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Short report

Vancomycin use in surrounding patients during critical illness and risk for persistent colonization with vancomycin-resistant Enterococcus

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SUMMARY

The optimal duration of contact precautions for vancomycin-resistant enterococcus (VRE)-colonized patients is uncertain and individual patient characteristics alone may not predict risk of prolonged colonization. Using a cohort of adult patients who underwent testing for VRE at intensive care unit (ICU) admission, we tested the association between local (unit-level) vancomycin use and persistent colonization with VRE. Higher unit-level vancomycin use significantly prolonged VRE colonization (P=0.03) independent of patient-level vancomycin use and unit VRE density.

Introduction

Accurate estimation of duration of colonization with multidrug-resistant organisms such as VRE is an important prerequisite for effective hospital infection control. Risk factors for prolonged VRE colonization have mostly been identified at the patient level, e.g., patient-level antibiotic exposure or being immunocompromised [1–3]. However, whether the risk of prolonged colonization is fully captured by these individual risk factors is unclear. In particular, antibiotic exposure in co-localized patients, a modulator of the microbiologic milieu, has not been addressed as a risk factor for prolonged VRE colonization. Using a cohort of adult patients who underwent standardized testing for VRE at intensive care unit (ICU) admission, we tested the association between local (unit-level) vancomycin use and persistent colonization with VRE. We hypothesized that high local vancomycin use would predispose to persistent colonization with VRE independent of patient-level use of vancomycin.

Materials and methods

Study population

This retrospective cohort study included hospitalized adults ≥18 years old at ICU admission in a large academic medical center from 1st January 2012 to 31st December 2016. Included subjects had an initial positive screen for VRE followed by repeat testing performed at a new ICU admission at least three

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months later, and within three years of the initial positive test. This study included six tertiary referral medical ICUs where admission VRE surveillance swabs were collected routinely. The institutional review board of Columbia University Medical Center approved this study with a waiver of informed consent.

VRE testing

ICU nurses carried out VRE testing using a standard protocol within 24 h of ICU admission. The patient was placed in a left lateral decubitus position with the swab inserted deeply into the rectal canal and rotated five times. Flocked rectal swabs (Copan Diagnostics) were used, transported in 1 mL of liquid Amies media via vacuum container tube, and directly cultured on to chromogenic differential media impregnated with 6 μg/ml of vancomycin (Remel) which identifies *Enterococcus faecalis* and *Enterococcus faecium*. Plates were incubated at 33–37°C under aerobic conditions for 24 h and interpreted according to the manufacturer's instructions.

Defining the hospital microenvironment at time of initial VRE positivity

The patient environment at the time of initial VRE detection was characterized by: (i) local use of vancomycin (the primary exposure) and, (ii) local density of VRE [4].

The local use of vancomycin was defined as the total number of patient-days of vancomycin used during the ICU admission of a specific patient divided by the number of days at risk. Receipt of vancomycin included oral or intravenous vancomycin at any dose or duration.

The local density of VRE was defined as the number of VRE-positive patients in the same ICU during the patient's ICU admission (summative VRE pressure) divided by the length of the patient's ICU admission (length of time at risk):

$$\text{VRE colonization pressure} = \frac{\sum \text{Daily exposure to VRE positive patients (sum VRE pressure)}}{\text{Length of time at risk}}$$

Both these variables were dichotomized into two categories (above median vs equal to or below the median for the data set).

Patient-level risk factors for VRE persistence

We examined multiple patient-level risk factors as potential confounders for prolonged VRE colonization. These included demographics (age, sex) and clinical characteristics (primary diagnosis, use of immunosuppression, surgical interventions, and dialysis), at the time of initial VRE positivity. We also assessed laboratory values at the time of initial VRE positivity – WBC count, hematocrit, creatinine and albumin. Immunosuppression was defined based on concurrent use of an immunosuppressing agent including steroids ≥5 mg daily of prednisone or equivalent. Patient–level vancomycin use was examined in two ways: first by looking at cumulative days of vancomycin use during the initial admission where the patient tested positive; and second, categorically based on receipt of vancomycin at any dose or duration during hospitalizations between the two VRE swabs.

Table I
Characteristics of patients in high- and low-vancomycin-use environments

	Low vancomycin (*N*=55)	High vancomycin (*N*=44)	*P*
Male sex	34 (61.8%)	19 (43.2%)	0.1
Age (mean)	66.1	57.3	0.04*
Ward VRE density (mean)	0.1	0.1	0.2
Laboratory values mean (standard deviation)			
WBC × 10^9/L	11.6 (10.0)	9.2 (4.9)	0.1
Hematocrit	30.8 (6.6)	32.2 (1.8)	0.1
Creatinine (mg/dL)	1.6 (1.3)	1.4 (1.1)	0.4
Albumin (g/dL)	2.8 (0.6)	2.8 (0.6)	0.9
Sodium (mEq/L)	137.9 (4.5)	138.1 (4.5)	0.8
Patient characteristics			
Immunosuppression	11 (20%)	9 (20.5%)	0.9
Recent surgery	4 (7.3%)	3 (6.8%)	0.9
Mechanical ventilation	17 (30.9%)	15 (34.1%)	0.1
Dialysis	1 (1.8%)	1 (2.3%)	0.1
Patient antibiotic use			
Vancomycin exposure days (mean)	112	111	0.5
Number of interval admissions with any vancomycin use	2 (3.6%)	2 (4.5%)	0.7
Use of non-vancomycin antibiotics	39 (70.5%)	33 (75%)	0.8

VRE, vancomycin-resistant enterococcus.

