Environmental Air in Three European Hospitals Following Implementation of a Closed-System Drug Transfer Device

Paul J. M. Sessink[1*], Tibor Nyulasi[2], Emmie L. M. Haraldsson[3] and Branislava Rebic[4]

[1]Exposure Control Sweden AB, Backsippevägen 2, 47537 Bohus-Björkö, Sweden; [2]Intensive Care Department, Szent János Hospital, Dr. Manninger Vilmos stny., 1125 Budapest, Hungary; [3]Department for Infectious Diseases, Central Hospital, Värendsgatan 8, 35185 Växjö, Sweden; [4]Pharmacy Department, University Children's Hospital, Tirsova 10, 11000 Belgrade, Serbia

*Author to whom correspondence should be addressed. Tel: +46-702-692-260; e-mail: info@exposureconrol.net

Submitted 23 May 2018; revised 7 January 2019; editorial decision 10 January 2019; revised version accepted 29 January 2019.

Abstract

Purpose: Occupational exposure of nurses to antibiotics may result in adverse health effects such as hypersensitivity, allergic reactions, resistance, and anaphylactic shock. The purpose of this study was to measure surface and air contamination with antibiotics in three hospitals during the preparation of the drugs using conventional techniques or using the Tevadaptor® closed-system drug transfer device (CSTD).

Methods: Surface contamination was measured by taking wipe samples. Stationary air samples were collected in preparation areas and personal air samples were collected in the working environment of the nurses. Contamination was reassessed after several weeks following implementation of the CSTD. Surface contamination was compared before and after CSTD introduction. Vancomycin, meronem, augmentin, ceftriaxone, cefotaxime, piperacillin, and benzylpenicillin were monitored. Wipe and air samples were analyzed using liquid chromatographytandem mass spectrometry (LC-MS/MS).

Results: Using conventional preparation techniques, widespread contamination with antibiotics up to 767 ng cm^{-2} was detected. After implementation of the CSTD, contamination levels significantly decreased for the most frequently prepared antibiotics in the three hospitals.

Using the conventional preparation technique, three antibiotics were detected in environmental air of seven nurses in two hospitals (0.01–5 µg m^{-3}), and one antibiotic was found in environmental air above a preparation surface (0.02 µg m^{-3}). After implementation of the CSTD, the same antibiotic was detected in environmental air above the same preparation surface (1.39 µg m^{-3}) but no antibiotics were detected in environmental air of the nurses in the three hospitals.

Conclusions: Using the conventional preparation techniques, surfaces and air were widely contaminated with antibiotics whereas the use of the CSTD significantly reduced contamination. Systematic use of a CSTD significantly reduces exposure to hazardous antibiotics and consequently reduces potential adverse health effects for healthcare providers.

Keywords: antibiotics; air contamination; closed-system drug transfer device; nurses; surface contamination

Introduction

Antibiotics are used in the treatment and prevention of bacterial infections but are also used in patients at high risk for developing infections (CDC, 2017). They are used to kill or inhibit the growth of bacteria. Preparation and administration of antibiotics is widespread over many departments in hospitals and many healthcare workers, especially nurses, are involved in handling these drugs daily.

Side effects of antibiotics in patients can range from mild allergic reactions to severe adverse effects (CDC, 2017). Side effects are variable from patient to patient and from antibiotic to antibiotic. Most common side effects include diarrhea, nausea, vomiting, rashes, itching, and interactions with other drugs. Antibiotic resistance, allergic reactions, and especially anaphylaxis are the most severe side effects (CDC, 2017).

Adverse health effects of occupational exposure to antibiotics in healthcare personnel are scarcely published. Weak and moderate effects include hypersensitivity (itching, runny nose, irritation of the eyes), allergic skin reactions (eczema, rash, dermatitis), and respiratory symptoms (asthma and wheezing) (Stenton *et al.*, 1995; Gielen and Goossens, 2001; Cetinkya *et al.*, 2007; Kim *et al.*, 2012; Marraccini *et al.* 2013; Whitaker, 2016; Pinheiro *et al.*, 2018). More severe effects include drug resistance and even anaphylactic shock (Rudzki and Rebandel, 1985; Tadokoro *et al.*, 1994). Nurses handling antibiotics frequently report that they smell the drugs, have a bitter taste in their mouth, and observe splashes and leakages during the preparation.

Considering all these aspects, there is concern that nurses continuously exposed to antibiotics may have adverse acute and chronic health effects, raising a need to reduce this exposure as much as possible

The aim of this study was to measure potential reduction of contamination from antibiotics exposure during preparation for injections using the conventional techniques compared to using a closed-system drug transfer device (CSTD) that prevents release of the drugs during preparation and administration. As far as we know, such a study has not been published previously in the literature.

