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Modeling Interventions and Contact Networks to Reduce the Spread of Carbapenem-Resistant Organisms Between Individuals in the ICU

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Abstract

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AUTHORS' CONTRIBUTIONS

Dr. Martinez had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Martinez, Lessler, Milstone, Klein.

Acquisition, analysis, and interpretation of data: All authors.

Drafting of the manuscript: Martinez, Lin, Paul, Milstone, Klein.

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Importance: Contact precautions are widely used to prevent the transmission of carbapenem-resistant organisms (CROs) in hospital wards. However, evidence for effectiveness in natural hospital environments is limited.

Objective: To determine which contact precautions, healthcare-worker-patient interactions, and patient and ward characteristics are associated with greater CRO infection or colonization risk.

Design, Setting, and Participants: CRO clinical and surveillance cultures from two high-acuity wards were assessed through probabilistic modeling to characterize a susceptible patient's risk of CRO infection or colonization during ward stay. User- and time-stamped electronic health records were used to build healthcare-worker-mediated contact networks between patients. Probabilistic models were adjusted for patient (antibiotic administration) and ward characteristics (hand hygiene compliance, environmental cleaning). The effects of risk factors effects were assessed by adjusted odds ratio (adj. OR) and 95% Bayesian credible intervals (CrI).

Exposures: The degree of interaction with CRO-positive patients, stratified by whether CRO-positive patients were on contact precautions.

Main Outcomes and Measures: CRO prevalence and number of new carriers (i.e., incident CRO aquisition).

Results: Among 2,193 ward visits, 126 (5.8%) patients became incidentally CRO-colonized or infected. Susceptible patients had 4.8 daily interactions with CRO-positive individuals on contact precautions (versus 1.9 with those not on contact precautions). Contact precautions use for CRO-positive patients was associated with a reduced rate (7.4 vs. 93.5 per 1,000 patient-days at risk) and odds (adj. OR 0.03, 95% CrI 0.01–0.17) of CRO acquisition among susceptible patients, resulting in an estimated 9.0% (95% CrI 7.6–9.2%) absolute risk reduction. Also, carbapenem administration to susceptible patients was associated with increased odds of CRO acquisition (adj. OR 2.38, 95% CrI 1.70–3.29).

Conclusions and Relevance: In this population-based cohort study, contact precaution use for patients colonized or infected with CRO were associated with lower risks of CRO acquisition among susceptible patients, even after adjusting for antibiotic exposure. Further studies that include organism genotyping are needed to confirm these findings.

Keywords

Operations Research; Transmission; Healthcare Worker-Patient; Universal Precautions; Carbapenems; Antibacterial Drug Resistance

INTRODUCTION

Carbapenem-resistant organisms (CRO) are a significant and growing source of healthcare-associated infections with high morbidity and mortality.[1–8] CRO colonization or infection (acquisition) in the hospital setting is driven by transmission from contaminated healthcare workers (HCWs) or equipment.[9–11] However, these sources are complemented by endogenous patient factors, such as selective pressure exerted by antibiotics.[9–11] Infection control measures for CRO include interventions such as the use of contact precautions, environmental cleaning, hand hygiene, and antibiotic stewardship. Contact precautions

are assumed to reduce the likelihood that HCWs become contaminated and transmit organism horizontally to other patients. However, contact precautions are typically included as part of a bundle of interventions, which has challenged studies to demonstrate their effectiveness.[12–15]

The majority of studies investigating interventions to control the spread of CROs have been cross-sectional.[9–11,16] The difficulty with this design is that it can be challenging to differentiate the effect of interventions, such as contact precautions, from other factors mediating incident acquisition.[17] Evidence limited to vancomycin-resistant Enterococci (VRE) and *Pseudomonas aeruginosa*, for example, highlights the importance of understanding dominant acquisition routes for tailored infection control—cross-transmission was the dominant acquisition route for VRE and endogenous colonization for *P. aeruginosa*.[18] Thus, most studies, including many of longitudinal design,[18–22] have been restricted to the conclusion that contact precautions are associated with lower prevalence of CRO in a hospital population. However, it is still unknown the extent to which contact precautions are associated with a lower risk of incident CRO acquisition at the patient level, and how exogenous sources and endogenous patient characteristics modulate this risk. A better understanding of CRO acquisition dynamics is important for developing evidence-based CRO control interventions and programs. In this retrospective longitudinal study, we assessed whether contact precautions protect susceptible patients from CRO acquisition from other colonized patients.

