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Original article

Controlling the hospital aquatic reservoir of multidrug-resistant organisms: a cross-sectional study followed by a nested randomized trial of sink decontamination

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A B S T R A C T

Objectives: The hospital water environment is an important reservoir of multidrug-resistant organisms (MDROs) and presents a risk for patient safety. We assessed the effectiveness of thermal and chemical interventions on sinks contaminated with MDRO in the hospital setting.
Methods: We conducted a cross-sectional assessment of MDRO contamination of sinks and toilets in 26 clinical wards of a tertiary care hospital. MDRO-contaminated sink traps were then replaced and randomized (1:1:1) to receive chemical (sodium hypochlorite), thermal disinfection (steam), or no intervention. Interventions were repeated weekly for 4 weeks. Sinks were resampled 7 days after the last intervention. The primary outcome was the proportion of decontaminated sinks. MDROs of interest were extended spectrum beta-lactamase (ESBL) producing and carbapenemase-producing *Enterobacterales,* and non-fermentative Gram-negative bacilli.
Results: In the cross-sectional assessment, at least one MDRO was identified in 258 (36%) of the 748 samples and in 91 (47%) of the 192 water sources. In total, 57 (42%) of the 137 sinks and 34 (62%) of the 55 toilets were contaminated with 137 different MDROs. The most common MDRO were ESBL *Enterobacterales* (69%, 95/137), followed by Verona Integron-Borne Metallo-β-Lactamase (VIM) carbapenemase producing *Pseudomonas aeruginosa* (9%, 12/137) and *Citrobacter spp.* (6%, 5/137). In the nested randomized trial, five of the 16 sinks (31%) in the chemical disinfection group were decontaminated, compared with 8 of 18 (44%) in the control group (OR 0.58; 95% CI, 0.14–2.32) and 9 of 17 (53%) in the thermal disinfection group (OR 1.40; 95% CI, 0.37–5.32).
Discussion: Our study failed to demonstrate an added benefit of repeated chemical or thermal disinfection, beyond changing sink traps, in the MDRO decontamination of sinks. Routine chlorine-based disinfection of sinks may need to be reconsidered. **Gaud Catho, Clin Microbiol Infect 2024;30:1049**

Introduction

The water environment in healthcare settings (which includes faucets, sinks toilets and plumbing infrastructure) favours microbial colonization [1]. Eradication of reservoirs of multidrug-resistant organisms (MDROs) from the hospital water environment is challenging; several mitigation strategies have been reported with varying degrees of success in ending outbreaks of MDRO infections among patients and little effect on eradicating MDROs from the water environment [2]. The removal of sinks and implementation of water-free care in intensive care units (ICUs) has proven to be successful [3,4]. However, this strategy is not feasible

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in non-ICU wards and alternative solutions are urgently needed to reduce the transmission risk for patients.

We therefore conducted a cross-sectional study followed by a nested randomized trial, with the aims of (a) quantifying the burden of MDROs in the water environment of a tertiary care hospital to measure the potential exposure risk for patients and (b) assessing the added impact of two sink disinfection methods (chemical and thermal) on MDRO decontamination of sinks after systematic sink trap replacement.

Methods

Setting

This study was conducted between 12 July 2021 and 28 February 2022 at a tertiary care hospital located in Geneva, Switzerland.

Study design

This study had two parts (Fig. 1). First, we performed a cross-sectional assessment of the extent of MDRO contamination of sinks and toilets in all participating clinical wards ($n = 26$). We then conducted a randomized, controlled superiority trial among a random selection of sinks contaminated with at least one MDRO.

Inclusion criteria

All 26 clinical wards that provide inpatient care in the oldest building of the hospital were included in the cross-sectional study. This included ten medical wards, seven surgical wards, eight private mixed wards (medico-surgical), and one ICU (Table 1 and Table S1b). All wards except the ICU were equipped with sinks located in patient rooms. Since 2020, the ICU ward provides water-free care following an outbreak of VIM-producing *Pseudomonas aeruginosa* [4], but some preparatory sinks remain in non-patient areas of the ICU and were included in the sampling scheme of the current study. Descriptions of the sampling strategy used for the included wards are in the Supplementary material.