Methods

Monitoring sites

Three hospitals across Europe participated in this study. In all hospitals, the preparation of antibiotics is performed on dedicated surfaces by nurses, and these nurses also administer the drugs and care for the patients. All wards included in the study routinely use multiple types of antibiotics.

Hungary

The Hungarian site was an Intensive Care Department. In addition to the nurses, a physiotherapist treats patients but does not handle antibiotics. The antibiotics are prepared using a needle/syringe combination with no special personal protection.

Sweden

The Swedish site was a Department of Infectious Diseases. The antibiotics are prepared on surfaces partially protected by a disposable mat for the purpose of collection of potential antibiotic spills. The mats are changed daily during the night shift. The antibiotics are prepared with a needle/syringe or with a needle/spike/syringe combination. Gloves are used for personal protection (nitrile powder-free non-sterile Medical Examination Gloves, Abena, Denmark).

Serbia

The Serbian site was a Department of Infectious Diseases for children. The antibiotics are prepared using a needle/syringe combination. There is no special personal protection.

Closed-system drug transfer device

The CSTD that was chosen for this study is Tevadaptor® (Teva-Medical Ltd, Israel). This is a system under the ONB product code of the Food and Drug Administration; it prohibits the release of drug in vapor, aerosol, or liquid form during preparation and administration and prevents the introduction of microbial and airborne contaminants into the drug or fluid path, allowing the system to minimize exposure of individuals, healthcare personnel, and the environment to hazardous drugs. Drug containment in the Tevadaptor® Vial Adaptor is accomplished by the TOXI-GUARD® system, which contains an activated carbon drug binding matrix and a 0.2-µm hydrophobic and oleophobic membrane (Wilkinson *et al.*, 2014, 2018). Drugs are prepared using the Tevadaptor® in a needleless technique by combination of the Vial adaptor, which connects in a 'closed-system' manner to the drug vial, and a Syringe adaptor, which connects in a 'closed-system' manner to the syringe

Study design and sample collection

Hungary

Environmental contamination was measured by taking wipe samples from 10 potentially contaminated surfaces in the preparation area of both rooms and beside a patient's bed (administration). Stationary air samples were collected in the preparation room and close to a patient's bed. Personal air samples were collected from three nurses during all activities (preparation, administration, and patient care) and from a physiotherapist handling patients. Vancomycin, meronem, ceftriaxone, and augmentin were monitored.

Wipe and air samples were taken while the conventional needle/syringe preparation technique was being used. Immediately after the sampling, the CSTD was implemented and used thereafter for all preparations and administrations with the four mentioned antibiotics. Five months after the implementation of the CSTD, environmental contamination was resampled by wipe and air testing and compared with the previous monitoring.

Sweden

Environmental contamination was measured by taking wipe samples from 10 potentially contaminated surfaces in the preparation room and beside patient's beds (administration). Stationary air samples were collected in the preparation area and close to a patient's bed. Personal air samples were collected from 10 nurses during all activities (preparation, administration, and patient care). Vancomycin, meronem, ceftriaxone, cefotaxime, piperacillin, and benzylpenicillin were monitored.

Wipe and air samples were taken while the conventional needle/syringe or needle/syringe/spike preparation technique was being used. Immediately after the sampling, the CSTD was implemented and used for all preparations and administrations with the six mentioned antibiotics. Seven weeks after the implementation of the CSTD, environmental contamination was resampled by wipe and air testing and compared with the previous monitoring.

Serbia

Environmental contamination was measured by taking wipe samples from 13 potentially contaminated surfaces in the preparation room and beside a patient's bed (administration). Stationary air samples were collected in the preparation room and close to a patient's bed. Personal air samples were collected from 5 nurses during all activities (preparation, administration, and patient care). Vancomycin, meronem, ceftriaxone, and piperacillin were monitored.

Wipe and air samples were taken while the conventional needle/syringe preparation technique was being used. Immediately after the sampling, the CSTD was implemented and used for all preparations and administrations with all antibiotics in the ward. Three weeks after the implementation of the CSTD, environmental contamination was resampled by wipe and air testing and compared with the previous monitoring.

Sample preparation

Sampling was performed under responsibility of Exposure Control Sweden AB.

The wipe samples were taken with AB Wipe Kits (Exposure Control Sweden AB). The kits contain materials to take wipe samples from several types of surfaces (paper tissues, droppers with 17 ml distilled water, containers for sample storage, and gloves for personal protection).

