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MAJOR ARTICLE

Control of Multidrug-Resistant *Pseudomonas aeruginosa* in Allogeneic Hematopoietic Stem Cell Transplant Recipients by a Novel Bundle Including Remodeling of Sanitary and Water Supply Systems

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Background. Infections by multidrug-resistant *Pseudomonas aeruginosa* (MDRPa) are an important cause of morbidity and mortality in patients after allogeneic hematopoietic stem cell transplantation (HSCT). Humid environments can serve as a reservoir and source of infection by this pathogen. To minimize the risk of infection from these reservoirs, we performed extensive remodeling of sanitation and water installations as the focus of our hygiene bundle.

Methods. During the reconstruction of our transplantation unit (April 2011–April 2014) we implemented several technical modifications to reduce environmental contamination by and subsequent spreading of MDRPa, including a newly designed shower drain, disinfecting siphons underneath the sinks, and rimless toilets. During a 3-year study period (2012–2014), we tracked the number of patients affected by MDRPa (colonized and/or infected) and the outcome of infected patients, and monitored the environmental occurrence of this pathogen. We further performed whole-genome sequencing of nosocomial MDRPa strains to evaluate genotypic relationships between isolates.

Results. Whereas 31 (9.2%; 18 colonized, 13 infected) patients were affected in 2012 and 2013, the number decreased to 3 in 2014 (17%; 3 colonized, 0 infected). Lethality by MDRPa similarly decreased from 3.6% to 0%. Environmental detection of MDRPa decreased in toilets from 18.9% in 2012–2013 to 6.1% in the following year and from 8.1% to 3.0%, respectively, in shower outlets. Whole-genome sequencing showed close relationships between environmental and patient-derived isolates.

Conclusions. Hospital construction measures aimed at controlling environmental contamination by and spread of MDRPa are effective at minimizing the risk of highly lethal MDRPa infections.

Keywords. multidrug-resistant *Pseudomonas aeruginosa*; infection control; hospital acquired infection; immunocompromised hosts; hospital water system.

Resistance rates in gram-negative bacteria are increasing and pose a threat for patients with hematologic malignancies [1]. Patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) are especially at risk for acquiring *Pseudomonas aeruginosa* infections due to their immunocompromised state [2], which also puts them at higher risk for a fatal outcome [3, 4]. Multidrug-resistant *Pseudomonas aeruginosa* (MDRPa) outbreak situations were repeatedly described on hematological-oncological wards [5–7] and were associated with a death rate of up to 80% [8].

In outbreak situations, various environmental reservoirs have been identified. The sanitary and water supply system is a common reservoir for *P. aeruginosa* biofilm formation [9]. As a consequence, hospital construction design needs to consider these sources of transmission of MDRPa from the environment. We hypothesized that environmental reservoirs pose a severe risk to patients undergoing HSCT for acquiring MDRPa and developing invasive disease. Therefore, during a substantial reconstruction and expansion of our transplantation unit starting in 2011, we implemented a bundle of measures that included a variety of hygiene measures with the major focus on comprehensive renovation and a new design of the sanitary and water supply system to ultimately reduce the number of MDRPa infections. Over the following 3 years, in which the measures in hospital construction design were performed, we studied microbiological surveillance data, determined the relationship between MDRPa isolated from both patients and the environment using whole-genome

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sequencing (WGS), and monitored patient outcome with respect to MDRPa infections.

METHODS

Patients and Treatment

The Center for Bone Marrow Transplantation of the University Hospital Muenster serves a catchment area of 5 million people in the northwest of Germany. It consists of an outpatient clinic and an interdisciplinary inpatient unit with 10 high-efficiency particulate air (HEPA)–filtered single-patient rooms, all of which were equipped with separate bathrooms and an anteroom. In March 2011, the inpatient unit was extended by a second, similarly constructed ward resulting in a total capacity of 20 rooms. Room-by-room renovation of the existing ward was started at the same time and completed in April 2014.

