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ORIGINAL ARTICLE

Improved control of nosocomial *Clostridium difficile* transmission by daily use of an oxygen-releasing sporicidal disinfectant

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Abstract

Contaminated surfaces contribute to transmission of *Clostridium difficile* in the healthcare setting. The aim of the investigation was to assess the effectiveness of an environmental disinfection protocol consisting of daily use of the oxygen-releasing sporocide Oxygenon® Liquid (Antiseptica) (i.e. new protocol) in preventing nosocomial CDI, compared to daily surface disinfection with a quaternary ammonium compound-based product plus the oxygen-releasing sporicide Perform® (Schülke+) for targeted sporicidal environmental disinfection (i.e. usual protocol). In a pre-post single group study with patients of two internal medicine wards (A and B) between February 2008 and May 2011, we compared the CDI rate between the pre- and post-intervention phase by calculating the post-pre phase CDI rate-difference and preventable fraction. In a pre-post parallel groups study from August 2009 until May 2011, the post-pre phase CDI rate-difference of the experimental group (internal medicine ward B) was compared with the post-pre CDI rate-difference of a control group (general surgery department) by calculating the between-group difference in the post-pre CDI rate-difference. In the pre-post single group study, among patients ≥ 70 year olds, the post-pre phase CDI rate reduction of 14.0/10,000 bed-days was significant, and preventable fraction of CDI was 60.2% (95%CI: 15.6%-82.8%). The results of the pre-post parallel groups study suggested a superiority of the new environmental disinfection protocol at borderline

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significance. The post-pre CDI rate-difference in the experimental group was greater than the post-pre rate-difference in the control group by 10.4/10,000 bed-days. Using a sporicide for daily surface decontamination may be superior to targeted sporicidal disinfection in preventing nosocomial transmission of *C. difficile*.

Key words: *Clostridium* infections and prevention and control; Cross infection and prevention and control; Disinfection and method

Introduction

Over the past decade, *C. difficile* infection (CDI) has evolved to become the main contributor to healthcare-associated infectious diarrhoea.[1] Contaminated surfaces contribute greatly to the transmission of *C. difficile* in the healthcare setting.[2-4]

Background

In Austrian hospitals, surfaces adjacent to patients and frequently touched objects are disinfected daily, primarily using quaternary ammonia-based products due to their excellent compatibility with most surface materials and inoffensive smell.[5] However, quaternary ammonium compounds demonstrate no effect against *C. difficile* spores. Oxygen-releasing and chlorine-based biocides have sporicidal activity (defined as spore reduction by at least 3 $\log_{10}$ steps) and are used for targeted sporicidal surface disinfection in the majority of European healthcare facilities.[6,7] Offensive smell and potential for harm can hinder continuous use of chlorine-based disinfectants.[8] Following European guidelines, Austrian hospitals use sporicides for surface disinfection in rooms where a case of CDI has occurred (so-called "targeted" sporicidal environmental disinfection).[9] The aim of our study was to assess the effect of daily use of the sporicide Oxygenon® Liquid (Antiseptica chem.-pharm. Produkte GmbH, Pulheim/Brauweiler, Germany) on the rate of nosocomial CDI compared to targeted sporicidal disinfection using the sporocide Perform® (Schülke+ GmbH, Norderstedt, Germany).

Materials and Methods

Study population and study designs

A hospital-based, pilot intervention study was conducted in a tertiary-care hospital in Salzburg, Austria. We applied a pre-post single group design in the internal medicine department (wards A and B) from February 2008 until May 2011. In order to adjust for possible interference of external circumstances, we additionally used a pre-post parallel groups design, including the internal medicine ward B as the experimental (intervention) group and the general surgery department as the control group from August 2009 until May 2011.[10] Referring to the annual hospital CDI rate in 2007 (5.2/10.000 bed-days), the internal medicine department represents a high CDI-incidence department (annual rate: 14.3/10,000 bed-days, ward A: 17.0; ward B: 10.7) and the department of general surgery a low CDI-incidence department (annual rate: 2.9/10,000 bed-days).