The wipe samples were taken by dripping 17 ml distilled water on the surfaces. Next, one paper tissue was used to spread the liquid over the whole surface. The second paper tissue was used to dry the surface. Both tissues were collected in the storage container.

The air samples were collected with IOM samplers (sampling head) connected to VSS-5 Buck pumps. For personal sampling, the IOM sampler was attached on the shirt collar or lapel of the nurse, in proximity to the breathing zone (less than 30 cm from the mouth). The sampling pump was secured on a belt on the nurse. For stationary sampling, the IOM sampler and the sampling pump were fixed at specific locations close to potential sources of emission. Total particulate matter was collected on polytetrafluoroethylene filters (Whatman, 25-mm diameter and 1.0-µm pore size). The flow rate was 2.0 l min^{-1}.

All samples were stored at room temperature after sampling and during transport until arrival at the laboratory. In the laboratory, they were stored at 4°C until sample preparation and analysis.

The wipe samples were prepared for analysis by adding distilled water up to a total volume of 100 ml.

After extraction, a part of the extract was used for analysis. For the air filters, the preparation was similar except that 10 ml distilled water was used.

Equipment and LC-MS/MS analysis

Analysis was performed with a Xevo TQ-S micro mass spectrometer combined with an Acquity UPLC H-Class sample manager and quaternary solvent manager controlled by masslynx software (Waters, Milford, MA, USA). An Acquity HSS T3, 1.8-µm, 100-mm separation column operated at 40°C was used for gradient separation of the antibiotics with a flow of 0.35 ml min^{-1}. Elution started with a composition of 100 % solvent A (100% MilliQ RO-water with 0.1 % formic acid) hold for 2 min. Between 2 and 5 min, the composition changed to 50% A and 50% B (100% acetonitrile with 0.1% formic acid). Starting conditions were restored between minutes 5 and 5.1. Total runtime was 10 min. The mass spectrometer was operated with a capillary voltage of +3 kV, a desolvation temperature of 500°C, and a nitrogen flow of 1000 l min^{-1}. Cone gas flow was set at 50 l min^{-1} (nitrogen). Argon was used as collision gas.

For the wipe samples, recovery tests were performed for each of the antibiotics. The contamination per square centimeter is calculated based on 94% recovery and wipe efficiency for augmentin and cefotaxime, 90% for vancomycin, 87% for benzylpenicillin, 82% for ceftriaxone, 65% for meronem, and 21% for piperacillin as tested under laboratory conditions. The wipe sample results presented are corrected for recovery. Recovery tests for the air samples were not performed and 100% recovery is assumed. The detection limit is 1 ng ml^{-1} distilled water.

Statistical analysis

Contamination on the surfaces was compared between the conventional preparation techniques and the use of the CSTD for all antibiotics monitored on the three sites. Friedman's two-way analysis of variance by ranks was used (related samples and two-sided test). *P* values below 0.05 were considered as significantly different.

Results

The results of surface and environmental air contamination were compared between preparation with the conventional techniques and preparation with the CSTD.

Surface contamination

The results of surface contamination with antibiotics are presented in Tables 1–3 and more in detail in the online edition (Supplementary data, available at *Annals of Occupational Hygiene* online).

Hungary

The results show substantial spread of contamination with all antibiotics over all surfaces using the conventional needle/syringe preparation technique (Table 1). The contamination score is 88% (the score is 100% if all antibiotics were found on all surfaces). All surfaces were contaminated with vancomycin, ceftriaxone, and augmentin, and half of the surfaces were contaminated with meronem. Median levels of contamination vary between the surfaces and between the antibiotics (ceftriaxone > vancomycin > augmentin > meronem).

Table 1. Surface contamination with vancomycin (VAN), meronem (MER), ceftriaxone (CEF), and augmentin (AUG) in the Hungarian hospital (percentage of positive samples indicated).

Description of the surface	VAN–[a]	VAN+[a]	MER–	MER+	CEF–	CEF+	AUG–	AUG+	All 4–[b]	All 4+[b]
Preparation surfaces (*n* = 3)	100	100	100	0	100	67	100	0	100	42
Floors in front of preparation surfaces (*n* = 2)	100	100	0	0	100	0	100	0	75	25
Non-preparation surfaces (*n* = 3)	100	100	67	0	100	0	100	0	92	25
Floor in front drug storage cupboard (*n* = 1)	100	100	0	0	100	0	100	0	75	25
Floor aside bed patient (*n* = 1)	100	0	0	0	100	0	100	0	75	0
All surfaces (*n* = 10)	100	90	50	0	100	20	100	0	88	28
Contamination (ng cm^{-2})										
Min	0.4	<0.02	<0.03	<0.02	2	<0.01	0.1	<0.01	<0.03	<0.01
Max	56	0.6	3	<0.03	767	0.3	17	<0.02	767	0.6
Median	4	0.08	0.1	<0.03	7	<0.02	0.5	<0.02	2	<0.03
P value	0.002		0.025		0.002		0.002		<0.004	

[a] –, preparation according to standard preparation techniques; +, preparation with the CSTD.
[b]Total of four antibiotics.