Statistical approach

We compared patient-level variables between patients in the high and low local vancomycin-use groups. Wilcoxon-rank sum tests or *t*-tests were used based on distribution for continuous data. Chi-squared or Fishers exact tests were used for categorical variables.

We used a Cox proportional hazards model for the outcome of having a negative VRE swab at least 3 months after the first positive swab. Patients were followed from the time of ICU admission to death, a negative VRE swab or up to a maximum of 3 years. The proportional hazards assumption was validated by testing for a non-zero slope in the Schoenfeld residuals. The log-rank test was used to test for significant differences between the survival functions. Variables were tested in a stepwise manner and only those with a significant independent

relationship, or those altering the β-coefficients representing local vancomycin use by 10% or more were included. Continuous variables were dichotomized based on the median value if the distribution was non-normal using the Shapiro–Wilk test. All analyses were performed using R (Foundation for Statistical computing, Vienna) and were conducted as two-tailed *P*-values at the $\alpha = 0.05$ level of significance.

In additional analyses, we compared characteristics (age, sex, and immunosuppression) of patients who had repeat VRE testing to all VRE surveillance positive patients during the study period to assess generalizability. We also compared the distribution of ICU types between high and low local vancomycin use units, to test for whether unmeasured unit-level factors could contribute to any observed effect.

Results

Study population

There were 99 patients with positive VRE tests who underwent repeat testing for VRE within a 3-year window of the initial test. Among these, 44 patients, were exposed to local vancomycin use exceeding the median. Fewer patients in the high local vancomycin use group (17, 39%) tested negative for VRE subsequently, compared with 25 (51%) percentage in the low local vancomycin use group (*P*=0.20). Patients in the high local vancomycin use group, had a longer median time to the first negative test (415 days vs 267 days).

Demographic and clinical characteristics

Patients in the high local vancomycin use group were younger. There were no other significant differences in other demographic or clinical variables (Table I). Patient-level vancomycin use as well as unit VRE colonization density were comparable between high and low local vancomycin use groups.

Cox proportional hazards model

In the time to event model, patients with high local vancomycin use were colonized with VRE significantly longer compared to patients with low vancomycin use (P=0.03) (Figure 1). Local VRE density did not have a significant independent association with time to VRE negativity.

Additional analysis

There was no significant difference in ICU types between patients in the high and low local vancomycin units (*P*=0.24). The overall group of patients who tested positive for VRE (*N*=270) compared to this current study group were similar in age (mean age 63.3 years vs 62.2 years), sex distribution (3.7% males vs 53.5%), similar rates of undergoing surgery during ICU stay (14.2% vs 9.1%) but were more likely to be immunocompromised (41.8% vs 20.2%, *P*<0.01).