Pre-post single group design and environmental disinfection protocol

For the pre-post single group design, patients admitted to ward A (21 beds) from February 2008 until April 2009 or to ward B (24 beds) from August 2009 until June 2010 were included as study subjects of the pre-intervention phase (pre-phase). After introduction of the intervention (end of April 2009 in ward A; end of June 2010 in ward B), patients admitted to ward A from May 2009 until July 2010 and to ward B from July 2010 until May 2011 were included as study subjects of the post-intervention phase (post-phase). Patients admitted in the pre-phase and still hospitalised after introduction of the intervention were included accordingly to the period of stay in both phases.

In the pre-phase, internal medicine wards A and B underwent the environmental disinfection protocol as previously applied. In all patient rooms patients' adjacent surfaces and frequently touched objects, such as door handles and light switches, were disinfected daily using Terralin® protect (Schülke+), a quaternary ammonium compounds-based surface disinfectant. In the event of a laboratory confirmed case of CDI, the floor, patients' adjacent surfaces and frequently touched objects in the CDI patient room were disinfected daily using Perform®

(Schülke+) with the concentration-exposure time relationship as recommended by the manufacturer. This targeted sporicidal environmental disinfection was sustained until cessation of diarrhoea of the CDI patient(s). The disinfectant Perform® (Schülke+) is an oxygen-releasing product with pentapotassium-bis-(peroxymonosulphate) bis(sulphate) as the active compound. The manufacturer states that the agent achieves a 3-$\log_{10}$ level reduction of viable spores at 1% concentration and two hours contact time in the presence of organic matter (i.e. dirty conditions), tested according to DIN EN 13697. According to hospital staff, the sensory perception of the product is unpleasant.

During the post-phase, the internal medicine wards A and B underwent the experimental environmental disinfection protocol (i.e. new protocol). In all patients' rooms, patients' adjacent surfaces and frequently touched objects, and in CDI patient rooms, also the floors were disinfected daily using the sporicide Oxygenon® Liquid (Antiseptica) with the concentration-exposure time relationship as recommended. Oxygenon® Liquid is an oxygen-releasing product with the active compound potassiumperoxy-monosulphate-triplesalt. According to the manufacturer's statement, the agent achieves a 3 $\log_{10}$ reduction of viable spores at 3% concentration and 30 minutes contact time in the presence of organic matter, tested according to DIN EN 13704. The product is odourless and shows good material compatibility.

Pre-post parallel groups design and environmental disinfection protocol

For the Pre-post parallel groups design, patients admitted to the surgery department (70 beds) from August 2009 until May 2011 were included as the control group and patients admitted to the internal medicine ward B during the same period were included as the experimental group. The pre-phase was from August 2009 until June 2010 and the post-phase was from July 2010 until May 2011, following the introduction of the intervention at the end of June 2010 in ward B.

The experimental group (ward B) underwent the previous environmental disinfection protocol during the pre-phase and the new environmental disinfection protocol during the post-phase, as described above