After implementation of the CSTD, the overall median level of contamination for all antibiotics decreased significantly from 2 to <0.03 ng cm^{-2} ($P < 0.004$). The contamination score reduced to 28%. Vancomycin and to a lesser extent ceftriaxone were the only antibiotics detected and the contamination was just above the detection limit. Meronem and augmentin were not found.

Sweden

Using the conventional needle/syringe or needle/syringe/spike preparation technique, the results show substantial spread of contamination with all antibiotics on all surfaces (Table 2). The contamination score is 74%. All surfaces were contaminated with cefotaxime and piperacillin and almost all with benzylpenicillin and vancomycin. Median levels of contamination vary between the surfaces and between the antibiotics (piperacillin > cefotaxime > ceftriaxone > vancomycin >> benzylpenicillin > meronem).

After implementation of the CSTD, the overall median level of contamination for all antibiotics decreased significantly from 1 to 0.03 ng cm^{-2} ($P = 0.006$). The contamination score reduced to 50%. All surfaces were contaminated with at least one of the antibiotics. If calculated for each of the antibiotics, the decrease is significant for vancomycin, cefotaxime, piperacillin, and benzylpenicillin. No significant differences are observed for meronem and ceftriaxone. Both antibiotics were not frequently used, which is most probably the explanation why no significant differences were found. Contamination with ceftriaxone was most frequently observed. Median levels of contamination vary between the surfaces and between the antibiotics (ceftriaxone ~ piperacillin >> vancomycin ~ cefotaxime ~ meronem ~ benzylpenicillin).

Serbia

The results show substantial spread of contamination with all antibiotics over all surfaces using the conventional needle/syringe preparation technique (Table 3). The contamination score is 71%. All surfaces were contaminated with ceftriaxone and almost all with meronem. Median levels of contamination vary between the surfaces and between the antibiotics (piperacillin > ceftriaxone > meronem >> vancomycin).

After implementation of the CSTD, the overall median level of contamination or all antibiotics decreased significantly from 0.2 to <0.05 ng cm^{-2} ($P < 0.02$). The contamination score reduced to 23%. Most surfaces were contaminated with one of the antibiotics. If calculated for each of the antibiotics, the decrease is significant for meronem, ceftriaxone, and piperacillin. No significant difference is observed for vancomycin. Vancomycin was not frequently used, which could explain the very low contamination levels before and after the implementation of the CSTD. Contamination with ceftriaxone and vancomycin was most frequently observed. Median levels of contamination were the same for all antibiotics.

Environmental air contamination

Hungary

Using the conventional needle/syringe technique, vancomycin was found in personal air samples of all

Table 2. Surface contamination with vancomycin (VAN), meronem (MER), ceftriaxone (CEF), cefotaxime (CEFO), piperacillin (PIP), and benzylpenicillin (BEN) in the Swedish hospital (percentage of positive samples indicated).

Description of the surface	VAN–[a]	VAN+[a]	MER–	MER+	CEF–	CEF+	CEFO–	CEFO+	PIP–	PIP+	BEN–	BEN+	All 6 –[b]	All 6+[b]
Preparation surfaces ($n = 4$)	100	75	25	0	50	100	100	100	100	100	100	25	83	67
Floors in front preparation surfaces ($n = 4$)	100	100	50	0	100	100	100	50	100	50	100	25	88	54
Computer desks ($n = 2$)	0	0	0	50	50	50	100	0	100	50	50	0	50	25
Floors aside bed patient ($n = 2$)	50	50	0	0	0	50	100	50	100	50	50	0	50	33
All surfaces ($n = 12$)	75	67	25	8	58	83	100	58	100	67	83	17	74	50
Contamination (ng cm^{-2})														
Min	<0.02	<0.02	<0.03	<0.03	<0.02	<0.02	0.08	<0.02	0.4	<0.09	<0.02	<0.02	<0.02	<0.02
Max	106	0.7	66	0.03	16	6	171	4	176	169	7	0.1	176	169
Median	1	0.04	<0.03	<0.03	3	0.5	9	0.02	36	0.4	0.1	<0.02	1	0.03
P value	0.003		>0.05		>0.05		0.001		0.004		0.002		0.006	

[a] –, preparation according to standard preparation techniques; +, preparation with the CSTD.
[b]Total of six antibiotics.