During the observation period of this study from January 2012 to December 2014, 474 pediatric and adult patients underwent HSCT on either ward of the unit, accounting for a total of 517 admissions, including 43 readmissions for transplant-associated complications. Key demographic and medical characteristics of the 474 patients are summarized in Table 1. In general, patients undergoing allogeneic HSCT are treated for 4–6 weeks as inpatients. Standard antibacterial prophylaxis consisted of ciprofloxacin starting upon admission; the standard regimen for empiric antibacterial therapy for neutropenic fever consisted of piperacillin-tazobactam plus gentamicin. Death caused by an MDRPa infection was diagnosed by the treating physicians

Table 1. Characteristics of Patients Receiving an Allogeneic Hematopoietic Stem Cell Transplant in the Transplantation Unit, 2012–2014

Characteristics of HSCT Patients	Patients in 2012 (n = 161)	Patients in 2013 (n = 153)	Patients in 2014 (n = 158)
Adult/pediatric patients, no./No. (%)	133/28 (83/17)	132/21 (86 /14)	135/23 (85/15)
Median age at HSCT, y (range)			
Adult patients	53 (19–71)	54 (20–77)	56 (20–73)
Pediatric patients	10 (0.7–20)	13 (0.7–19)	16 (0.7–19)
Male sex, No. (%)	106 (66)	106 (69)	99 (63)
Diagnosis, No.			
Acute myeloid leukemia	82	66	63
Acute lymphatic leukemia	28	26	19
Myelodysplastic syndrome	9	17	22
Non-Hodgkin/Hodgkin lymphoma	11/0	13/6	15/2
Multiple myeloma	8	8	8
Chronic lymphatic leukemia	7	5	4
Chronic myeloid leukemia	6	3	6
Myelofibrosis	2	3	9
Aplastic anemia	1	4	7
Other	7	2	3
Remission status prior to HSCT, No. (%)			
First complete remission	50 (34)	37 (24)	27 (17)
2nd or 3rd complete remission	17 (11)	21 (14)	16 (10)
Active/refractory disease	79 (49)	74 (48)	86 (54)
Primary disease, untreated[a]	15 (9)	21 (14)	29 (18)
Donor, No. (%)			
Related (sibling)	44 (27)	50 (33)	40 (25)
Haploidentical	1	1	
Unrelated	117 (73)	103 (67)	118 (75)
Conditioning regimens, No. (%)			
Full-toxic conditioning	60 (37)	47 (31)	51 (32)
Dose-adapted/reduced intensity conditioning	40 (25)	71 (46)	71 (45)
Sequential conditioning (refractory/active AML)	59 (37)	32 (21)	36 (23)
Other	2	3	
Cumulative incidence of nonrelapse death rate after HSCT, % (95% CI)			
At day +30	3 (1–7)	9 (5–14)	7 (4–12)
At day +100	9 (6–15)	22 (17–30)	15 (11–22)
Overall survival, % (95% CI)			
At day +100	87 (83–93)	77 (70–83)	82 (76–88)
At 1 y	63 (56–71)	58 (50–66)	67 (59–74)
At 2 y	57 (49–64)	53 (45–61)	62 (54–69)

Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; HSCT, hematopoietic stem cell transplantation.

[a]For example, myelodysplastic syndrome without specific treatment before HSCT.

in the case of detection of MDRPa in blood cultures directly obtained from patients with a severe sepsis, which resulted in death within a few hours (no evidence for other causes/no detection of other bacteria).

The causality of death after allogeneic HSCT was defined as being non–relapse related in cases of an ongoing remission after transplantation and relapse related in the case of a relapsed disease after transplantation, even in cases with a subsequent remission. The exact cause of death, especially of patients with a longer follow-up after transplantation, is usually only known in a small proportion of cases, as the treatment of late complication was also performed outside the transplant center.