Interventions and procedures

Among all MDRO-contaminated sinks identified through the cross-sectional study, a subset was selected for a nested randomized trial. The sink traps of all sinks in the nested trial were replaced by new, identical sink traps. Thereafter, each of the sinks was randomized on a 1:1:1 ratio to one of the two intervention arms (chemical or thermal disinfection, further details are provided in the Supplementary material) or to the control arm. The randomization sequence of sinks from each ward was computer-generated by a statistician who was not directly involved in the study.

The chemical disinfection intervention consisted of the application of a liquid disinfectant containing 2.5% chlorine (1 L water containing 2.5% of sodium hypochlorine) in the sink trap, which was closed for 15 minutes to allow the liquid to remain in contact with the drain line. The thermal disinfection intervention consisted of applying a steam generator to the sink drain line for 15 minutes. In the control arm, no intervention occurred following the initial replacement of the sink trap.

Each intervention was performed once a week for 4 weeks. Interventions were performed by members of the research team with appropriate personal protective equipment. Swabs from each of the sinks were collected 7 days after the last intervention, and repeated again three months after the start of the intervention.

Environmental sampling

For both the cross-sectional analysis and the randomized trial, we used sterile swabs for environmental investigations (SRK® Hygiene Monitoring Kit − Single Wrapping containing one regular FLOQSwab in a tube with 1 mL SRK® premoistening solution). Four samples from different locations were collected on each sink (further details are provided in the Supplementary material).
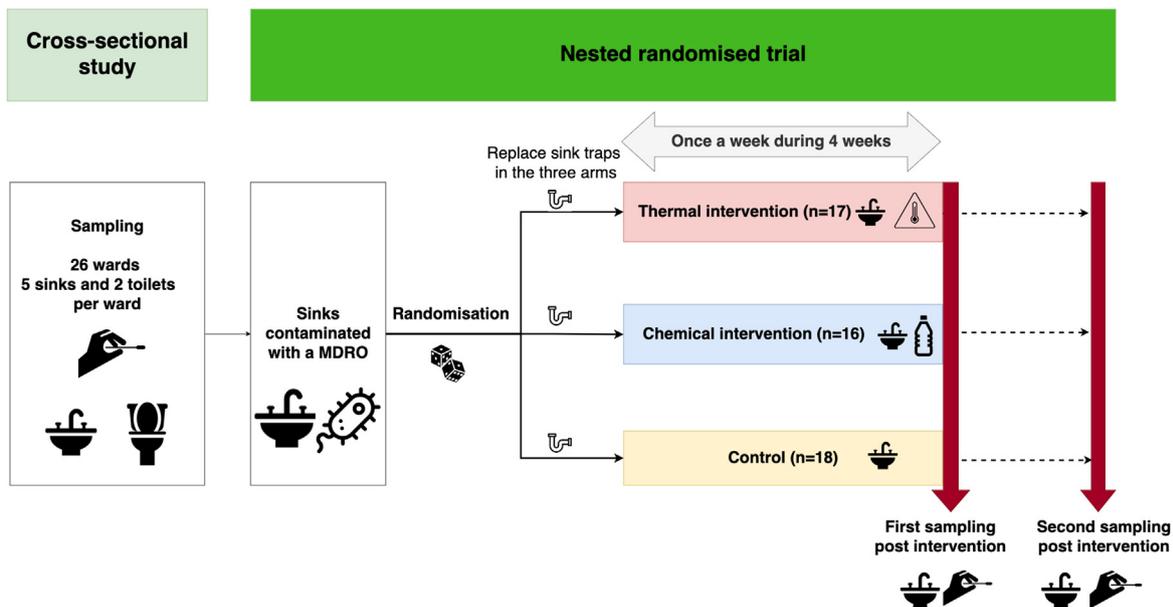

Fig. 1. Flowchart of the cross-sectional study and the nested randomized trial.