Table 3. Surface contamination with vancomycin (VAN), meronem (MER), ceftriaxone (CEF), and piperacillin (PIP) in the Serbian hospital (percentage of positive samples indicated).

Description of the surface	VAN–[a]	VAN+[a]	MER–	MER+	CEF–	CEF+	PIP–	PIP+	All 4–[b]	All 4+[b]
Preparation surfaces (n = 6)	0	0	100	0	100	83	83	33	71	29
Floors in front preparation surfaces (n = 4)	100	100	75	0	100	0	25	0	75	25
Computer desk (n = 1)	0	0	0	0	100	0	0	0	25	0
Floor fridge (n = 1)	100	0	100	0	100	0	0	0	75	0
Floor aside bed patient (n = 1)	100	100	100	0	100	0	100	0	100	25
All surfaces (n = 13)	46	38	85	0	100	38	54	8	71	23
Contamination (ng cm^{-2})										
Min	<0.05	<0.04	<0.02	<0.02	0.06	<0.02	<0.02	<0.02	<0.02	<0.02
Max	0.08	0.02	6	<0.08	12	0.5	157	0.4	157	0.5
Median	<0.05	<0.05	0.5	<0.05	0.8	<0.05	2	<0.05	0.2	<0.05
P value	>0.05		0.001		0.0005		0.016		<0.02	

[a] –, preparation according to standard preparation techniques; +, preparation with the CSTD.
[b] Total of four antibiotics.

three nurses (0.6, 3, and 5 µg m^{-3}) and ceftriaxone was detected in personal air samples of two nurses (0.02 and 0.06 µg m^{-3}). After implementation of the CSTD, no antibiotics were detected in environmental air. Air was sucked for 290–463 min.

Sweden

Using the conventional needle/syringe or needle/syringe/spike preparation technique, vancomycin was detected in personal air samples of four nurses (0.01, 0.02, 0.03, and 0.19 µg m^{-3}) and piperacillin was found in a personal air sample of one nurse (0.05 µg m^{-3}) and above one of the preparation surfaces (0.02 µg m^{-3}). After implementation of the CSTD, only piperacillin was detected in environmental air above the same preparation surface (1.39 µg m^{-3}). Air was sucked for 118–670 min.

Serbia

None of the antibiotics were detected in personal air samples of the nurses, or above the preparation surfaces at any stage of the study. Air was sucked for 226–423 min.

Discussion

Over the last decades, many studies have been published showing adverse health effects in healthcare workers exposed to antineoplastic drugs (ISOPP, 2007a). To prevent exposure, extensive safety precautions have been implemented such as biological safety cabinets and isolators, clean room facilities and ventilated rooms, special mixing techniques for preparation and administration, CSTDs, robotic systems, and personal protective equipment (PPE) such as gloves, gowns, and masks. In addition, training in the handling of the vials and ampoules, for example equalization of the pressure in the vials by withdrawal of the air before adding the diluent, the covering of the puncture area with a swab, and the use of an ultrasonic plate to increase the rate of solution have all been shown to be effective in the handling of antineoplastic drugs (Easty *et al.*, 2015). All these measures have the common aim to offer maximum protection for healthcare workers handling these hazardous drugs.

Compared with the handling of antineoplastic drugs, the safety precautions and personal protective measures for handling antibiotics in hospitals are poor (ISOPP, 2007b; Easty *et al.*, 2015). Furthermore, in those where protection does exist, mostly only gloves are used. This is disturbing specifically as the number of preparations and administrations of antibiotics is substantially higher than for antineoplastic drugs, treatments are spread over more departments in hospitals, and consequently, more healthcare workers are involved in handling antibiotics than antineoplastic drugs. Thus, the focus on the potential hazards of the antibiotics should be given additional thought and caution to minimize exposure and subsequent hazards arising. One of the main exposure sites is surface contamination in preparation and administration areas.

The aim of our study was primarily focused on air contamination and surface contamination to measure the presence of antibiotics in the hospital environment to demonstrate the scope of contamination levels and spread that nurses and patients are exposed to.