Hospital Construction

To reduce the risk of biofilm formation and subsequent transmission of bacterial pathogens to the patients, we developed a new shower drain design. These drains are characterized by a 15.3 cm wide and 36 cm deep outlet, which is easy to clean and disinfect (Figure 1). To prevent aerosol formation, the drain is covered by a heavy stainless steel lid to discourage intentional and prevent accidental removal by patients (Figure 1A). Part of the design includes a stainless steel bubble cap, which prevents the spread of odors (Figure 1B). This bubble cap can be removed for cleaning, disinfection, and sterilization (Figure 1C).

Shower heads and faucets were equipped with Pall Aquasafe water filters (Pall Cooperation, Port Washington, New York). We installed Biorec disinfection siphons (Biorec Dr. Schluttig, Lauta, Germany) under all washbasins (Figure 2A). These siphons use ultraviolet light, frequent vibration (50–200 Hz), temperature (85°C), and an antibacterial coating to prevent biofilm formation.

Because we had also detected MDRPa in toilets, we also decided to replace all toilets with rimless toilets (Figure 2B) and a system that provides the flushing water with disinfectant containing 0.5% glucoprotamin.

Disinfection and Sterilization

Patient rooms, including all bathroom items, were cleaned and disinfected on a daily basis and when a patient was discharged during the entire study period. In addition, surfaces with frequent hand contact were disinfected repeatedly. The bubble cap and heavy lid of the shower drains were sterilized weekly and after the discharge of every patient. Disinfectants contained either quaternary ammonium compounds or glucoprotamin at a concentration of 0.5%. These practices continue to be implemented.

Sampling

Patients were screened for MDRPa upon admission and weekly thereafter during their stay via rectal swabs starting in April 2011 as part of our routine surveillance strategy for the control of multidrug-resistant (MDR) bacteria. Colonization and infection were considered to be nosocomial when screening upon admission was negative and/or MDRPa was isolated >48 hours after admission.

In parallel, we began a systematic environmental sampling including every new room upon completed renovation. The environmental sampling included swabs from shower outlets and washbasins as well as toilets starting in March 2012. Sampling took place at least once a month in every room and following the discharge of a colonized or infected patient.

Identification of Bacteria

Samples were plated on Columbia sheep blood agar and *Pseudomonas* selective cetrimide agar (both Oxoid, Wesel, Germany). Environmental swabs were enriched in tryptic soy broth for 24 hours at 36°C before being plated again on Columbia sheep blood agar. Species identification was confirmed by

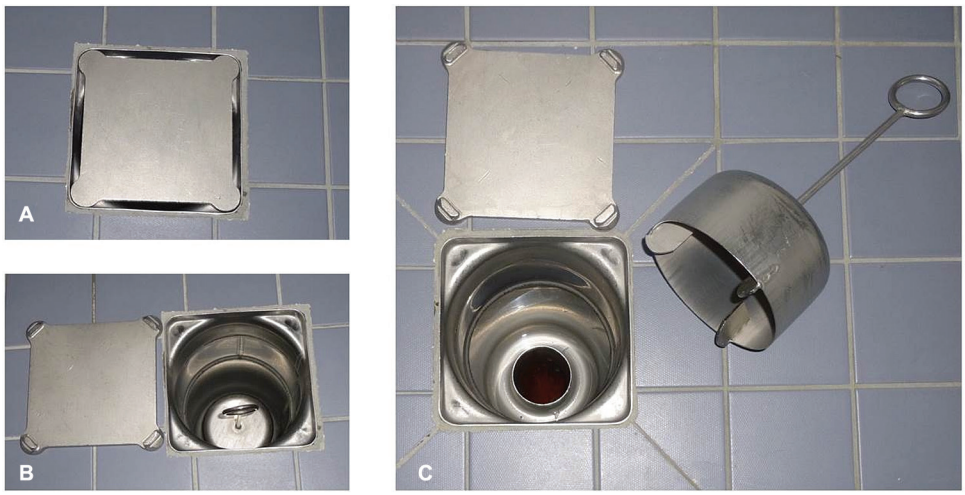

Figure 1. Shower drain design. The whole installation is covered by a heavy stainless steel lid (*A*), which is designed to discourage patients from opening and to prevent accidental removal. The drain (*B*) is designed to be wide, so it can be easily cleaned and disinfected. A bubble cap insert (*C*) prevents odors and splashing and can be removed for sterilization.