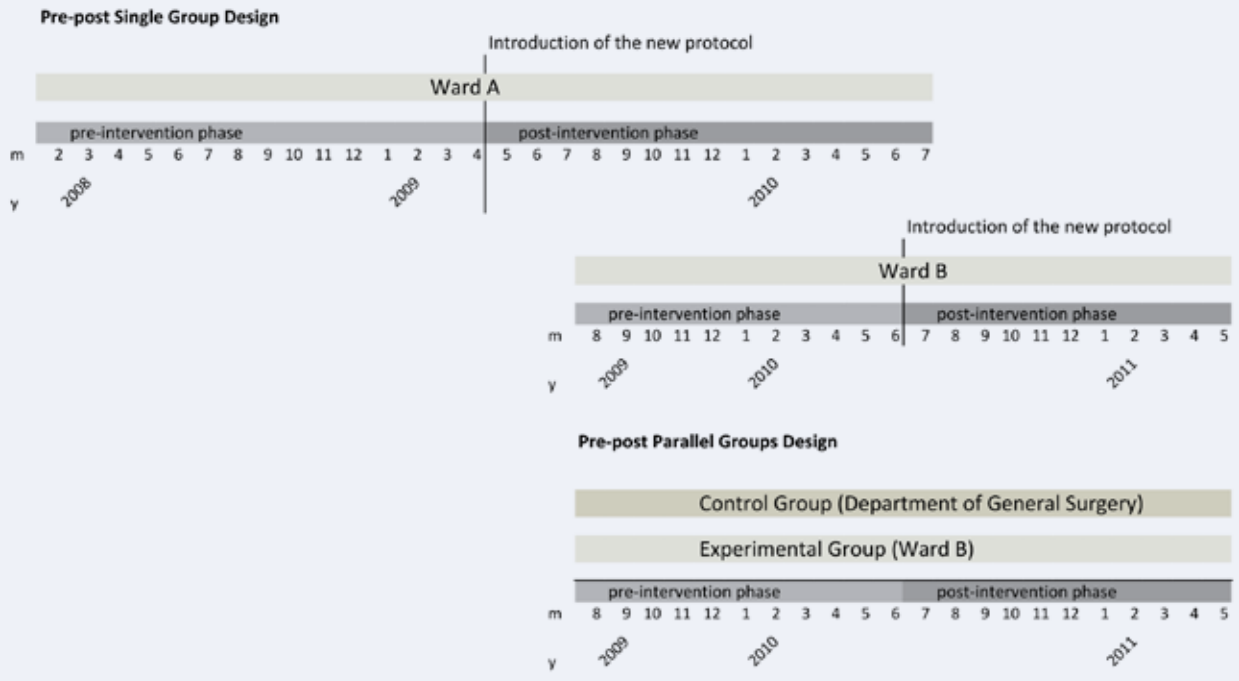

Figure 1. Study designs: pre-post single group design and pre-post parallel groups design; (m=month; y=year)

for the pre-post single group design. In the control group (department of general surgery), the previous environmental disinfection protocol was followed during both study phases (pre- and post-phase). Patients admitted with community-associated CDI were excluded from both studies. Figure 1 depicts the two study designs.

Any other control measures for nosocomial *C. difficile* transmission, including contact precautions (i.e. wearing of gloves and gowns during patient care, change of gloves and hand washing after each patient care), single room isolation or cohorting of CDI patient(s) provided with private toilets or bed pans (thermally disinfected after usage), nursing of CDI patients by designated staff, thorough cleaning and disinfection of the affected area after discharge and a restrictive antibiotic policy, were applied similarly in the pre- and post-phase and the experimental and control group.

Data collection and statistical analysis

We obtained information on study patient's age, comorbidity (based on ICD-10 codes), admission and discharge dates and occurrence of nosocomial CDI by reviewing medical charts and hospital discharge data. A case of nosocomial CDI was defined as the occurrence of (i) diarrhoea or toxic megacolon in a patient ≥ 48 hours following patient's admission with (ii) positive stool specimen for *C. difficile* toxin A or B or for toxigenic *C. difficile*. Comorbidities were categorized into low and moderate/severe comorbidity subgroups using the Charlson comorbidity index.[11]

In order to assess potential confounding on the effect measure, we compared between the pre- and post-phases of both studies the cumulative antibiotic use (number of defined daily doses (DDD) per 100 admissions), the prevalence of admission-CDI (number of community-associated (CA)-CDI per 1,000 admissions) and the prevalence of comorbidities associated with CDI-risk among the study subjects. Community-associated CDI was defined as occurrence of CDI at admission or within 48 hours after admission acquired in the community or in any other health care facility (CA-CDI). The measure of the study outcome,

Table I. Findings of the crude and age-stratified analyses in the pre-post parallel groups study; CDI rate difference/10.000 bed-days (bds), 95%CI