The results show spread of contamination with antibiotics on all surfaces at all sites using the conventional preparation techniques. Most surfaces were contaminated with at least 75% of the drugs. As gloves were not used in two hospitals, it is unavoidable that the nurses' hands have been in contact with contaminated surfaces. This will result in drug uptake *via* their skin as observed in comparable working situations and tasks for hospital workers handling antineoplastic drugs (Fransman *et al.*, 2004, 2005). In addition, studies have shown that nurses have very high incidences of dermatitis that can facilitate uptake of drugs through the skin (Anderson and Meade, 2014; Kadivar and Belsito, 2015; Higgins *et al.*, 2016). The results also show that cleaning of the working environment was not effective in reducing contamination of the surfaces on a daily basis.

After implementation of the CSTD, a significant reduction of the contamination was observed for all antibiotics in the three hospitals except for meronem and ceftriaxone in the Swedish hospital, and for vancomycin in the Serbian hospital. For these antibiotics, no significant differences were found due to low and mostly undetectable levels of contamination before and after the implementation of the CSTD. This can be explained by low frequent use.

In 2011, a Swedish study performed in 16 hospitals published findings of antibiotic contamination of 12 antibiotics across 21 wards (Nygren and Lindahl, 2011). The results showed spill and leakage in all wards, with half of them in the high contamination levels (>0.5 ng cm^{-2}). Wards using a CSTD showed the lowest spill and leakage, whereas wards using open venting systems showed the highest spill and leakage.

Compared with the Swedish study, this study shows higher contamination levels on surfaces using the conventional preparation techniques and more or less the same levels of contamination using a CSTD. This study confirms the results of the Swedish study on a different range of antibiotics confirming the existence of widespread contamination of antibiotics across variable wards and drug types.

There are no published threshold limit values indicating what levels are considered safe for surface contamination of antibiotics. Thus, prevention of contamination is of great importance as skin contact with contaminated surfaces is expected to be a relevant exposure route, and sensitization *via* skin contact is considered an adverse health effect (Kim *et al.*, 2012; Marraccini *et al.*, 2013; Whitaker, 2016; Pinheiro *et al.*, 2018). Prevention is possible with a CSTD as demonstrated in this study. In addition, frequent cleaning is substantial; this can be done with soap and water, as well as donning PPE such as gloves. To further improve safety of the workers, one may, for example, consider centralized reconstitution in a controlled environment in the hospital pharmacy comparable to the reconstitution of antineoplastic drugs. In institutions in which this central preparation is not logistically possible, a good alternative could be the use of a CSTD as presented in this study. It is obvious that costs to healthcare facilities are a consideration so the cost of additional devices to the ward should be weighed compared with the reduction of occupational health expenditure.

Using the conventional preparation techniques, antibiotics were also detected in environmental air of nurses in the Hungarian and in the Swedish hospitals. Lacking respiratory protection, this exposes the nurses to antibiotics *via* inhalation. After implementation of the CSTD, none of the antibiotics were found in environmental air of the nurses. Piperacillin was detected in environmental air above one of the preparation surfaces in the Swedish hospital. Preparation of Piperacillin is considered to be complex as the vial has to be shaken thoroughly to dissolve the drug. This vigorous shaking may increase the release of small invisible droplets and can possibly explain why Piperacillin is extensively present on the surfaces and in environmental air.

Swedish authorities have established occupational exposure limits (OELs) for many chemicals in environmental air (Arbetsmiljöverket, 2015). In 2011, an OEL of 100 µg m^{-3} was established for penicillin as inhalable dust indicating that adverse health effects will be observed above this level. It was also indicated that penicillin is a sensitizing drug that may cause allergy and hypersensitivity by skin contact and inhalation.

In this study, vancomycin, ceftriaxone, and piperacillin were detected in environmental air. For vancomycin the concentrations were 0.01–5 µg m^{-3}, for ceftriaxone 0.02–0.06 µg m^{-3}, and for piperacillin 0.02–1.39 µg m^{-3}. These levels are far below the penicillin OEL. However, it should be noticed that the OEL was set for penicillin and not for vancomycin, ceftriaxone, and piperacillin. Piperacillin is a penicillin type of drug. One may use the penicillin OEL for comparison as more or less the same adverse health effects might be expected. But this is different for vancomycin and ceftriaxone that are non-penicillin type of antibiotics.

For respiratory allergens, the derivation and use of OELs are rather complex. Threshold levels below which workers will not get sensitized are hard to determine and it has been posed that any exposure, even if very small, entails some risk of sensitization (Topping, 2001; Health Council of the Netherlands, 2008). Once the sensitization reaction has taken place, any further exposure to the substance, even minimal amounts, may produce symptoms. OELs for local effects to the skin do not exist. Basically, the general rule should be to limit skin and respiratory exposure to allergens as much as possible.