Figure 2. Hygiene siphon and rimless toilet. The Hygiene siphon uses vibration (50–200 Hz), high temperatures (85°C), and ultraviolet light to prevent biofilm formation. It is covered to discourage a frequent change of settings and for cleaning and disinfection purposes.

matrix-assisted laser desorption/ionization (MALDI) time-of-flight mass spectrometry using the MALDI-Biotyper system (Bruker Daltonics, Bremen, Germany). We performed the antibiotic susceptibility testing using VITEK 2 (bioMérieux, Marcy-l'Étoile, France) for patient-derived isolates and disk diffusion for environmental isolates; both were interpreted in accordance to the European Committee on Antimicrobial Susceptibility Testing breakpoints (version 2.0, 29 October 2011). Isolates resistant against piperacillin, third-/fourth-generation cephalosporins, fluoroquinolones, and carbapenems were rated as MDR in accordance with the recommendations set forth by the national German Robert Koch Institute [10].

Whole-Genome Sequencing–Based Typing

Whole-genome sequencing was used to determine possible clonal relationships between environmental and patient-derived isolates from the transplantation unit as part of our routine surveillance strategy. DNA extraction, WGS library preparation, sequencing, and subsequent data analysis were performed as recently described [11]. Using *P. aeruginosa* strain PAO1 (GenBank accession number NC_002516) as the reference sequence, coding regions were compared in a gene-by-gene approach based on up to 3842 genes [11] using the SeqSphere$^+$ software version 2 (Ridom GmbH, Muenster, Germany). Isolates that differed in a pairwise comparison in >14 alleles were assumed to be unrelated [11]. The clonal relationship is displayed in a minimum-spanning tree. For backwards compatibility with classical molecular typing—that is, multilocus sequence typing (MLST)—the MLST sequence types (STs) were extracted from the WGS data in silico.

Infection Control Measures

According to the national guideline [10], every patient colonized or infected with any MDR bacteria undergoes contact isolation. An infection control nurse was present on the ward at least once a week and ward rounds were accompanied by an infection control physician. Moreover, a pharmacist is present on the ward 3 times a week. Since January 2013 a supervisor who underwent special training and stood in close contact with the infection control team was added to the cleaning team.

Statistical Analysis

All patient and environmental data are expressed as absolute numbers or percentages, if not stated otherwise. Statistical analyses were performed using the Fisher's exact test for categorical data. Statistical significance was considered using a P value of <.05. For the analysis of the effectiveness of the implemented measures on colonization and infection rates, we compared the occurrence in patients and the environment in the years 2012–2013 with our findings in 2014. To estimate accuracy, the relative risk and 95% confidence interval were calculated for affected patients and the lethality by MDRPa.

RESULTS

Occurrence in Patients

One hundred seventy-one and 167 patients were screened for MDRPa in 2012 and 2013, respectively. They were compared to the 179 patients treated in 2014. The number of patients nosocomially affected (colonized and/or infected) by MDRPa decreased from 31 (9.17%) in 2012–2013 to 3