METHODS

We use probabilistic models and CRO clinical and surveillance cultures to describe a susceptible patientś risk of CRO infection or colonization during hospitalization. This was done by measuring and comparing patient exposure to other colonized patients with and without contact precautions. As part of a research protocol,[23] all patients were screened for CRO colonization (or infection) in a non-outbreak setting where these screening results where not available in real-time and, therefore, did not guide antibiotic management or contact precaution usage. The effectiveness of contact precautions was studied using probabilistic models to isolate the relative contributions of individual characteristics (antibiotic administration, contact precautions), sources of potential transmission (healthcare worker hand hygiene), and unit characteristics (environmental cleaning). The Johns Hopkins Medicine institutional review board (IRB00074840) approved this study, with a waiver of informed consent.

Study Design and Setting

We conducted a retrospective cohort study of patients admitted to a medical intensive care unit (MICU) and a comprehensive transplant unit (CTU) from July 1, 2016 to June 30, 2017. Although the CTU is not considered an intensive care unit (ICU), it deliveres ICU-level care and, along with the MICU, has private patient rooms and uses contact precautions (gown and gloves) for those with a history of multidrug-resistant organisms or recent (<6 months) international hospitalization.[23] All patients admitted to the MICU and CTU had perirectal ESwabs™ (Copan Diagnostics, Inc.) collected at unit admission and weekly thereafter as

part of a longstanding vancomycin-resistant Enterococci surveillance program. As part of a research protocol (previously described [24]), residual media from this surveillance program, in addition to those cultures resulting from clinical care, were analyzed for the presence of CRO: *Enterobacterales* resistant to ertapenem, meropenem, and/or imipenem, which were classified as CRE, as well as glucose non-fermenting (NF) Gram-negative bacilli resistant to meropenem and/or imipenem, which were classified as NFCRO. CRO were further identified as carbapenemase-producing-(CP) versus non-CP- CRO by the phenotypic modified carbapenem inactivation method.[25,26]

Outcomes

The main outcome under study was incident acquisition of CRO, which was defined as 1) a patient that had a negative clinical or surveillance culture at unit admission and 2) a clinical or surveillance culture that was obtained more than two days after unit admission and grew a CRO. Each positive culture was assigned to either *potentially transmission-mediated* or *not potentially transmission mediated*.[18] Potentially transmission-mediated CRO acquisition was assumed when a patient grew a CRO of the same species as another patient in the same unit that had overlapping days of care. Not potentially trnamission mediated was assumed when no other patient with the same CRO species was in the unit. Patients could be incident cases more than once if they acquired a CRO of different species and met the above criteria. Once a patient became incidentally colonized or infected for a given CRO species, he (or she) was no longer included in the analysis of incident acquisition risk, but he (or she) remained in the study as contributing to the risk of transmission to others.

Exposure, Covariates, and Contact Data

Trained research staff rounded on each unit during weekdays to determine whether patients were on contact precautions for any indications (e.g., methicillin-resistant *S. aureus*, *Clostridioides difficile*, influenza virus). Staff from the Department of Hospital Epidemiology and Infection Control measured HCW hand hygiene and unit environmental cleaning compliance. The monitoring method to assess unit cleaning practice was based on fluorescent markers.[27]

Patient encounter data were retrospectively collected using bulk extraction methods from the hospital's electronic health records (EHR) system. Patient data included demographic information, laboratory test results, medication administration, and room assignments.