Study patients	**Pre-phase**	**Post-phase**		
	rate/10,000 bds	**rate/10,000 bds**	**Post-Pre rate difference /10.000 bds** (95%CI)	**P-value**
All patients			**Group-specific**	
Experimental group	16.19	6.85	-9.34 (-20.29, 1.61)	0.10
Control group	5.93	6.94	1.01 (-3.60, 5.61)	0.67
	Phase-specific	**Phase-specific**	**Between-group**	
Experimental-Control Rate Difference (95%CI)	**10.26 (0.58, 19.92)**	**-0.09 (-6.99, 6.81)**	**-10.35**	0.13*)
P-value	0.01	1.00		
Age group ≥60 yrs				
Experimental group	19.03	7.45	-11-58 (-24.99, 1.83)	0.10
Control	8.13	7.85	-0.28 (-6.81, 6.26)	0.94
***Experimental-Control Rate Difference** (95%CI)*	**10.90 (-1.24, 23.06)**	**-0.40 (-9.05, 8.25)**	**-11.30**	0.24*)
P-value	0.05	0.96		
Age group <60 yrs				
Experimental group	2.27	5.52	3.26 (-2.51, 9.03)	0.30
Control group	6.12	5.18	-0.94 (-16.64, 14.76)	0.92
***Experimental-Control Rate Difference** (95%CI)*	**3.85 (-8.54, 16.24)**	**-0.35 (-11.59, 10.89)**	**4.20**	0.54*)
P-value	0.47	1.00		

*) Statistical significance of the between-group difference in the post-pre CDI rate difference was tested using a Cox Regression model

nosocomial CDI, was the incidence rate of the disease per 10,000 bed-days.

In the pre-post parallel groups design, we compared the CDI rate of the internal medicine ward A and B between pre-phase and post-phase by calculating the post-pre phase CDI rate difference (RD), the rate ratio (RR) and the preventable fraction among the patients exposed to the intervention (PFe: 100 x [rate $_{\text{pre-phase}}$ – rate $_{\text{post-phase}}$] /rate $_{\text{pre-phase}}$). The statistical significance of the effect measures was tested using the Mid-P exact test.

In the pre-post parallel group study, we compared the CDI rate of the experimental group (internal medicine ward B) and of the control group (department of general surgery) between the pre- and post-phase by calculating the group-specific post-pre rate differences (i.e. within-group comparison), the phase-specific experimental-control rate differences (i.e. between-group comparison) and the between-group difference in the post-pre rate difference. In order to adjust for the pre-phase rate difference between experimental and control group, and for the pre-post phase difference in the control group we run a Cox regression including the covariates study phase (pre/post) and study group (experimental/control), and an interaction term between these two. Age was treated as a dichotomous variable determined by the median age of the study patients. In both studies we performed stratified analyses by age based on the median age of each study population. All analyses were performed using Stata version 13 (StataCorp, College Station, TX).

Microbiology

Stool specimens obtained from patients who developed diarrhoea ≥ 48 hours after admission were tested for *C. difficile* toxins A and B using enzyme linked immunoassay (RIDASCREEN Clostridium difficile Toxin A/B; R-Biopharm AG, Darmstadt, Germany) and cultured for toxigenic *C. difficile*.

Results

Study population

In the pre-post single group design, a total of 4,214 patients admitted to the internal medicine wards A and B from February 2008 until May 2011 were included; 2,084 patients during the pre-phase and 2,130 during the post-phase (ward A pre-phase: 1,268; ward A post-phase: 1,231; ward B pre-phase: 816; ward B post-phase: 899). Of the study subjects 49.3% (2,079/4,214) were 70 years or older (median age: 70 years; interquartile range, IQR: 54-85 years). Underlying diseases and comorbidity severity were not found to be associated with CDI. Age ≥ 70 years was identified as an independent risk factor for acquiring CDI among the total pre-post single group study patients.