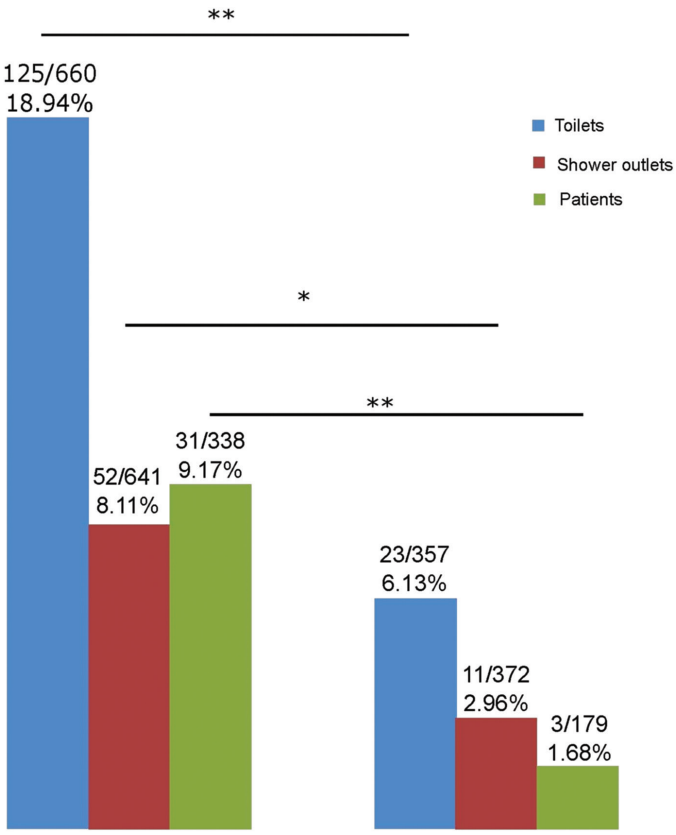

Figure 3. Comparison of occurrences of multidrug-resistant *Pseudomonas aeruginosa* (MDRPa) in the environment and patients. Bars of different shades give the percentage of occurrence of MDRPa in toilets, shower outlets, and patients. Absolute numbers are given on top of each column for 2012–2013 and 2014. The pairwise comparisons and statistical analysis between the findings of the years 2012–2013 and 2014, when all renovation was completed, are shown in vertical lines. *$P < .01$; **$P < .001$.

(1.68%) in 2014 ($P < .001$; Figure 3). In total, 13 patients were infected in 2012 and 2013 (3.85%); this number decreased to 1 patient in 2014 (0.56%) ($P < .05$). In 2012 and 2013, 12 patients died of MDRPa infection (3.55%) whereas this number decreased to 0 in 2014 (0%) ($P < .05$). In the 2 years following the initial study period, 8 of 376 patients were affected, (2.13%) 4 of whom died. The annual distribution of affected patients and further clinical details (infection and colonization) are shown in Table 2.

Environmental Detection

Environmental sampling detected MDRPa in 125 of 660 samples taken from toilets (18.94%) and 52 of 641 samples taken from shower outlets (8.11%) in the years 2012 and 2013. These numbers decreased to 23 of 375 toilets testing positive (6.13%; $P < .001$) and 11 of 372 shower drains testing positive (2.96%; $P < .01$) in 2014 (Figure 2).

During follow-up, we found occurrence of MDRPa in 29 of 725 toilets (4%) as well as 33 of 719 shower drains (5.59%).

Table 2. Annual Distribution and Clinical Details of Patients Colonized or Infected With Multidrug-Resistant *Pseudomonas aeruginosa*

		No. of Patients With:				
Year	No. of Patients Treated	BSI	Pneumonia	Colonization	Total No. of Affected Patients (%)[a]	Lethality, %[b]
2012	171	4	0	14	18 (10.5)	2.3 (n = 4)
2013	167	8	1	4	13 (7.8)	4.8 (n = 8)
2014	179	1	0	2	3 (1.7)	0 (n = 0)
2015	183	4	0	3	7 (3.8)	2.2 (n = 4)
2016	193	0	0	1	1 (0.5)	0 (n = 0)

Abbreviation: BSI, bloodstream infection.

[a] $P < .001$ (relative risk [RR], 5.5; 95% confidence interval [CI], 1.6–22.3).