Time-stamped in-room visits by HCWs were extracted from the electronic health records system to estimate a patientś social network. That is, HCW-mediated connections with other patients in the hospital ward. We considered two patients, say patients A and B, were epidemiologically linked if the same HCW visited their rooms within a 60 minutes period. HCW interactions with patients were estimated through timestamps of in-room medication administrations, laboratory specimen collections, assessments, and other in-room routine care tasks based on the methodology developed by our team and presented in [16].

Statistical Analysis

The primary statistical analysis involved the specification of a probabilistic model describing the risk of a susceptible patient becoming colonized or infected as a function of measured attributes of the individual, surrounding patients, and the unit environmental cleaning levels. A Bayesian hierarchical logistic regression model was fitted with the Markov Chain Monte Carlo method (see Parameter Estimation in the Supplement). Outputs from the model were adjusted odds ratios (adj. OR) and 95% credible intervals (CrI). The OR and CrI estimates were reported and used to estimate the absolute risk reduction in susceptible individuals. All statistical analyses were performed in R version 3.5.1, using the freely distributed statistical package *BayesianTools* version 0.1.6.[28]

The probabilistic model had two levels, with information about transmission-mediated sources at level-1 and other sources at level-2 (see Model Formulation in the Supplement). To control for varying length-of-stay among patients, we modeled the risk of CRO acquisition per day. All model levels were assessed simultaneously to disentangle spatiotemporal patterns of each outcome, manifesting across each acquisition mechanism with respect to the individuals' characteristics, their HCW-mediated social network, and the broader unit characteristics.

Since carbapenemase-producing (CP)-CROs were considered the highest threat due to their resistance to multiple antbiotic classes and potential for plasmid transmission,[24,29] the acquisition dynamics of CP- versus non-CP-CRO were analyzed independently. The clinical and surveillance data did not allow us to ascertain the exact moment when a patient acquires a new CRO (unobservable clinical event). To evaluate the possibility that unobserved events might explain associations, we also examined if randomization of the actual acquisition date, between the dates of the last known CRO-negative culture and the CRO-positive culture, substantially impacted the direction and size of the estimated effects (see Extension of Main Results in the Supplement).

We evaluated our results' robustness by varying the time window of 60 minutes that established a patient's HCW-mediated social network from 15 minutes to 12 hours, the latter was included because it is consistent with the maximum length of most HCWs' shifts. We also studied acquisition dynamics at each hospital ward in separate models (see Robustness of Main Results in the Supplement).

RESULTS

Study Sample and Demographic Characteristics

The study cohort included 2,193 unit admissions (1,715 unique patients) to the MICU and the CTU (Table 1). Patients were predominantly adults between 45 and 59 years old (724/2,193, 35%), male (1,131/2,193, 52%), black (1,085/2,193, 50%), non-Latino (2,098/2,193, 96%), and Maryland residents (1,893/2,193, 86%) who were typically admitted as an emergency or urgent case (1,951/2,193, 89%). Patients in the cohort were connected through 216,069 distinct HCW-mediated connections, representing a daily average of 591 HCW-mediated contacts between patients. Most patients in the cohort were on contact precautions for CRO or some other antibiotic-resistant organism (87.4%

and 88.9% amongst non-incident and incident CRO admissions, respectively). Susceptible patients had on average 4.8 daily connections through HCWs with CRO-positive patients on contact precautions and 1.9 with CRO-positive patients not on contact precautions.

Colonization and Infection

A total of 126 out of 2,193 (5.8%) unit visits had a negative swab on admission and at least one positive swab more than 2 days after admission and were classified as incident for CRO acquisition (Table 1).[30] Amongst the 126 visits, 120 (93.0%) were linked with potentially transmission-mediated CRO acquisition events, because the patient grew a CRO of the same species as another patient in the hospital ward, while all of the 126 visits (100%) were detected to have at least one CRO acquisition event with no evidence of transmission. We recall the reader that patients could be incident cases more than once if they acquired a CRO of different species an met the criteria out outcome definition criteria. Non-incident and incident CRO patients had similar baseline demographics at unit entry. However, incident CRO individuals were more likely to have HCW-mediated contacts with CRO-positive individuals who were not on contact precautions (median (IQR), 1 (1–2) vs. 2 (1–2)). Compared to non-incident CRO patients, incident CRO patients were more likely to receive carbapenems (10.0% vs. 47.6%).

