

Wastewater Hospital Plumbing Intervention to Prevent Transmission of Multi-species *Klebsiella pneumoniae* Carbapenemase (KPC) Producing Organisms

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28 **40 word summary**

29 Nosocomial transmission of carbapenemase-producing organisms is poorly understood, and reports
30 increasingly indicate hospital wastewater plumbing may play a role. (e.g. Environmental interventions
31 targeting wastewater decreased *Klebsiella pneumoniae* carbapenemase-producing organisms (KPCO)
32 infections and acquisitions in a single institution.

33

ABSTRACT

Background: Increasing prevalence of nosocomial carbapenemase-producing Enterobacteriaceae is a concern; however, transmission is poorly understood, especially for multispecies outbreaks. There is increasing recognition that hospital wastewater plumbing may play an important role.

Methods: Covers were installed on all hoppers in adult ICUs in a university hospital with an associated long-term acute care hospital; in the surgical ICU (SICU) both hopper covers and sink trap heating/vibration devices were installed. Patient acquisitions (measured by peri-rectal colonization or clinical culture) of *Klebsiella pneumoniae* carbapenemase (KPC)-producing organisms (KPCO) in 15-month pre-intervention and intervention periods were compared.

Results: Sixty hopper covers and 23 sink trap devices were installed over three months. A total of 77 new multispecies KPCO acquisitions occurred pre-intervention compared to 40 KPCO acquisitions during the intervention. Decreases per total patient admissions were observed for all KPCO acquisitions (odds ratio [OR] 0.519; 95% confidence interval [CI]: 0.345-0.77; $p=0.0008$) and KPCO-positive clinical cultures (OR 0.393; CI: 0.19-0.768; $p<0.0045$). The incidence rate ratio was 0.49 [0.31 – 0.77 95% CI] fold lower for all KPCO acquisitions after the intervention. There was no difference in acquisition in the SICU, although the proportion of sink drain and sink trap water cultures positive for KPCO decreased (12/15 [80%] sites sampled pre-intervention versus 40/825 [5%] sampled weekly during the intervention; $p=0.04$).

Conclusions: An intervention targeting wastewater plumbing by installing hopper covers in adult ICUs demonstrated a hospital-wide decrease in patient KPCO acquisitions. Considering wastewater reservoirs in transmission of multispecies carbapenemase-producing Enterobacteriaceae may be critical.

Significance and Background

Antimicrobial-resistant bacteria are predicted to be one of the greatest threats to human health[1]. Carbapenem-resistant Enterobacteriaceae are among some of the most concerning emerging organisms because carbapenemase genes often reside on mobile genetic elements, such as plasmids, that can be rapidly exchanged between pathogenic and environmental bacteria. Although the wastewater environment of hospitals was identified as a potential nosocomial source for antibiotic-resistant Gram-negative bacteria as far back as the 1970s[2], it has been increasingly implicated in outbreaks with carbapenem-resistant organisms (CRO), and may act as a reservoir that amplifies resistance[3, 4]. Traditional models of patient-patient transmission and interventions targeting this mode of spread may not be appropriate for non-clonal, plasmid-mediated outbreaks of carbapenemase or other β -lactamase resistance genes, where adherence to standard precautions (i.e. promotion of hand hygiene, implementation of contact precautions, etc.) does not seem to have a significant effect[5]. Our understanding of transmission networks involving wastewater reservoirs and the efficacy of intervention efforts have not been rigorously studied, except in studies describing outbreaks in single medical units[6].

Many recent reports have focused on sink traps and sink drains as a potential CRO transmission reservoir[4]. We recently demonstrated a mechanism for dissemination in a sink laboratory model where biofilm spread from the sink trap to the sink drain and organisms were then dispersed when impacted by water from the sink faucet[7]. Particle and organisms have been shown to disperse to the wider environment from toilet flushing[8], albeit this work has been performed largely in relation to *Clostridium difficile*[9-11]. Gram-negative organisms, including CROs, could plausibly be similarly dispersed by hopper/toilet flushing.