Table 1
Characteristics of the sinks and toilets of the cross-sectional study

		Sinks N = 137 (%)	Toilets N = 55 (%)
MDRO contamination[a]		57	34
Type of ward	Surgical	18/57 (31.6)	13/34 (38.2)
	Medical	28/57 (49.1)	16/34 (47.0)
	Mixed (medico-surgical)	7/57 (12.3)	3/34 (8.8)
	Intensive care unit	4/57 (7.0)	2/34 (5.8)
Location of the positive samples in the sinks	Strainer of the sink bowl	17/57 (29.8)	—
	Tailpipe of the drain	44/57 (77.2)	—
	Horizontal trap arm	44/57 (77.2)	—
	Water in the P-trap	41/47 (71.9)	—
Without MDRO contamination		80	21
Type of ward	Surgical	17/80 (21.5)	7/21 (33.3)
	Medical	27/80 (33.7)	0/21 (0)
	Mixed (medico-surgical)	33/80 (42.2)	13/21 (61.9)
	Intensive care unit	3/80 (3.7)	1/21 (4.8)

MDRO, multidrug-resistant organism.

[a] MDRO contamination defined as at least one positive sample for a MDRO from that sink or toilet.

Microbiological analysis

Environmental samples were processed by the bacteriology laboratory of the hospital, using the procedure described in the Supplementary material. The same bacterial species with similar resistance profiles isolated from a single water source were aggregated (e.g. two *Klebsiella pneumonia* strains producing New Delhi metallo-beta-lactamase (NDM) carbapenemase isolated in different samples in the same sink were counted only once).

Outcomes

For the cross-sectional analysis, the primary outcome was the proportion of water sources (sinks and toilets) in all participating wards that were contaminated with at least one MDRO, defined as at least one positive sample for an MDRO from that sink or toilet. The following pathogens were considered as MDROs: Extended spectrum betalactamase (ESBL) or carbapenemase-producing *Enterobacterales* (CPE) and carbapenemase-producing, non-fermentative Gram-negative bacilli such as *Acinetobacter spp.*, *Pseudomonas spp.*, and *Achromobacter spp.* Secondary outcomes of the cross-sectional analysis included the relative distribution of MDROs in sinks and toilets, distribution of contaminated sinks and toilets by ward type (surgical, medical, mixed, and ICU) and distribution of contaminated sinks by sample locations within the sinks.

For the randomized trial, the primary outcome was the proportion of sinks that were decontaminated in each arm 7 days after the last disinfection intervention. A sink was considered decontaminated if there was no MDRO detection on any of the post-intervention samples collected from the sink. The secondary outcome was the proportion of sinks that remained decontaminated in each arm at 3 months following the start of the intervention period. The number of patients detected as newly colonised by an MDRO in any of the included ward was also collected (details in Supplementary material).

Statistical analysis

We compared the outcomes of the three arms of the nested randomized trial using univariable and multivariable logistic regression analyses, adjusting firstly for type of ward (surgical wards versus others) and secondly for specific sampling location within the sink (i.e. strainer of the sink bowl versus the three other locations). The purpose of multivariable analyses was to adjust for two factors (i.e. type of ward and sampling location of the sink) which were not taken into account during the randomization

process. Independent variables (i.e. type of ward and sampling location of the sink) were selected as clinically relevant adjustment variables. The Holm–Bonferroni method was used to account for multiple testing of the primary outcome in the two superiority, pairwise comparisons. Therefore, a p value of <0.025 was considered statistically significant.

All analyses were performed blinded to the intervention allocation. Statistical analyses were performed using R statistical software (R Foundation for Statistical Computing, version 4.0.2).

Sample size calculation

We expected no effect in the reduction of MDRO contamination in the control arm. For both the chemical and thermal disinfection intervention arms, however, a minimally relevant effect was considered as a 50% reduction in the MDRO contamination of the sinks seven days after the last disinfection intervention. Assuming a false positive rate of 2.5% and accounting for multiple comparisons using a Bonferroni correction, 51 contaminated sinks needed to be included in the nested randomized trial (i.e. 17 in each arm) with 90% power to detect a statistically significant reduction in MDRO contamination. Assuming a sink baseline contamination rate of 40%, 127 sinks needed to be included in the cross-sectional study.