Modeling Results

The use of contact precautions for CRO-positive patients was associated with reduced rate and odds of CRO acquisition among susceptible individuals (7.4 vs. 93.5 per 1,000 patient-days at risk; adj. OR 0.03, 95% CrI 0.01–0.17). The estimated absolute risk reduction of contact precautions for CRO-positive patients, compared with CRO-positive individuals without contact precautions, was 9.0% (95% CrI 7.6–9.2%), corresponding to 3 events prevented per 1,000 patient-days at risk. For susceptible individuals, recent exposure to carbapenems (last seven days) was the primary driver of CRO acquisition (adj. OR 2.38, 95% CrI 1.70–3.29) (Table 2).

The mechanism of resistance appeared to be important. When the cohort was restricted to the acquisition of CP-CRO (versus non-CP-CRO), recent carbapenem exposure in susceptible patients had no statistically meaningful (i.e., Bayesian significance) relationship with incident CP-CRO acquisition (adj. OR 2.19, 95% CrI 0.96–4.56), whereas carbapenem exposure was significantly asscociated with non-CP-CRO acquisitions (adj. OR 2.01, 95% CrI 1.33–2.95). The use of contact precautions for CRO-positive patients, however, was linked with reduced rate and odds of CP- (48.0 vs. 417.6 per 1,000 patient-days at risk; adj. OR 0.04, 95% CrI 0.01–0.19) and non-CP-CRO acquisition (12.1 vs. 157.8 per 1,000 patient-days at risk; adj. OR 0.03, 95% CrI 0.01–0.16) among susceptible patients (Table S1).

We evaluated the robustness of our results to unobservable clinical events, i.e., our inability to precisely determine the actual CRO acquisition date during the patient stay (Table S2). We randomized the CRO acquisition date in our models within a reasonable time interval, from the last known CRO-negative culture and the CRO-positive culture. As presented in Table S2, the direction and magnitude of effects shown in Table 2 remained similar.

We also investigated the robustness of our results to our definition of a patient's social network: HCW-mediated contacts with other patients in the ward. When modifying the time-lapse of 60 minutes from 15 minutes to 12 hours, we found that the magnitude and direction of the contact precautions' effect were virtually unchanged (adj. OR ranges between 0.03 and 0.04). However, we found much uncertainty (95% CrI 0.01–0.17) within the posterior coefficient estimation (Table S4), signaling potential workflow differences between wards. To determine if workflow differences explained some of the variability in the effect of contact precautions, we fitted separate models for each ward. We found no significant differences in the effect of contact precautions between the MICU (adj. OR 0.03, 95% CrI 0.01–0.13) and the CTU (adj. OR 0.05, 95% CrI 0.01–0.28).

DISCUSSION

Contact precautions are a common intervention used to prevent transmission from patients colonized or infected with multi-drug resistant organisms. However, evidence for the effectiveness of contact precautions in natural hospital environments for methicillin-resistant *Staphylococcus aureus* and VRE is limited,[13] and is restricted to theoretical models and aggregate secondary analyses of clinical trial data for CRO.[21,31] This uncertainty is due in part to the low frequency of CRO acquisition events in the hospital and the challenge of observing these events in the absence of robust surveillance. Furthermore, there is rapid turnover in the patient population, large numbers of HCWs and staff that attend each patient or room, and sharing of equipment among units that make it challenging to assign causal factors to acquisition events.[32] Disaggregate (patient-level) probabilistic models can overcome some of these challenges. By explicitly decomposing distinct longitudinal patient and environmental factors of CRO acquisition, we found that contact precautions might reduce CRO acquisition risk, even after adjusting for carbapenems exposure.