Nosocomial acquisition of *Klebsiella pneumoniae* carbapenemase-producing organisms (KPCO; ~20 species) occurs with low frequency in our institution, despite a robust screening and isolation program and early adoption of the Centers for Disease Control and Prevention (CDC) toolkit to prevent CRO

transmission[12, 13]. We previously used genomics to characterize transmission networks and found that the majority of transmission could not be explained by patient-to-patient events[14]. These findings suggest that there was an overlooked, non-patient, nosocomial reservoir contributing to transmission of multispecies KPCO. In this paper we investigate the presence of KPCO in the wastewater environment and the impact of environmental interventions on patient KPCO acquisition and rates of KPCO-positive clinical cultures.

Methods

Setting

A single center, prospective, observational intervention study was performed at the University of Virginia 619-bed tertiary care hospital and 44-bed associated long term acute care facility (UVaMC) from November 1st, 2014 to July 31st, 2017. A KPCO peri-rectal surveillance program existed throughout the study period, which included the following: screening on admission to the medical intensive care unit (MICU) and long term acute care hospital (LTACH), screening on admission and discharge to the surgical intensive care unit (SICU), and weekly screening of all patients at the LTACH, the MICU and SICU as well as units where any known KPCO-colonized patient was present[13]. During the intervention period additional discharge screening was also performed in the MICU. Screening was performed as previously described from the start of the study period through January 2017[13], then in February 2017 the indirect carbapenemase test was replaced with the modified carbapenemase inactivation method (mCIM)[15]. Clinical Enterobacteriaceae and Aeromonadaceae with an elevated ertapenem or meropenem minimum inhibitory concentration (MIC) by VITEK2 (Biomérieux, Durham, NC) immediately underwent CarbaR (Cepheid Sunnyvale, CA) carbapenemase PCR testing.

Definitions

The study was divided into three time periods: A 15 month pre-intervention period (Nov-1-14 to Jan-31-16); a three month implementation period (Feb-1-16 to Apr-30-16) during which hopper covers and sink

trap heater devices were installed; and a 15-month intervention period (May-1-16 to July-31-17) following cover/device installation (Figure 1).

Patients were classified as “imported” cases of KPCO if they did not have any prior admission to UVaMC and either had a *bla*_{KPC}-positive Enterobacteriaceae isolated ≤ 48 hours of admission, or had a carbapenem-resistant Enterobacteriaceae culture before transfer to UVaMC with or without a subsequent isolate at UVaMC confirmed as *bla*_{KPC}-positive. New acquisitions were only considered if first identified within the pre-intervention or intervention study periods. Patients with KPCO cultured from peri-rectal surveillance screens were classified as “colonized”. Patients with KPCO from a non-peri-rectal culture site were classified as having a “clinical culture”. Numbers of patient days, admitted patients and peri-rectal screens were all used as denominators. Patients from units where peri-rectal KPCO surveillance was never performed were excluded from analysis, namely: neonatal ICU, psychiatry unit and labor and delivery.

Interventions

Patient rooms in the following intensive care units each had a solid waste disposal system called a hopper (Figure 2A): MICU (n=16 rooms), Cardio-thoracic (12), Cardiac (10), SICU (12), Neurological (10) and Pediatric (12). Sixty hopper covers (Figure 2B) were installed in all adult ICUs with hoppers during the installation period. Hopper covers were already in place in the pediatric intensive care unit. Staff education accompanied hopper cover installation and included instructions to close prior to flushing and not place patient care items on the lids. As the SICU historically had the highest rates of KPCO acquisition, 23 sink trap heaters/vibration units (Moveosiphon ST24; MoveoMed, Dresden, Germany) were installed on all sinks (15 patient room, 2 staff bathroom, 1 staff lounge, 2 nursing station/medication preparation, 1 anteroom, 1 procedure room and 1 soiled utility room sink; Figure 2C) in addition to the installation of hopper covers in that unit. The devices were set to be highly sensitive to temperature decrease and therefore were heating between 75-85°C almost continuously. Our standard ICU room

layout has a hopper in one corner and the sink in the other with the bed in between (Figure 3). During the intervention period weekly independent hopper use audits were performed to assess compliance and sink trap heater devices were checked for problems (e.g. malfunction, leakage).