Ethical considerations

The collection and analysis of environmental samples did not require approval by an Ethics Committee.

Results

Cross-sectional study

From 12 July 2021 to 29 July 2021, a total of 713 samples were collected (548 from sinks and 165 from toilets). At least one MDRO was identified in 258 (36.2%) samples and in 91 (47.4%) of the 192 water sources: 41.6% (57/137) of the sinks and 61.8% (34/55) of the toilets (Table 1). In total, 137 different MDROs were identified in 91 water sources (57 sinks; 34 toilets, Table S1). All species combined, ESBL-producing bacteria were the most common (97/137; 70.8%), followed by VIM-producing bacteria (20/137; 14.6%) and OXA-48-producing bacteria (12/137; 8.8%). At least one MDRO was found from water sources in all but two clinical wards.

The distribution of MDROs varied between the water sources (sinks versus toilets). Among the 57 contaminated sinks, the most common MDRO isolated were ESBL-producing *Enterobacterales*

(59/81; 58.0%), followed by VIM-producing *P. aeruginosa* and *Citrobacter spp.* (Fig. S2 and Table S1). Among the 34 contaminated toilets, the most common MDRO isolated were ESBL-producing *Enterobacterales*, followed by OXA-48-producing *Citrobacter spp.* and *Klebsiella spp.* (Fig. S2 and Table S1).

Across the different locations of the sinks that were sampled (Fig. 1), the frequency of MDROs was similar (between 41 [71.9%] and 44 [77.2%] of the 57 positive sinks), except for the strainer of the sink bowl, from which samples from only 17 (29.8%) of the 57 sinks were positive (Table 1).

Randomized trial

Of the 57 sinks contaminated with at least one MDRO, 51 were randomized and included in the nested randomized trial: 16 received chemical disinfection, 17 received thermal disinfection, and 18 were in the control arm (Fig. 1). The baseline contamination of the 51 sinks by ESBL- and carbapenemase-producing Gram-negative bacteria were similar across the three groups (Table S2).

Seven days after the last disinfection intervention, 5 of 16 sinks (31.2%) in the chemical disinfection arm (OR 0.58; 95% CI, 0.14—2.32) and 9 of 17 sinks (52.9%) in the thermal intervention disinfection arm (OR 1.40; 95% CI, 0.37—5.32) were decontaminated. In the control arm, 8 of 18 sinks (44.4%) were decontaminated (Table 2). Multivariable logistic regression analysis adjusted by type of ward or by sampling location within the sink, showed no significant difference in the primary outcome (Fig. 2). No missing data were observed for this randomized controlled study.

Three months after the start of the intervention period, four of the 16 sinks (25%) in the chemical disinfection arm (OR 0.43; 95% CI, 0.07—2.21) and eight of the 17 sinks (47.1%) in the thermal disinfection arm (OR 1.11; 95% CI, 0.24—5.11) remained decontaminated. In the control arm, 8 of 18 sinks (44.4%) remained free of MDRO contamination (Table S3).

The number of patients detected with an MDRO acquisition in any of the included wards during the study period is provided in the Supplementary materials (Table S4).

Discussion

In this study of the water environment of a tertiary care hospital, we found a high proportion of sinks and toilets in clinical wards to be contaminated with MDRO. In a nested randomized trial of sinks contaminated with MDRO, we did not observe any added effect of either chemical disinfection or thermal disinfection, beyond sink trap replacement alone, in achieving sink decontamination by MDROs.

Our findings from the cross-sectional assessment are consistent with those of a recent study which showed that, compared with other environmental and frequently touched surfaces in hospitals, sink drains have the highest level of MDRO contamination [5]. Our study revealed MDROs in nearly all clinical ward water sources, with toilets notably contaminated. Sinks, prone to rapid biofilm formation [1], pose a transmission risk for MDRO acquisition, and healthcare-associated infections, especially in ICUs [2]. The potential for MDRO transmission through sink and toilet splashes is concerning, yet the dynamics are poorly understood. Comprehensive longitudinal studies incorporating regular environmental and patient sampling, along with molecular analysis, are crucial for a deeper understanding of these transmission mechanisms and developing effective control strategies.