Our patient-level probabilistic modeling approach contributes to recent aggregate (hospital ward-level) data suggesting the use of contact precautions in intensive care environments is associated with a non-statistically significant decrease in CRO acquisitions.[21,31] By quantifying acquisition dynamics with observable (covariates) and unobservable (outcome) clinical events, our disaggregate models are sensitive to the uncertainty of the epidemic process (e.g., endogenous versus exogenous acquisition mechanism), and include longitudinally dynamic parameters of particular interest (e.g., contact precautions). The use of Bayesian hierarchical logistic regression allows for more mechanistic insights on acquisition risk factors which is advantageous over machine-learning models that lack interpretability.[33] However, contrary to a recent study suggesting increased HCW-mediated connections were significantly associated with transmission of enteric pathogens,[16] our results for the role of HCWs were not significant (95% CrI 0.05–18.58). Multiple reasons can explain this difference. Our disaggregated models included contemporaneous overlap in the hospital ward as a prerequisite to epidemiologically link two patients, which challenges our ability to disentangle overlap in the department from strength of connection on a day-to-day basis. Alternatively, the HCW connectivity data are based on electronic health records entries which might miss important connections that are not well documented. Also, surface contamination may result in indirect transmission that is not specific to direct

patient-HCW-patient connectivity. Thus, further analysis of these network connections and the relative importance of HCWs to acquisition are needed.

We found that the primary driver of CRO acquisition was exposure to carbapenems, highlighting the opportunity for CRO-targeted antibiotic stewardship programs. Carbapenems may exert selective pressure that induces endogenous flora to evolve to become CRO or enriches existing CRO below the limit of detection of culture methods.[34] Alternatively, they can disrupt flora and make the patient more susceptible to colonization upon exogenous exposure—either way emphasizes the potential role of antibiotic stewardship.[35]

A limitation of any effort to capture transmission of a pathogen in a hospital with so many potential opportunities for transmission is that the actual date of acquisition is typically unknown (i.e., unobservable clinical event). This somewhat inconclusive direct evidence fed into our models produced estimates of effect with wide credible intervals, signaling considerable uncertainty about the true value of the effect size. To account for the uncertainty in the colonization date, we estimated the parameters for the model assuming a random acquisition date. That is, if a patient in week one is known to be CRO negative and in week two is known to be CRO positive, we evaluated the model assuming the CRO acquisition event took place at some random time period between these two surveillance tests. The results of randomizing the acquisition date did not qualitatively impact the direction and size of the estimated effects, suggesting the use of contact precautions in CRO patients is still better than no intervention.

While we attempted to collect detailed data on patient hospitalizations and infections, limitations remain to the estimated transmission parameters. One limitation is the observation scope of transmission-mediated acquisitions being limited to departments offering ICU-level care in a tertiary research hospital, which means our results may not be generalizable to other hospitals given patient diversity, varying clinical guidelines and protocols, and location-specific transmission pathways. Still, the process by which the CRO data were collected and analyzed should be suitable in analogous situations where healthcare-worker interactions, contact precautions, and carbapenem exposure is a risk. Second, clinical risk factors that impact acquisition dynamics, such as history of previous overseas hospitalization, were not explicitly incorporated into our assessment. Third, some activities and contacts might not be logged into the EHR system by individuals. Still, contact networks between patients and providers built with data regularly collected in most EHRs are surrogates for understanding the extent of connectivity between individuals. This facilitates the translation of this research to operational infection control practices scalable across institutions with an EHR system. Fourth, not all patients in our cohort were screened at discharge, which might result in ascertainment bias. In post hoc analyses, we found that 97.5% of patients were screened within 8.3 days of discharge and 99% within 11.6 days. We therefore expect ascertainment bias to be minimal and not have significant impact in our results. Lastly, our classification of CRO types may benefit from better diagnostic methods of microbial genotyping, which can distinguish cross and environmental transmission events more precisely. We assumed that all colonized patients with the same CRO type could be a transmission source, which we think is a reasonable assumption.

CONCLUSION

The analysis of extensive longitudinal clinical and surveillance data from two tertiary high-acuity hospital wards demonstrated that the use of contact precautions might be an effective intervention for preventing CRO acquisition among susceptible patients, even after adjusting for antibiotic exposure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY POINTS

Question:

Which contact precautions, healthcare-worker-patient interactions, and patient and hospital ward characteristics are associated with more significant CRO infection or colonization risk during hospitalization?