Antimicrobial resistance and healthcare-associated infections are among the most serious public health problems, globally and in Europe. ECDC estimated that approximately 4 million patients acquire a healthcare-associated infection each year in all EU member states and that approximately 37 000 deaths directly result from these infections (ECDC, 2017). Long-term adverse health effects of daily exposure to small amounts of different antibiotics are unknown but might probably cause asthma and resistance to antibiotics for healthcare workers. In addition, one wonders whether there is an adverse health effect for patients treated in an environment contaminated with several antibiotics. Will consistent low levels of antibiotic contamination have an effect on the resident flora contributing to the development of bacterial resistance as has been observed in many hospital-acquired infections?

The study has a limitation, which is the fact that the intervention with the procedural affairs of the ward may have had an unconscious effect of raising awareness of the proposed problem thereby affecting the actions of the ward staff, which may in itself reduce the contamination rate. Second, it is obvious that direct measurements of exposure such as the air exposure measured in this study and dermal exposure by wiping or rinsing hands are more favorable than indirect measurements of possible dermal exposure by wipe sampling of surfaces. Follow-up studies are planned to measure skin and air exposure in combination with the analysis of some marker antibiotics or metabolites in urine reflecting exposure to all antibiotics. It should also be recognized that there are other sources of antibiotic contamination, for example the patient. All body fluids will contain trace amounts of the antibiotics administered. So, coughing, vomiting, urine, etc., will lead to contamination that cannot be controlled by a CSTD (Fransman *et al.*, 2004, 2005). Contamination on the outside of drug vials, as observed for antineoplastic drugs, is another source of contamination that could result in dermal exposure and cannot be controlled by a CSTD (Fleury-Souverain *et al.*, 2014; Power *et al.*, 2014).

The European Framework Directive on Safety and Health at Work 89/391/EEC requires that employers assess hazards and risks at the workplace and take measures to control exposure where needed (EU-OSHA, 1989). The Directive prescribes a hierarchy of control measures, which has been adopted by all member states. Preferably, measures to control exposure and prevent health effects caused by substances should be taken at source, for example by closed handling. If this is not possible, one may take technical or organizational measures or, finally, use personal protection.

This study can be considered a pilot study as there are no references for comparison. The main question that should be raised is, whether this is a local issue or rather a more widespread national or even international one. More research is needed to substantiate and confirm our study and to put focus on the adverse health effects in healthcare workers. We must remember, antibiotics are designed to cure patients with infectious diseases without concomitantly adding harm to healthcare workers. Optimum measures of ensuring their health should be implemented.

Conclusions

The results show environmental contamination with antibiotics both on surfaces and in the air following handling of the drugs, which as a result cause drug exposure of the nurses. As antibiotics have been shown to cause severe health effects, and safety levels are not set, it is important to strive for maximum safety for the nurses by preventing environmental contamination and keeping exposure as low as possible. Use of a CSTD has resulted in a substantial and significant reduction of environmental contamination and is a simple and effective tool in the prevention of exposure of healthcare workers handling these hazardous drugs.

Supplementary Data

Supplementary data are available at *Annals of Work Exposures and Health* online.

Funding

Financial support for this study was provided by Teva Medical Ltd.

Acknowledgements

Statistical support from Dr Rogier Donders, PhD (Biostatistician at the Department for Health Evidence, Radboud University Medical Centre, Nijmegen, the Netherlands), is kindly acknowledged. We kindly thank V'Iain Fenton-May for reviewing the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

Anderson SE, Meade BJ. (2014) Potential health effects associated with dermal exposure to occupational chemicals. *Environ Health Insights*; **8** (Suppl. 1): S51–S62.

Arbetsmiljöverket. (2015). Hygieniska gränsvärden. *AFS*; **2015**: 71 (in Swedish)

CDC. (2017). *Antibiotic use in the United States: progress and opportunities*. Atlanta, GA: US Department of Health and Human Services.

Cetinkya F, Ozturk AO, Kutluk G *et al*. (2007) Penicillin sensitivity among hospital nurses without a history of penicillin allergy. *J Adv Nurs*; **58**: 1455–61.

Easty AC, Coakley N, Cheng R *et al*. (2015) Safe handling of cytotoxics: guideline recommendations. *Curr Oncol*; **22**: e27–37.

ECDC. (2017) Surveillance of antimicrobial resistance in Europe 2016. Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Available at http://ecdc.europa.eu/sites/portal/files/documents/AMR-surveillance-Europe-2016.pdf. Accessed November 2017.