Our finding that there was no added impact of either chemical disinfection or thermal disinfection, beyond sink trap replacement alone, in decontamination of MDRO challenges routine environmental cleaning practices. The use of chlorine for the cleaning of sink drains is common practice worldwide, particularly in ICUs. A

Table 2
Results of sampling of the 51 sinks included in the nested randomized trial 7 days after the last disinfection intervention

	Control N = 18 (%)	Chemical intervention n = 16 (%)	Thermal intervention n = 17 (%)
Sink contamination post-intervention[a]	10/18 (55.6)	11/16 (68.8)	8/17 (47.1)
ESBL-producing bacteria	9/10 (90.0)	10/11 (90.9)	6/8 (75.0)
Carbapenemase-producing bacteria	4/10 (40.0)	5/11 (45.5)	4/8 (50.0)
Sink contamination by bacteria[a]			
ESBL-producing *Citrobacter* spp.	2/10 (20.0)	2/11 (18.2)	0/8 (0)
ESBL-producing *Enterobacter cloacae*	3/10 (30.0)	2/11 (18.2)	1/8 (12.5)
ESBL-producing *Escherichia coli*	1/10 (10.0)	2/11 (18.2)	0/8 (0)
ESBL-producing *Klebsiella* spp.	3/10 (30.0)	4/11 (36.4)	5/8 (62.5)
VIM-producing *Citrobacter* spp.	0/10 (0)	0/11 (0)	0/8 (0)
VIM-producing *Pseudomonas aeruginosa*	4/10 (40.0)	3/11 (27.3)	2/8 (25.0)
OXA-48-producing *Citrobacter* spp.	0/10 (0)	1/11 (9.1)	0/8 (0)
OXA-48-producing *Klebsiella* spp.	0/10 (0)	1/11 (9.1)	2/8 (25.0)
Type of ward			
Intensive care unit	0/10 (0)	0/11 (0)	1/8 (12.5)
Medical	5/10 (50.0)	7/11 (63.6)	3/8 (37.5)
Mixed (medico-surgical)	3/10 (30.0)	2/11 (18.2)	1/8 (12.5)
Surgical	2/10 (20.0)	2/11 (18.2)	3/8 (37.5)
Location of the positive samples in the sinks			
Strainer of the sink bowl	3/10 (30.0)	6/11 (54.5)	0/8 (0)
Tailpipe of the drain	6/10 (60.0)	8/11 (72.7)	3/8 (37.5)
Horizontal trap arm	9/10 (90.0)	9/11 (81.8)	7/8 (87.5)
Water in the P-trap	5/10 (50.0)	7/11 (63.6)	3/8 (37.5)

ESBL, extended spectrum betalactamase.
[a] Some cultures had polymicrobial growth.

survey of 73 French ICUs showed that while one third of the ICUs routinely disinfect sink drains by daily bleaching, 25% of these remained contaminated [6]. A systematic review of outbreak reports of CPE associated with the hospital water environment found that, of the ten studies that implemented sink drain bleaching, only two described CPE elimination from the environment; two studies only reported halting the outbreak among patients, and the remaining six reported no effect [2]. The fact that several sinks were decontaminated in each arm after replacing the sink traps highlight the positive impact of removing the biofilm on this location of the sinks and suggest that routine replacement of sink traps could be a suitable alternative for MDRO decontamination in some settings, particular in the context of high contamination pressure with a large proportion of patients being MDRO carriers.

There is currently no specific disinfection procedure that is recommended for the decontamination of the healthcare water environment due to uncertainty and lack of consensus in terms of effectiveness, toxicity, logistical challenges, and cost [7]. A study showed effectiveness of foam products combining hydrogen peroxide and peracetic acid in reducing recovery of Gram-negative bacilli on days immediately after treatment, but with a return to baseline by day seven post-intervention [8]. Other interventions have been proposed with varying degrees of success [8].