Environmental Sampling

Environmental sampling was performed using both a drain swab sample collected by inserting dual swab BBL CultureSwab EZ collection and transport systems (Becton, Dickinson, Franklin Lakes, NJ) into drain holes 2.5 cm below the drain, and by collecting 50 mL of water from the sink trap and hopper at the start of the intervention period. Weekly sampling for the sinks hosting the sink trap heating devices in the SICU took place during the intervention period. The drain swabs were placed in 4.5 mL tryptic soy broth (TSB) with a 10 µg ertapenem disk. The 50mL of sink trap or hopper water was spun at 3,000 RPM for 15 minutes followed by removal of the supernatant with the remaining 1 mL of pelleted water and debris inoculated into 4.5 mL TSB with a 10 µg ertapenem disk. Swabs and water were incubated overnight at 34°C and then plated to a Colorex KPC agar (North East Laboratories, Waterville, ME) and again incubated overnight at 34°C. Pigmented colonies suggestive of Enterobacteriaceae or Aeromonadaceae were sub-cultured to blood agar followed by phenotypic carbapenemase testing with the indirect carbapenemase test and if positive, *bla_{KPC}* PCR[16] and species identification with MALDI-TOF (BioMerieux, Durham, NC) were performed.

Data and Statistics

Patient data from electronic medical records were collected in a data warehouse. Data analysis was performed in R using the Stats and survival packages(R version 3.3.2; Oct-31-2016). Fisher's exact test was performed to compare rates of acquisitions (per patient days and patient admissions), for pre-intervention to the intervention periods, clinical cultures per patient admissions and new peri-rectal colonizations per surveillance screens.

We performed Poisson regression to model the number of new acquisitions per month using the time period as a categorical variable and the monthly patient days as an offset. Interrupted time series was also conducted comparing the two analysis periods with new acquisitions per month[17].

Survival analysis techniques modeled KPCO acquisition in the pre-intervention and intervention periods, where patients acquiring KPCO were compared with patients who had ≥ 1 peri-rectal screen and remained negative during the period of analysis for a 60-day period after admission[18].

We used Cox regression to model hazard rates for acquisition[18]. The covariates were hours spent in hopper units and non-hopper units by patients, along with a categorical variable to represent the time period to which the patient belonged[18]. The population of patients included patients who acquired KPCO, or patients with ≥ 1 peri-rectal screen who remained negative. Patients were right censored upon discharge from the hospital without KPCO acquisition.

Ethics

Interventions were put in place for quality improvement purposes. Patient data review was performed under the University of Virginia Institutional Review Board Protocol (#18393 and #18776).

Results

Intervention Analysis

There were a total of 77 new KPCO acquisitions in the pre-intervention period compared to 40 during the intervention period, representing a decrease using both total patient admissions and patient days as denominators. Statistically significant reductions were observed for both clinical cultures and peri-rectal colonizations even with an increase in peri-rectal screening during the intervention period (Table 1).

The Poisson analysis showed a decrease in the monthly incidence rates in the intervention period. The incidence rate ratio for KPCO acquisition was 0.49 [0.34 – 0.72 95% CI] during the intervention compared to the pre-intervention time period (Figure 4). Interrupted time series analysis showed no

significant dependence on time (as represented by number of months from November 2014) when classifying by intervention period (incidence rate ratio is 0.98; $z = -1.38$; $p = 0.19$).

The 60-day survival curves in Figure 5 show the time to acquisition for each period. The log rank test on the survival curves demonstrated that the observed number of acquisitions for the intervention period was lower than the expected number of acquisitions ($z = 23.6$; $p\text{-value} < 0.001$).