Study patients of the pre-phase and post-phase did not differ significantly in age and in the prevalence of comorbidities associated with increased CDI risk (i.e. chronic renal disease, inflammatory bowel diseases and malignancy). There was no significant difference found in the prevalence of CA-CDI between the two study-phases (11.2 CA-CDI/1,000 pre-phase admissions; post-phase: 12.5 CA-CDI/ post-phase 1,000 admissions). The cumulative antibiotic exposure was significantly lower in the pre-phase than in the post-phase (220.8 DDD/100 pre-phase admissions; 248.6 DDD/100 post-phase admissions; $p<0.01$).

In the pre-post parallel groups design, a total of 8,914 patients of the general surgery department were included into the control group (pre-phase: 4,427; post-phase: 4,487) and 1,715 patients of internal medicine ward B were included in the experimental group (pre-phase: 816; post-phase: 899). The median age was 61 years (IQR: 45-73 years).

The pre- and post-phase of the experimental group and the control group did not significantly differ in the prevalence of CA-CDI and in the total number of DDD per 100 admissions. The study subjects of the pre-phase and post-phase were similar in age and comorbidities associated with CDI in the experimental group and likewise, in the control group.

Intervention effect

Pre-post single group study

We observed a CDI rate reduction of 5.7/10,000 bed-days (95CI%: -12.4, 0.9/10,000) from the pre-phase to the post-phase at a significance level of 10%. When stratified by age, among the ≥ 70 years old, the CDI rate reduction of 14.0/10,000 bed-days (95%CI: -24.4, -3.7/10,000) between the pre- and post-phase was

significant (p=0.01); the rate ratio was 0.4 (95%CI: 0.2, 0.8) and the prevented fraction of CDI among patients of the post-phase attributable to the intervention was 60.2% (95%CI: 15.6%, 82.8%). Similar findings, at borderline significance, were observed when stratified by the two wards (ward A and B) and by age (according to the median age of 70 years). Among study patients ≥ 70 years old, the rate ratio was 0.4 (95%CI: 0.2, 1.1; p=0.05) in ward A and 0.3 (95%CI: 0.1- 1.3; p=0.09) in ward B. Among patients less than 70 years old, the CDI rates did not differ significantly between pre- and post-phase.

Pre-post parallel groups study

Univariate Analyses

Group-specific post-pre difference (i.e. within-group comparison): The CDI rate of the control group remained stable between the pre-phase and post-phase (control post-pre difference: 1.0/10.000 bed-days; p=0.67). In the experimental group, a CDI rate reduction was observed from the pre-phase to the post-phase at a significance level of 10% (experimental post-pre difference: -9.3/10.000 bed-days). Results of the stratified analyses by age (≥ 60/< 60 years; according to the median age of 60 years) are shown in table I.

Phase-specific experimental-control difference (i.e. between-group comparison): In the pre-phase, the CDI rate of the experimental group was significantly higher than the CDI rate of the control group (pre-phase experimental-control difference: 10.3/10.000 bed-days; p=0.01). In the post-phase, the CDI rate was no longer significantly different between the two study groups (post-phase experimental-control difference: -0.09/10.000 bed-days; p=1.00).

Between-group difference in the post-pre difference: The post-pre CDI-rate difference in the experimental group was greater than the post-pre CDI-rate difference in the control group by 10.4/10,000 bed-days. Among study patients ≥ 60 years old, the between-group difference in the post-pre CDI rate differences was 11.3/10,000 bed-days (Table I).

Multivariate Analyses

Findings of the Cox regression analysis supported the results of the univariate analysis, adjusted for the baseline difference in the CDI rates between the experimental group and control group (pre-phase experimental-control HR: 2.21 95%CI: 1.02, 4.80; p=0.05). In the post-phase, the CDI rate was no longer significantly different between the experimental group and control group (post-phase experimental-control