To combat MDRO outbreaks, some ICUs have removed sinks from patient areas, significantly reducing MDRO colonization and
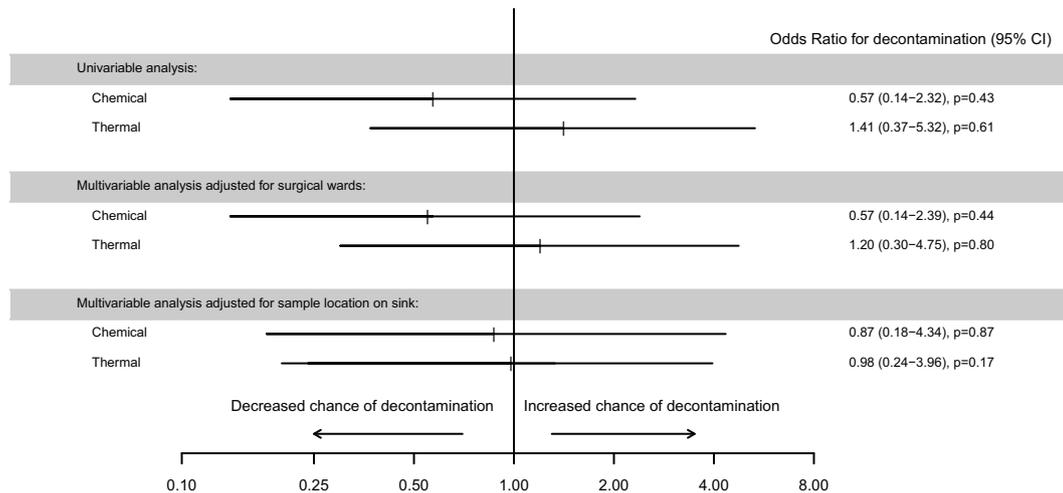
	Odds Ratio for decontamination (95% CI)
Univariable analysis:	
Chemical	0.57 (0.14–2.32), p=0.43
Thermal	1.41 (0.37–5.32), p=0.61
Multivariable analysis adjusted for surgical wards:	
Chemical	0.57 (0.14–2.39), p=0.44
Thermal	1.20 (0.30–4.75), p=0.80
Multivariable analysis adjusted for sample location on sink:	
Chemical	0.87 (0.18–4.34), p=0.87
Thermal	0.98 (0.24–3.96), p=0.17

Decreased chance of decontamination — Increased chance of decontamination

0.10 0.25 0.50 1.00 2.00 4.00 8.00

Fig. 2. Odds ratios (95% CI) of decontamination by intervention arm in univariable and multivariable logistic regression analysis.

healthcare-associated infections [3,4,9]. However, implementing waterless patient care beyond ICUs is challenging. Alternatives include sink modifications and devices producing heat or vibrations to minimize contamination [10,11]. Innovations like sophisticated sink designs featuring ultraviolet light and ozonated water have shown promise in reducing bacterial growth, deserving further clinical evaluation [12].

Our study has several limitations. First, the intervention was performed weekly with a 2.5% bleach solution, so we cannot conclude on the effects of daily use or higher concentrations, although this would involve logistical challenges and the risk damage to plumbing infrastructure. Secondly, the initial sink trap change precluded evaluation of disinfection alone. However, biofilm formation requires removal before effective disinfection, and our intervention applications required specific drain lines for chemical or thermal methods. Third, without prospective patient sampling, the clinical impact remains unclear. In addition, non-standardized environmental sampling makes comparisons of bacterial load difficult. Finally, we could not determine whether the same or different MDROs were involved in sink recontamination over time.

In conclusion, in a setting with a high contamination of water sources with MDRO, our study did not demonstrate any added effect of either regular chemical or thermal disinfection beyond sink trap replacement alone in sink decontamination, however the sample size was limited. Regular replacement of sink traps may be effective in reducing bacterial load and reducing the potential transmission risk. Chemical disinfection of sink drains with bleach is routine in many hospitals around the world; further studies are needed on the effectiveness of such practices.

Author contributions

GC and SH designed the study. GC, YM, CC, and JC conducted the study. NB provided methodological advice and help for the analysis. GC wrote the original draft of the manuscript. SH and RG reviewed and substantially improved the manuscript. All the authors provide feedback and approved the final version.