The Cox regression analysis showed that patients in the pre-intervention period had a hazard ratio of 2.57 [1.72-3.8 95%CI] for acquisition over the intervention period. The number of hours spent in a room with a hopper showed a significant contribution to risk of acquisition during the pre-intervention period (Hazard ratio 1.004-1.008 $p\text{-value} = 0.03$) but not during the intervention period (Hazard ratio 0.996-1.022, $p\text{-value} = 0.14$) when modelled separately. However, there were no significant interactions between intervention period and hours spent in hopper units when modelled together (Hazard ratio 0.9824-1.008, $p\text{-value} = 0.43$). Interestingly, 30/77 KPCO-positive patients pre-intervention and 14/40 during the intervention had no exposure to the ICUs where hopper lids were installed, consistent with a more widespread effect.

Evaluating patients who acquired KPCO while present in the SICU where the sink trap device and hopper covers were installed, there were no statistically significant differences between the study periods per patient admission (15/1548 patients pre-intervention versus 7/1472 patients during the intervention, $p\text{-value} = 0.1357$).

Species analysis of newly acquired KPCO demonstrated that colonizing/infecting organisms continued to be multi-species, including *Serratia marcescens*, *K. pneumoniae*, *Citrobacter freundii*, *Enterobacter cloacae* complex as the most prominent species in both periods (Table 2).

Intervention Audits

The SICU sink trap heaters were monitored weekly for 49 weeks with 734 observations: on four occasions the sink trap was noted to be dry, three- leaking of water, two- the unit was found unplugged and on one occasion the unit was not functioning requiring a device exchange. There were seven leakage events in total (three observed in audits and four noted by hospital staff) which all took place more than eight months after the initial installation. New gasket rings were provided and replacement took place over a three-week period during month 12 of the 15-month intervention. No new leaks have been noted since this replacement.

Hopper cover use was also audited weekly in the SICU over 36 weeks, beginning roughly three months into the intervention period with 431 unique observations. The following were noted as non-compliance events: 21 cases where an item was placed on the hopper lid (most commonly a urinal [n=8] or bedpan [n=6]; 14 where dialysate was running into the hopper from continuous venous hemodialysis; six where the hopper cover was ajar with a patient in the room. Outside of the audit process but early in the intervention period there was noted to be a practice of placing a reusable canister for biliary refeeding on the hopper cover[19]. This practice was modified four months after the start of the intervention period to use a new canister with each collection with no additional events noted in the subsequent independent audits.

Environmental analysis

All hoppers were sampled in a point prevalence survey prior to the installation period; during this survey, 74% (53/72) were positive for KPCO (*Enterobacteriaceae* or *Aeromonas* spp). Thirty-one percent (22/72) of hoppers had multiple species (Table 2). Sink traps and drains were also sampled in the SICU prior to installation of the sink trap devices with 80% (12/15) of patient sinks positive for KPCO (by either drain swab, sink trap water or both) with a similar variety of species (Table 2). For non-patient sinks located in common areas, the two staff bathroom sinks were positive for KPCO while the other six non-patient sinks were negative. During the intervention period the SICU sink drains and sink traps were sampled nearly

weekly with 55 complete sampling events. KPCO were identified in 40/825 sink samples collected during the intervention (4.9%), representing a significant decrease compared to baseline (12/15 [80%], $p=0.037$). During the intervention, the positive sinks were distributed across the unit, often positive when a colonized patient was in the room, and there was one day where four unique drains were positive for *S. marcescens* roughly two weeks into the intervention period.

Discussion

We demonstrate that environmental interventions targeting wastewater in intensive care units decreased nosocomial acquisition of multispecies KPCO across the entire hospital. Although this was done in a bundled approach in response to concerns around transmission with both hopper covers in all adult ICUs and the addition of sink trap devices in a single surgical ICU, the impact on transmission appears to have been driven by the use of hopper covers.