Findings:

In this probabilistic modeling study of CRO acquisition among hospitalized patients in two high-acuity wards, the use of contact precautions for patients colonized or infected with CRO was associated with lower risks of CRO acquisition among susceptible patients.

Meaning:

This study's findings suggest that using contact precautions might be an effective intervention to protect susceptible patients in hospital wards.

Table 1.

Study participant characteristics at study entry by CRO acquisition during observation in the longitudinal study of two tertiary high acuity units in Baltimore, Maryland, July 2016-June 2017 (n=2,193).

Variable	Non-incident[a]	Incident CRO[b]
Cohort size, *count of unit admissions*	2,067	126
Predicted outcomes, *count of incident CRO acquisitions*		
Potentially transmission-mediated	-	120
Not potentially transmission mediated	-	126
Demographics and arrival mode, *% of unit admissions*		
Age		
15–29	7.0	6.0
30–44	15.0	11.0
45–59	35.0	38.0
60–74	33.0	38.0
75–89	9.0	6.0
90+	1.0	1.0
Sex, male	51.4	54.0
Race, white	43.8	46.0
Race, black	49.8	44.4
Ethnicity, not Latino	95.6	96.8
Patient residence, Maryland	86.5	83.3
Patient residence, another state within the US	13.3	15.9
Patient residence, foreign	0.2	0.8
Admission type, emergency	88.6	95.2
Admission type, elective	8.5	4.0
Admission source, home	71.3	65.1
HCW-mediated connections to CRO-positive patients, *daily median and IQR*	2 [0–6.0]	3 [1–7.5]
Clinical variables, *% of unit admissions*		
Contact precaution order	87.4	88.9
Environmental cleaning compliance	88.9	87.4
Hand hygiene compliance	93.6	92.9
Carbapenems administration last 7 days	10.0	47.6

Abbreviations: HCW, healthcare worker; CRO, carbapenem-resistant organism; IQR, interquartile range.

[a]We are distinguishing patients who did become incidentally colonized with CRO versus those that did not become incidentally colonized.

[b]Patients could be incident cases more than once if they acquired a CRO of different species and met the folllowing criteria: An incident acquisition of CRO was defined as 1) a patient that had a negative clinical or surveillance culture at unit admission and 2) a clinical or surveillance culture that was obtained more than two days after unit admission and grew a CRO. Each positive culture was assigned to either *potentially transmission-mediated CRO acquisition* or *not potentially transmission mediated*. Potentially transmission-mediated CRO acquisition was assumed when a patient grew a CRO of the same species as another patient in the same unit that had overlapping days of care. Not potentially transmission mediated was assumed when no other patient with the same CRO species was in the unit.

Table 2.

Risk Factors for Incident CRO Acquisition Among Patients Hospitalized in a Medical Intensive Care Unit and a Solid Organ Transplantation Unit of a Tertiary Hospital by Mode of Acquisition.

Variable	Adj. Odds Ratio (95% CrI)
Level-1: Potential for transmission	
HCW-mediated connection to CRO patients	0.90 [0.05, 18.58]
Contact precaution on CRO-positive patients in the unit	0.03 [0.01, 0.17][a]
Environmental cleaning compliance >95%[b]	0.41 [0.03, 3.27]
Carbapenems exposure in the prior 7 days	0.39 [0.03, 2.97]
HCW hand hygiene compliance >95%[b]	0.33 [0.03, 2.47]
Level-2: Acquisition from sources other than a known infection	
Carbapenem exposure in the prior 7 days	2.38 [1.70, 3.29[a]]

Abbreviations: CRO, carbapenem-resistant organism; HCW, healthcare worker; OR, odds ratio; CrI, credible interval.

[a]Statistically significant (Bayesian significance).

[b]Hospital wards with an environmental cleaning compliance over 95% and HCW hand hygiene compliance over 95% represent the top-quartile performers in our sample.