[b] $P < .05$ (RR, 132.4; 95% CI, 1.3–8507.7).

Sinks tested positively in 6 of 641 (0.93%) samples in 2012–2013 and not at all in 2014. Occurrence in sinks could always be directly linked to a defected disinfection siphon.

Whole-Genome Sequencing

In total, 187 MDRPa isolates were analyzed by WGS (Supplementary Table 1). In this analysis we included 151 patients' and 36 randomly chosen environmental samples. All environmental isolates stemmed from our HSCT ward. Of the 151 patient-derived isolates, 19 originated from patients who were treated on oncological wards other than the HSCT unit and 32 from HSCT patients. The remaining 100 samples came from nononcological wards of the same hospital. Isolates from the HSCT ward mostly showed a genetic relationship and differed from those derived from patients treated on other wards of our hospital. Isolates from patients who were treated on oncological wards other than the HSCT ward were either closely or not at all related to the cluster from the HSCT ward. Extraction of MLST STs from the WGS data resulted in 51 different STs; of these, the most common ST in patients was ST235 (n = 35) (Supplementary Table 1). Comparison of WGS-based allelic profiles of up to 3842 genes (Figure 4) showed a close relationship between patient-derived isolates and environmental isolates in the majority of cases. In contrast, isolates from wards other than the transplantation unit were mostly unrelated, suggesting a relationship between patient-derived and environmental isolates on the transplantation unit.