Hospital wastewater is an ideal niche for the development of drug resistance [20], given that antimicrobials excreted in urine and stool (and thus wastewater) represent significant selection pressures, nutrients from general waste disposal support bacterial growth and there is continuous seeding with antibiotic-resistant bacteria from colonized patients. This environment can facilitate the exchange of resistance genes and mobile genetic elements amongst multiple species[3, 21]. Adherence to the CDC toolkit to decrease the nosocomial transmission of carbapenem resistant Enterobacteriaceae may be insufficient for multispecies outbreaks[12, 22, 23], and the data demonstrating efficacy of the toolkit interventions has been derived largely from clonal outbreaks, such as those with KPC-ST-258 *K. pneumoniae*[24, 25].

Most studies of CRO-associated environmental transmission have focused on sink drains[4]. Our bundled approach and low numbers decreased the power to assess the efficacy of the sink trap intervention alone. Others have shown that similar sink trap devices installed to manage a neonatal *Pseudomonas aeruginosa* outbreak and an adult ICU-associated ESBL-*K. oxytoca* outbreak reduced acquisition rates and

transmission of these organisms, respectively[26, 27]. We demonstrate that the sink trap device dramatically decreased, but did not eliminate the KPCO culture-positivity of drain and sink trap samples, with 40 KPCO-positive sink drains/sink trap cultures following installation. The elimination of entrenched KPCO may require the removal of water and drainage systems from the ICU altogether, as recently demonstrated with other gram negative organisms[6].

The cost for 60 hopper covers was \$48,000 (with installation costs) and \$50,000 for 23 sink trap heaters at roughly \$3000 per unit (without installation/maintenance cost). Hopper or toilet covers are not required in the current US environmental hospital standards[28]. Although the hoppers were behind a lateral barrier in the room, they were exposed to facilitate access for healthcare staff. In future hospital design, it might be optimal to have them outside the patient room. The hopper covers were made in-house by the facilities team in consultation with nursing and medical staff and were well received; relatively high compliance with lid closure and avoidance of using them as a storage/work surfaces was observed, although use was only thoroughly audited in a single unit.

Although CPOs have been identified in hospital effluent [20, 29], there has been limited recognition of highly-resistant organisms in toilet/hopper water, as was shown in our point prevalence survey. There was no intervention to alter the presence of KPCO in hopper water, and we did not perform longitudinal surveillance to assess this. The species profile of KPCO seen in the wastewater was consistent with that observed in our patient population, suggestive of exchange between the two. The principle behind hopper flushing is similar to that of a pressure-flushed toilet with a high energy flush (rather than a gravity-flushed toilet), which generates the maximum number of droplets during flushing compared to other mechanisms[8], and plausibly represents a major source for the dispersal of these organisms in rooms containing open hoppers or toilets.

There are several limitations to our study. Because our interventions were implemented as part of a quality effort to decrease transmission of KPCO it was felt that both hopper covers and sink trap devices

should be implemented simultaneously on the highest-risk unit (the SICU), limiting our ability to demonstrate independent effects of each of these approaches. A second challenge was accurately attributing acquisition to any given location as many patients in this study were frequently transferred to different units. We have attempted to address this by analyzing risk as a function of cumulative hours spent in a unit with hoppers during both analysis periods. Our data supports what has been previously demonstrated; that KPCO transmission is complex [30] and more frequent in critically ill patients (the interventions were all in ICUs)[31] with patient-to-patient transmission likely still occurring as not all patients were exposed to hopper containing rooms during both analysis periods. We use the number of acquisition events as a proxy for transmission, but have not performed any molecular typing of isolates to confirm transmission events between environmental sources and patients.

In conclusion, hospitals must understand and assess the role of the hospital wastewater plumbing in multispecies CRO transmission to facilitate appropriate interventions. Awareness of possible toilet and hopper transmission of highly resistant Gram-negatives contributes to mitigating these reservoirs and reducing patient CRO acquisition. Implementation and use of hopper and toilet covers represents a low-cost, acceptable, and effective intervention in these contexts.