EU-OSHA. (1989) Directive 89/391/EEC. OSH framework directive of 12 June 1989 on the introduction of measures to encourage improvements in the safety and health of workers at work. https://osha.europa.eu/en/legislation/directives/the-osh-framework-directive/1

Fleury-Souverain S, Nussbaumer S, Mattiuzzo M *et al*. (2014) Determination of the external contamination and cross-contamination by cytotoxic drugs on the surfaces of vials available on the Swiss market. *J Oncol Pharm Pract*; **20**: 100–11.

Fransman W, Vermeulen R, Kromhout H. (2004) Occupational dermal exposure to cyclophosphamide in Dutch hospitals: a pilot study. *Ann Occup Hyg*; **48**: 237–44.

Fransman W, Vermeulen R, Kromhout H. (2005) Dermal exposure to cyclophosphamide in hospitals during preparation, nursing and cleaning activities. *Int Arch Occup Environ Health*; **78**: 403–12.

Gielen K, Goossens A. (2001) Occupational allergic contact dermatitis from drugs in healthcare workers. *Contact Dermat*; **45**: 273–9.

Health Council of the Netherlands. (2008) *Prevention of work-related airway allergies. Recommended occupational exposure limits and periodic screening*. Publication no. 2008/03. https://www.healthcouncil.nl/documents/advisory-reports/2008/03/13/prevention-of-work-related-airway-allergies

Higgins CL, Palmer AM, Cahill JL *et al*. (2016) Occupational skin disease among Australian healthcare workers: a retrospective analysis from an occupational dermatology clinic, 1993-2014. *Contact Dermat*; **75**: 213–22.

ISOPP. (2007a) ISOPP standards of practice. Safe handling of cytotoxics. Section 1. Introduction. *J Onc Pharm Pract*; **13** (Suppl.): S3–S6.

ISOPP. (2007b) ISOPP standards of practice. Safe handling of cytotoxics. Section 6. Facilities for sterile cytotoxic reconstitution and personal protective equipment. *J Onc Pharm Pract*; **13** (Suppl.): S17–S26.

Kadivar S, Belsito DV. (2015) Occupational dermatitis in health care workers evaluated for suspected allergic contact dermatitis. *Dermatitis*; **26**: 177–83.

Kim JE, Kim SH, Jin HJ *et al*. (2012) IgE sensitization to cephalosporins in health care workers. *Allergy Asthma Immunol Res*; **4**: 85–91.

Marraccini P, Digiesi G, Pignatti P *et al*. (2013) [A clinical case of occupational allergy to piperacilline. A novel diagnostic method: basophil activation test (BAT)]. *Med Lav*; **104**: 434–9.

Nygren O, Lindahl R. (2011) Screening of spill and leakage of antibiotics in hospital wards. *J ASTM Int*; **8**: 1–24.

Pinheiro V, Pestana C, Pinho A *et al*. (2018) Occupational allergic contact dermatitis caused by antibiotics in healthcare workers—relationship with non-immediate drug eruptions. *Contact Dermat*; **78**: 281–6.

Power LA, Sessink PJM, Gesy K *et al*. (2014) Hazardous drug residue on exterior vial surfaces: evaluation of a commercial manufacturing process. *Hosp Pharm*; **49**: 355–62.

Rudzki E, Rebandel P. (1985) Occupational contact urticaria from penicillin. *Contact Dermat*; **13**: 192.

Stenton SC, Dennis JH, Hendrick DJ. (1995) Occupational asthma due to ceftazidime. *Eur Respir J*; **8**: 1421–3.

Tadokoro K, Niimi N, Ohtoshi T *et al*. (1994) Cefotiam-induced IgE-mediated occupational contact anaphylaxis of nurses; case reports, RAST analysis, and a review of the literature. *Clin Exp Allergy*; **24**: 127–33.

Teva Medical Ltd. Available at http://www.tevadaptor.com

Topping M. (2001) Occupational exposure limits for chemicals. *Occup Environ Med*; **58**: 138–44.

Whitaker P. (2016) Occupational allergy to pharmaceutical products. *Curr Opin Allergy Clin Immunol*; **16**: 101–6.

Wilkinson AS, Allwood MC, Morris CP *et al*. (2018) Performance testing protocol for closed-system transfer devices used during pharmacy compounding and administration of hazardous drugs. *PLoS One*; **13**: e0205263.

Wilkinson A-S, Vestrup Caspersen V, Allwood M *et al*. (2014) Extension of the practical shelf life of hazardous drugs using a Closed-System Transfer Device (CSTD) as a container system enabling Drug Vial Optimization (DVO) for up to 28 days. *Eur J Oncol Pharm*; **8** (Suppl): S39.