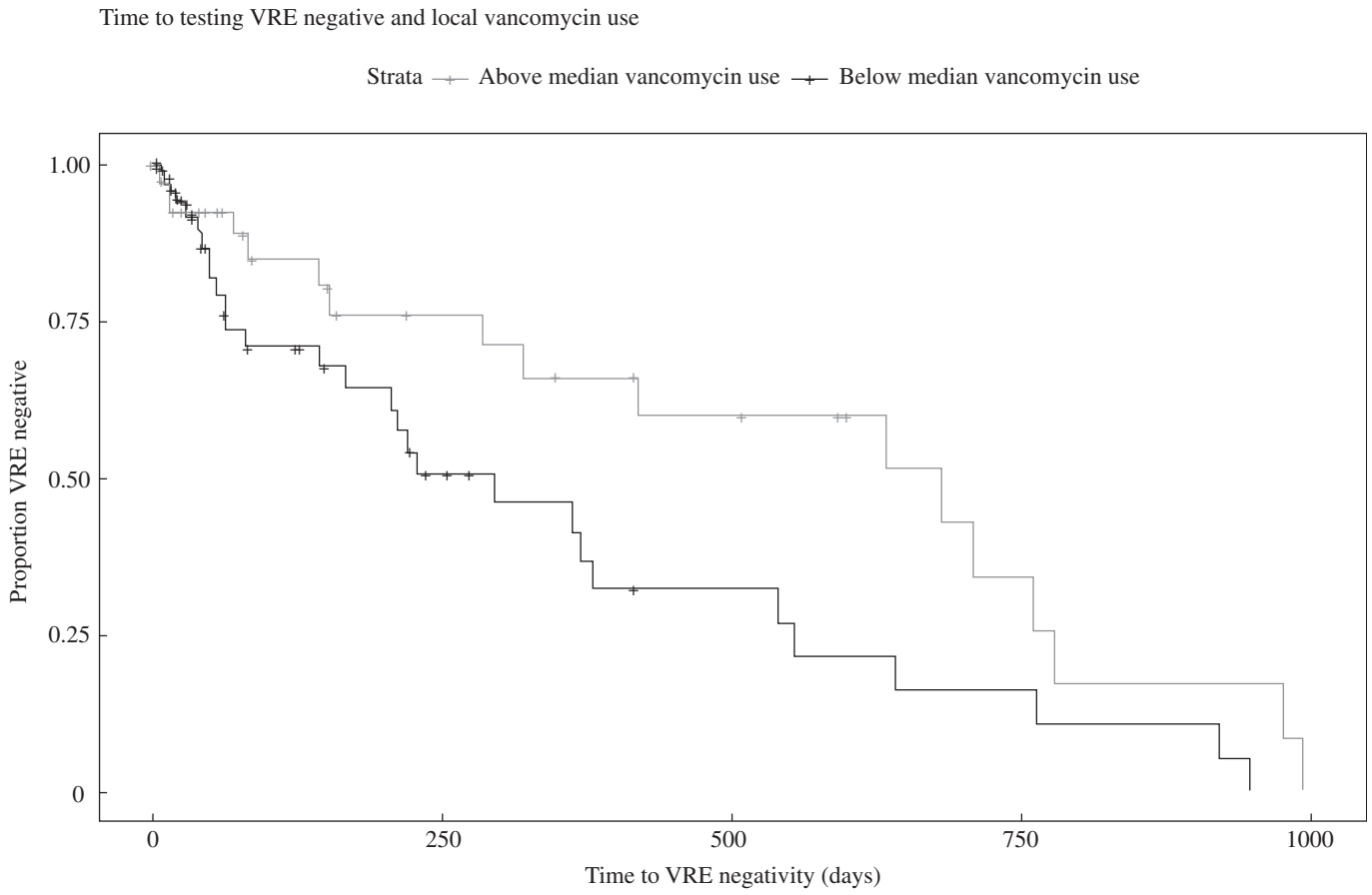

Figure 1. Time-to-event analysis for vancomycin-resistant enterococcus (VRE) persistence after an initially positive test, stratified by environmental vancomycin exposure.

Discussion

In VRE-positive ICU patients, high local vancomycin use significantly prolonged VRE colonization, independent of individual-level vancomycin use and unit VRE density. ICU Patient colonization with multi-drug-resistant organisms (MDROs) is determined by dynamic exchange of microbiota with the environment [5,6]. Patient-level antibiotic use is recognized as a crucial modifier for this environmental MDRO acquisition and persistence. What this data suggests is that in addition to patient-level antibiotic use, unit-level use of antibiotics may also be a predictor of persistent MDRO colonization.

There are plausible reasons why this might occur. Unit-level antibiotic use may be a more sensitive measure of the environmental burden of MDROs compared to organism detection because of the selective pressure of antibiotics on the local microbiota. Continued exposure to VRE which persists because of continuing vancomycin use in the ICU may lead to a higher and continuing inoculum and prolonged VRE colonization in an individual patient. It is also possible that ongoing selection pressure from antibiotic use in surrounding patients may alter the unit environment in a manner which makes it harder for patients to acquire competing microbiota (e.g., VSE) that could replace VRE. Antibiotics given to co-localized patients may lead to individual outcomes that may not be immediately apparent. Antibiotic use in prior bed occupants has been described as a risk factor for acquisition of *Clostridium difficile* [7].

These results have clinical implications. Patient-level variables and local VRE prevalence may not fully capture risk of prolonged colonization. It may be necessary to examine unit-level antibiotic use patterns to best risk-stratify patients in terms of duration of colonization. Unfortunately, such data may be difficult to be obtain in real time.

This study does have limitations. Timing of testing for colonization, though standardized at the admission specimen was subsequently dependent on clinical factors thus we cannot be certain of exactly when patients may have converted from colonized to non-colonized. However, the timing of re-testing is unlikely to be differential based on unit-level vancomycin use and therefore unlikely to bias these results. The effect of antibiotics other than vancomycin (e.g., quinolones) which could be risk factors for prolonged colonization were not assessed [8]. The use of a single swab for determination of 'negativity' could have led to false negatives. Our study population may also not be fully representative of the overall VRE-positive population.

In summary, local (unit-level) vancomycin use was associated with persistence of colonization with VRE. This information could be incorporated into risk-stratified isolation strategies for VRE if unit-level vancomycin use is known.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

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