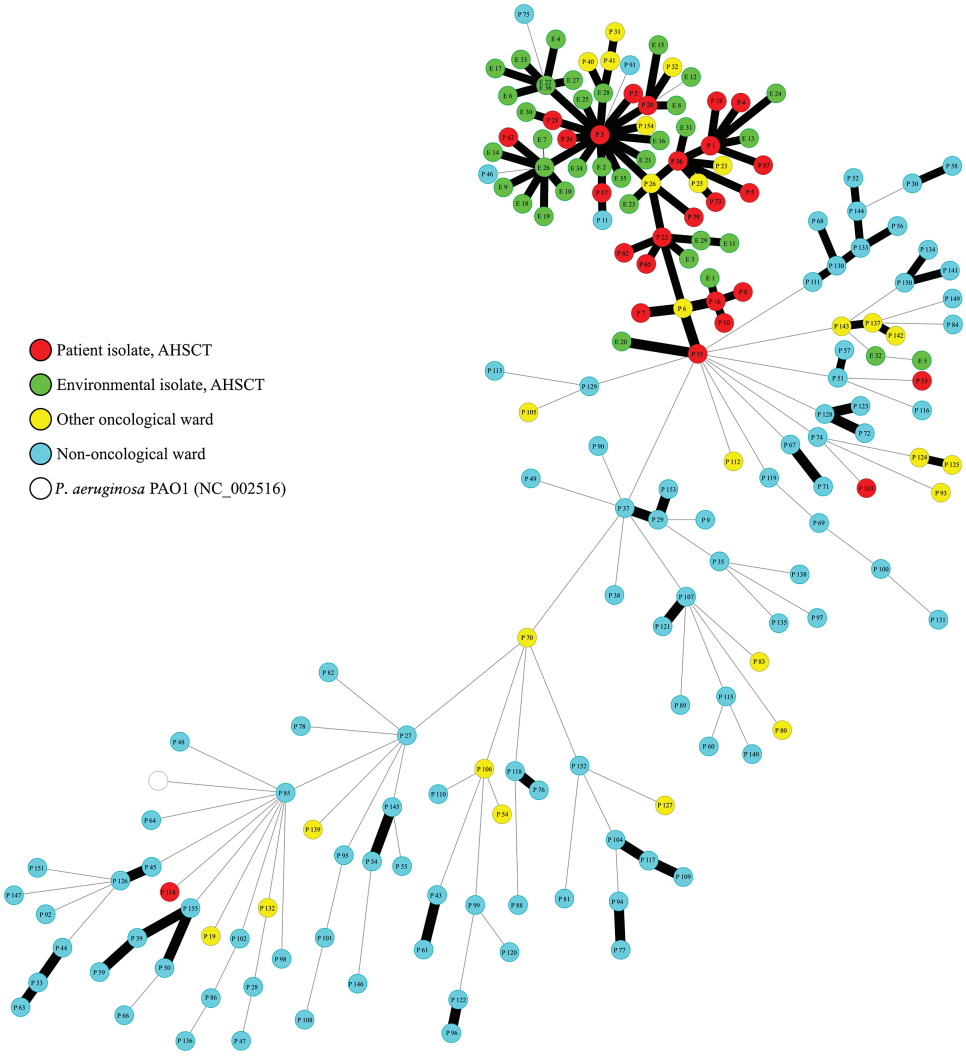

Figure 4. Minimum spanning tree of 187 MDRPa isolates either from patients (P) or environmental samples (E) originating from our transplantation unit and other oncological or nononcological wards of our hospital. Each circle represents a single genotype, that is, an allelic profile based on up to 3842 target genes present in the isolates with the "pairwise ignoring missing values" option turned on in the SeqSphere+ software during comparison. The circles are named with the isolate ID(s) and colored by ward and origin. Thick connecting lines between 2 genotypes display ≤14 differing alleles; thin lines display genotypic distances of >14 alleles' distance. Abbreviations: AHSCT, allogeneic hematopoietic stem cell transplantation.

DISCUSSION

Pseudomonas aeruginosa infection is a severe complication in the course of allogeneic HSCT. Different strategies were found to be effective in identifying and eliminating sources of this pathogen, thus preventing further transmissions. These include hygiene measures such as contact precautions [12], strengthening hand hygiene practices [13, 14], and the screening of patients [7, 14] as well as the installation of point-of-use water filters [7, 15, 16].

After detection of MDRPa in patients with fatal bloodstream infections, we did an extensive surveillance of common reservoir sites. As several isolates were detected in the patients' environment and, in particular, the water supply and sanitary system, acquisition of the organism from the environment was considered as the probable source of colonization and infection. Consequently, we applied extensive structural measures in combination with intensified standard cleaning procedures and intensive repetitive training of all staff with direct or indirect patient contact, including the cleaning and housekeeping personnel. Those measures were bundled together with prospective patient screening and the regular presence of an infection control nurse. This bundle led to a decrease of MDRPa detections in both the environment (shower outlets and toilets) and patients. Occurrence in washbasins was low in both periods and always directly linked to a nonfunctioning disinfection siphon. Disinfection siphons are an important part of our bundle, but their reliability was not questioned during the course of our study.

Most important, lethality due to MDRPa infections decreased to 0% at the end of the study period. By elucidating the close relationship between almost all MDRPa isolates from the transplantation unit, WGS underlined the impact of the interplay between the patient and the environment on the one hand and the importance to reduce or even eliminate this reservoir on the other hand. In contrast to other settings [5, 7, 9, 13, 15–18], we were not able to determine a specific single source for colonization and infection. There was no obvious correlation with specific patient rooms or the time of occurrence between environmental isolates and/or patient-derived isolates (Supplementary Figure 1). Other observations [6, 8] also were unable to differentiate whether an individual patient was colonized by the environment or the environment was contaminated by an already colonized patient.

Even after screening all patients for MDRPa at the time of admission to the transplant unit for MDRPa, it remains unclear to which extent patients acquired MDRPa during their hospital stay or were colonized before. Probably, standard microbiological screening methods might be not sensitive enough to detect MDRPa in patients with normal gut colonization. In contrast to the environmental screening swabs, we did not use broth enrichment on screening swabs from patients even though selective agar plates were used in both cases. Using broth enrichment might lead to an earlier detection of MDRPa colonization.