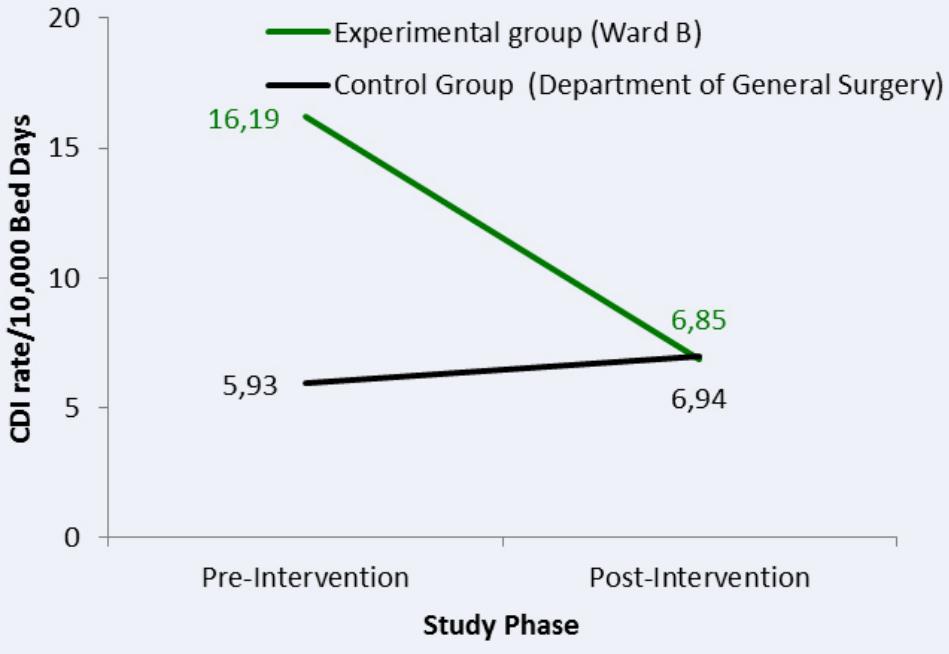

Figure 2. Findings of the pre-post parallel groups study; CDI rate difference/10.000 bed-days (bds)

HR: 0.84; 95%CI: 0.31, 2.29; p=0.73) since the CDI rate of the experimental group decreased from the pre-phase to the post-phase, (experimental post-pre phase HR: 0.45; 95%CI: 0.16, 1.28; p=0.13) and the CDI rate of the control group remained steady between the two study phases (control post-pre phase HR: 1.19; 95%CI: 0.58, 2.43; p=0.64). The between-group difference in the post-pre CDI rate difference was at borderline significance (p=0.13). Similar results were found among patients ≥ 60 (data not shown).

Discussion

Direct contact with CDI patients is considered the major pathway for acquisition of *C. difficile* onto healthcare worker hands with subsequent transmission to other patients.[15] Glove use in CDI patient rooms has proven to decrease the risk of *C. difficile* transmission by preventing the contamination of healthcare worker hands.[16] Strong evidence also underscores the involvement of contaminated hospital surfaces and medical equipment in the transmission of *C. difficile*.[17] To prevent environmental surface-mediated transmission, professional societies recommend daily disinfection of patients' adjacent surfaces and frequently touched objects in CDI patient rooms using sporicidal agents.[9,18,19] In contrast to oxygen-releasing based sporicidal wipe disinfectants, the effectiveness of chlorine-based agents for sporicidal disinfection in medical environments has been established in several studies.[19-21] However, the use of chlorine-based disinfectants is associated with health and safety concerns and material compatibility. Using a pre-post single group design and a pre-post parallel groups design, we compared two environmental disinfection protocols with respect to their effectiveness in reducing the nosocomial CDI rate. The previous disinfection protocol of the study site consisted of daily use of a quaternary ammonium-based disinfectant in all patient rooms plus targeted sporicidal disinfection with the oxygen-releasing sporicide Perform® (Schülke+) in CDI patient rooms; the experimental protocol comprised of the daily use of the oxygen-releasing sporocide Oxygenon® Liquid (Antiseptica) in all patient rooms, regardless of CDI occurrence. Both disinfectants have similar sporicidal efficacy, according to laboratory testing data provided by the manufacturers.