Transparency declaration

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2024.05.008.

References

[1] Kotay S, Chai W, Guilford W, Barry K, Mathers AJ. Spread from the sink to the patient: *In situ* study using green fluorescent protein (GFP)-expressing *Escherichia coli* to model bacterial dispersion from hand-washing sink-trap reservoirs. Appl Environ Microbiol 2017;83:e03327-16. https://doi.org/10.1128/AEM.03327-16. PMID: 28235877; PMCID: PMC5377511.

[2] Kizny Gordon AE, Mathers AJ, Cheong EYL, Gottlieb T, Kotay S, Walker AS, et al. The hospital water environment as a reservoir for carbapenem-resistant organisms causing hospital-acquired infections-A systematic review of the literature. Clin Infect Dis 2017;64:1435–44. https://doi.org/10.1093/cid/cix132.

[3] Fucini GB, Geffers C, Schwab F, Behnke M, Sunder W, Moellmann J, et al. Sinks in patient rooms in the ICUs are associated with higher rates of hospital-acquired infections: a retrospective analysis of 552 ICUs. J Hosp Infect 2023;139:99–105. https://doi.org/10.1016/j.jhin.2023.05.018.

[4] Catho G, Martischang R, Boroli F, Chraïti MN, Martin Y, Koyluk Tomsuk Z, et al. Outbreak of *Pseudomonas aeruginosa* producing VIM carbapenemase in an intensive care unit and its termination by implementation of waterless patient care. Crit Care 2021;25:301. https://doi.org/10.1186/s13054-021-03726-y.

[5] Sukhum KV, Newcomer EP, Cass C, Wallace MA, Johnson C, Fine J, et al. Antibiotic-resistant organisms establish reservoirs in new hospital built environments and are related to patient blood infection isolates. Commun Med (Lond) 2022;2:1–15. https://doi.org/10.1038/s43856-022-00124-5.

[6] Valentin AS, Santos SD, Goube F, Gimenes R, Decalonne M, Mereghetti L, et al. A prospective multicentre surveillance study to investigate the risk associated with contaminated sinks in the intensive care unit. Clin Microbiol Infect 2021;27. https://doi.org/10.1016/j.cmi.2021.04.032.

[7] Dancer SJ. Controlling hospital-acquired infection: focus on the role of the environment and new technologies for decontamination. Clin Microbiol Rev 2014;27:665–90. https://doi.org/10.1128/CMR.00020-14.

[8] Jones LD, Mana TSC, Cadnum JL, Jencson AL, Silva SY, Wilson BM, et al. Effectiveness of foam disinfectants in reducing sink-drain gram-negative

bacterial colonization. Infect Control Hosp Epidemiol 2020;41:280–5. https://doi.org/10.1017/ice.2019.325.

[9] Hopman J, Tostmann A, Wertheim H, Bos M, Kolwijck E, Akkermans R, et al. Reduced rate of intensive care unit acquired gram-negative bacilli after removal of sinks and introduction of 'water-free' patient care. Antimicrob Resist Infect Control 2017;6:59. https://doi.org/10.1186/s13756-017-0213-0.

[10] Aranega-Bou P, Cornbill C, Verlander NQ, Moore G. A splash-reducing clinical handwash basin reduces droplet-mediated dispersal from a sink contaminated with Gram-negative bacteria in a laboratory model system. J Hosp Infect 2021;114:171–4. https://doi.org/10.1016/j.jhin.2021.04.017.

[11] Yui S, Muzslay M, Karia K, Shuttleworth B, Ali S, Dudzinska N, et al. Evaluation of droplet production by a new design of clinical handwash basin for the healthcare environment. J Hosp Infect 2019;103:e110–4. https://doi.org/10.1016/j.jhin.2019.06.014.

[12] Cole K, Talmadge JE. Mitigation of microbial contamination from waste water and aerosolization by sink design. J Hosp Infect 2019;103:193–9. https://doi.org/10.1016/j.jhin.2019.05.011.