Previously, pulsed-field gel electrophoresis was frequently used for the detection of genetic relationships between strains isolated from different patients in suspected outbreak situations [5, 8, 12, 13, 17]; however, this methodology is nowadays increasingly replaced by WGS-based typing, which provides an even higher discriminatory genotyping [14, 19–22]. The introduction of WGS during the study period aimed to reveal an answer to this open question as WGS provides much more precise genomic comparison. As a result, a contamination from the environment could not be conclusively excluded.

The case fatality rate among infected patients was high, and it became obvious during the course of our study that colonization by MDRPa is often detected only shortly before the death of a patient. This is confirmed by other reports of highly virulent MDRPa clones, including MLST STs 111, 175, and 235 [23]. MLST can therefore provide risk analysis for the virulence of single isolates. Beyond this, WGS grants the possibility to reconstruct genetic relationships in outbreak situations in order to concentrate hygiene measures upon the original source. Of note, we also found a high number of ST235 in our isolates (Supplementary Table 1). The rapid evolution from colonization to severe infection is worrisome given that other groups found infection to be more likely in patients who were previously colonized [24].

The approach of implementing a bundle of infection control measures as the most effective strategy for the prevention of infection by MDR bacteria in patients with HSCT is also supported by the review of Ruhnke et al [4]. Given the environmental presence of MDRPa, we added environmental decontamination as the preventive measure for MDRPa infections. Antibiotic prophylaxis and first-line treatment did not change during the study period. Hand hygiene compliance was observed to be high by the infection control nurse and hand hygiene training was provided continuously during the entire study period. Given the obvious success of these measures, the study provides suggestions for specific preciously undescribed infection control considerations for the construction of patients' bathrooms, with a reciprocal effect to classic infection control measures. Even though the individual parts of our bundle are meant to enhance each other, we attribute the main effects to constructional changes that were specifically aiming at preventing MDRPa. A retrospective passive surveillance of bloodstream infections caused by other resistant pathogens shows a low baseline and no decline in infection rates (methicillin-resistant *Staphylococcus aureus*: n = 0 in 2012–2013, n = 2 in 2014; vancomycin-resistant enterococci: n = 2 in 2012–2013, n = 5 in 2014).

The study is limited because of the fact that no systematic data exist concerning environmental occurrence and patients affected prior to the start of the remodeling of the water supply and sanitary system. Moreover, in some cases, patients could not been screened weekly due to their clinical status. This might have led to a missed MDRPa colonization before the actual

detection. A detailed analysis of epidemiological and clinical data might help to identify predictive parameters for patients to acquire colonization or prediction for the clinical outcome of infection. Considering the low number of affected patients and the heterogeneous course of underlying disease and treatment, this would not lead to reliable results in our setting.

It is well known that in other cohorts, patients exchange isolates among each other. It may be evaluated whether this also happens in outpatient settings as other settings than the inpatient clinic are considered to possibly contribute to transmission [4, 25]. In this respect, we also consider reviewing our screening methods to improve selectivity and achieve an earlier detection, that is, while still in the state of colonization. In the 2 years following the study period, we experienced a higher number of preexisting colonizations in patients admitted to our transplantation unit (n = 3 each in 2015 and 2016). This increased colonization pressure might have been a reason for the slight rise in occurrence in patients (3.82%) and toilets (7.61%) in 2015. As a reaction to this, we performed extensive maintenance of toilets. In 2016, we could not detect MDRPa in toilets, and nosocomial occurrence in patients decreased to 0.5%. Overall occurrence remained low for a prolonged period of time.

Taken together, our study demonstrates that structural changes combined with a bundle of infection prevention measures can lead to a decrease in environmental occurrence and a reduction of MDRPa infections in HSCT patients. This strategy, with its special focus on hospital construction measures, may serve as a model for other institutions facing the daunting challenge of MDR bacteria in high-risk patients.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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