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Table 1. Difference in Acquisition in the Pre-intervention Period Compared to the Intervention Period

	Pre-intervention	Intervention	Odds Ratio[‡]	95% CI	p-value
	Nov 2014 - Jan 2016	May 2016 - Jul 2017			
KPCO Acquisitions	77	40			
KPCO Clinical Culture	33	13			
KPCO Colonization	44	27			
Total Patient Days	208,579	217,287			
Total Patient Admissions	33,808	33,817			
Total Peri-rectal Cultures	9,447	12,561			
Acquisitions per 10,000 Patient Days	3.69	1.84	0.498	0.331-0.739	0.0002
Acquisitions per 1,000 Patient Admissions	2.28	1.18	0.519	0.345-0.77	0.0008
Clinical Cultures per 1,000 Patient Admissions	0.98	0.38	0.393	0.19-0.768	0.0045
New Peri-rectal Colonizations per Surveillance Screens	4.66	2.15	0.399	0.255-0.615	<0.0001

[#]Excluded patients from units where peri-rectal surveillance does not occur (neonatal ICU, labor and delivery, psychiatry)., ^{*}Per patient admission, [‡]Difference per peri-rectal screening culture. *Klebsiella pneumoniae* carbapenemase (KPC), [‡]Fisher's Exact test

380 **Table 2. Species Breakdown of Patient and Environmental *Klebsiella pneumoniae* carbapenemase**
381 **(KPC) Producing Organisms from Different Time Points**

Species	Patient clinical and surveillance isolates		Environmental Samples		
	Species per Unique patient		Species per unique hopper (Adult ICUs)	Species per unique sink drain and sink trap (Surgical ICU only)	
	Pre-intervention	Intervention	Baseline positive hopper (one sampling)	Baseline positive sink (one sampling)	Prospective sampling during intervention (55 samplings)
Total	77 patients	40 patients	53/72 (74%)	12/15 (80%)	40/825 (5%)
<i>Serratia marcescens</i>	26	8	39	6	25
<i>Klebsiella pneumoniae</i>	17	9	0	0	1
<i>Enterobacter cloacae</i> complex	16	6	7	3	5
<i>Citrobacter freundii</i>	14	10	7	2	3
<i>Escherichia coli</i>	10	5	0	0	0
<i>Klebsiella oxytoca</i>	5	3	1	3	2
<i>Aeromonas</i> spp.	5	3	22	0	1

<i>Raoultella planticola</i>	0	4	0	0	1
<i>Citrobacter braakii</i>	0	1	0	0	0
<i>Citrobacter farmeri</i>	1	2	0	0	0
<i>Enterobacter aerogenes</i>	1	0	0	0	0
<i>Kluyvera intermedia</i>	0	1	0	1	0
<i>Morganella morganii</i>	1	0	0	0	0
<i>Pantoea</i> spp.	3	1	2	1	0
<i>Proteus mirabilis</i>	1	0	0	0	0
<i>Raoultella</i> <i>ornithinolytica</i>	1	1	1		2
<i>Citrobacter</i> spp.	1	0	0	0	0
Other Enterobacteriaceae	0	0	5	1	0

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Figure 1. Study periods for interventions and analysis

Figure 2. Interventions

2A Open hopper with adjacent barrier on left with attached open cover. 2B. Hopper cover in closed position. 2C MoveoMed Sink Trap heating and vibration device with electronics unit, as installed.

Figure 3. Adult intensive care unit layout of hopper and sink with general proximity to patient

Figure 4. Pre-intervention and intervention total monthly KPCO patient acquisition rates

Poisson Regression with monthly new KPCO acquisition count/10,000 patient days comparing the pre-intervention and intervention periods. The incidence rate ratio was 0.49 [0.34 – 0.72 95% CI] lower during the intervention compared to the pre-intervention period.

Figure 5. Sixty-day survival curves for *Klebsiella pneumoniae* carbapenemase producing organism acquisition for pre-intervention and intervention periods.

The log-rank test for the survival curves p-value<0.001.