The findings of the pre-post single group study suggested a significant superiority among patients ≥ 70 years of daily environmental disinfection using the sporicide Oxygenon® Liquid (Antiseptica) compared to targeted sporicidal disinfection. Findings of the pre-post parallel groups study indicated the superiority of the experimental disinfection protocol at borderline significance. We observed the post-pre CDI-rate reduction in the experimental group by 10.4/10,000 bed-days greater, as compared with the post-pre CDI-rate reduction in the control group.

Steevens *et al.* observed that the cumulative dose, number, and duration of antibiotics were independently associated with the development of CDI, with higher levels of exposure corresponding to greater risk.[22] In our single group study, the cumulative antibiotic exposure per study phase given by the total number of defined daily dose per 100 admissions was greater during the post-phase than during the pre-phase. This could have led to a higher CDI rate among the post-phase study subjects of the single group study and in an underestimation of the true magnitude of CDI-rate reduction due to the new disinfection protocol. It would explain finding the superiority of this experimental measure only among the high CDI-risk group (≥ 70 years old). In the parallel groups study, the supporting findings at borderline significance could be explained by the insufficient study power due to a too small study sample size.

The superiority of daily sporicidal environmental disinfection compared with targeted disinfection in preventing nosocomial transmission of *C. difficile* could be explained by the continuous lowering of this environmental contamination with *C. difficile*, which is caused by *C. difficile* excreting patients other than the diarrhoeal CDI patients. Sethi *et al.* found patients continuing to shed *C. difficile* following diarrhoea resolution.[23] Mutters *et al.* and McFarland *et al.* demonstrated that patients asymptomatically colonized with *C. difficile* play an important role in sustaining transmission in the hospital setting.[24,25]

One could argue that using the CDI rate instead of the prevalence of *C. difficile* environmental contamination as measure of the study outcome is a potential limitation of our studies because controlling for all risk

factors of CDI when testing a new disinfection protocol is nearly impossible. However, quantitative detection of environmental *C. difficile* contamination by culture- or non-culture-based methods is labor-intensive.[24,26,27] For our studies, an extensive sampling covering representative surfaces in all 115 patient rooms of the study site during the pre- and post-phases would have been required to reliably measure differences in *C. difficile* counts between the intervention site and non-intervention site. Furthermore, it is still unclear to which extent a reduction of environmental *C. difficile* is effective in reducing *C. difficile* transmission and infection.[28]

Strength of our studies was having information collected on conditions relevant to the risk of nosocomial *C. difficile* transmission during the pre- and post-phase. First, the prevalence of community-associated CDI was similar in the pre-phase and post-phase, suggesting a comparable importation of *C. difficile* into the environment of the study site during both study phases.[29] Secondly, the density of environmental contamination also increases due to admission of patients colonized with *C. difficile*.[30, 31] Admission screening for asymptomatic colonisation is not routinely performed in Austrian hospitals. But we can assume a similar admission prevalence of *C. difficile* carriage for the pre-phase and post-phase because underlying diseases strongly associated with colonisation, such as diabetes mellitus, renal disease, intestinal disease and current malignancy, did not differ significantly between the pre- and post-phase study subjects.[32-35] Finally, *C. difficile* transmission control measures, other than the environmental disinfection protocols under study, were equally executed in the pre- and post-phase, as indicated by nursing records.

User acceptability of disinfection protocols for medical environments is a key issue for sustaining an effective implementation of environmental disinfection.[36,37,38] High compliance with the new disinfection protocol is likely to be sustained by the lack of procedural change needed in the case of CDI occurrence, the short disinfectant exposure time and the lack of unpleasant odour of the sporocide Oxygenon® Liquid (Antiseptica). Our findings warrant the conclusion that using an oxygen-releasing sporicide for daily surface decontamination might be superior to targeted sporicidal disinfection in preventing nosocomial CDI.

Transparency Declaration

The authors declare no conflicts of interest. The study was funded by the Paracelsus Medical University Salzburg and the Austrian Agency for Health and Food Safety. There was no funding from the industry.

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