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Factors contributing to vancomycin-resistant *Enterococcus* spp. horizontal transmission events: exploration of the role of antibacterial consumption☆

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ABSTRACT

Background: The relationship between antibiotic consumption and resistance is relatively well defined at the population/ecologic level. Increases in antimicrobial consumption correlate with increased antibiotic resistance for clinical and surveillance isolates. However, the impact of antimicrobial consumption on nosocomial transmission of resistant bacteria is less well defined. This study explores the association between antimicrobial consumption, hand hygiene, and horizontal resistant organism transmission.
Methods: A retrospective cohort pilot study was conducted. Vancomycin-resistant *Enterococcus* spp. (VRE) horizontal transmission events during a 2-year period were identified. VRE transmission events were defined as isolation of genetically similar VRE strain-types (determined using pulsed field gel electrophoresis) from patients who were temporally and geographically co-localized within our hospital. The Centers for Disease Control and Prevention Antimicrobial Use and Resistance Module was utilized to collect antibacterial consumption data of commonly utilized agents. Hand hygiene was quantified using floor-by-floor peer audit data. Regression techniques were employed to assess population-level relationships between study variables and transmission events.
Results: One hundred nineteen transmission events were identified. Hand hygiene estimates were homogeneous and did not correlate with VRE transmission rates. Stepwise-multivariate linear regression revealed that aztreonam consumption was associated with a lower rate of transmissions in the medical intensive care unit ($P = 0.031$), and carbapenem consumption was associated with a higher rate of VRE transmission events on one of two oncology floors ($P = 0.033$).
Discussion/Conclusion: Consumption of aztreonam and carbapenems was associated with VRE horizontal transmission rates. Further studies are necessary to identify other associations and elucidate the full clinical significance of this finding.

1. Introduction

Antimicrobial consumption has been increasing in recent years. Among member organizations of the University HealthSystem Consortium between 2002 and 2006, antimicrobial consumption increased from a mean 798 days of therapy (DOTs) per 1000 patient days to a mean 885 DOTs per 1000 patient days ($P = 0.02$) (Pakyz et al. 2008). In this vein, broad-spectrum consumption increased from a mean 361 days DOTs per 1000 patient days to a mean 386 DOTs per 1000 patient days ($P = 0.01$) and was driven by increases in consumption of piperacillin-tazobactam ($P < 0.001$) and the carbapenems ($P < 0.001$) (Pakyz et al. 2008). Similar findings from a large Centers for Disease Control and Prevention (CDC) epidemiologic study confirm that broad-spectrum antimicrobials such as piperacillin-tazobactam dominate usage in hospitalized patients, and the broad-spectrum Gram positive agent vancomycin is the most commonly administered antimicrobial agent (Magill et al. 2014).

The increase in antimicrobial consumption, whether judicious or superfluous, has been shown to promote antimicrobial resistance. The

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CDC has classified the level of many of these commensals turned pathogens as 'urgent' or 'serious' threats (Cocohoba et al. 2012). Vancomycin-resistant *Enterococcus* spp. (VRE) comprise a pathogen group classified in the CDC Antibiotic Resistance Threats report as 'serious'(Cocohoba et al. 2012). Concern is justified, as patients infected with or colonized by VRE have been found to experience increased mortality, longer lengths of inpatient stay, and greater overall healthcare costs compared to patients without VRE (Cosgrove 2006).

The prevalence of VRE has been previously correlated with vancomycin usage (Fridkin et al. 2001); however, the genesis of the VRE is less clear. VRE may be created de novo in an individual as a function of random mutations and antimicrobial selection (Hollenbeck and Rice 2012; Rice et al. 2004a, b), or can be horizontally transferred between individuals with ultimate proliferation manifesting later (Bonten et al. 2001). Much has been written about methods of horizontal transmission, and hospital-based horizontal transmissions may be multifactorial in nature. Inadequate hand hygiene is one of the most frequently cited reasons for such transmission (Barnes et al. 2014; De Angelis et al. 2014). It is known that appropriate and thorough healthcare worker hand hygiene practices are a key step in mitigating the risk of horizontal transmissions among patients (Barnes et al. 2014; De Angelis et al. 2014; Kirchhoff, 2015; Pittet et al. 2006).

While hand hygiene compliance is one factor known to have an association with horizontal transmission of organisms, other factors such as antimicrobial consumption may also be involved. This study explored the association between antimicrobial consumption, healthcare worker hand hygiene, and the incidence of horizontal VRE transmission events within high-risk inpatient units.

2. Methods

2.1. Study design

A retrospective cohort pilot study was conducted. VRE transmission events occurring between January 1, 2012 and December 31, 2013 were evaluated at Northwestern Memorial Hospital, an 897-bed hospital in Chicago, Illinois. This study was approved by the institutional review boards at Northwestern University and Midwestern University.

2.2. VRE collection and identification

VRE from clinical or surveillance cultures were collected as previously described (McLaughlin et al. 2013). Briefly, clinical isolates were obtained as clinically indicated from blood, cerebrospinal fluid, or urine. Rectal surveillance cultures were obtained on admission and weekly. VRE were identified to the species level; per protocol, manual biochemical reactions were used for identification when necessary. Vancomycin susceptibility testing was performed with the Vitek 2 system (Vitek Systems; bioMerieux, St. Louis, MO). Vancomycin resistance was defined as a vancomycin MIC ≥32 mg/L (Baddour et al. 2015).

2.3. Determination of genetic relatedness

Pulsed field gel electrophoresis was performed in accordance with routine VRE epidemiologic procedures at our institution, and as previously described (McLaughlin et al. 2013; Scheetz et al. 2008). After digestion with SmaI restriction enzymes, visual inspection of DNA banding patterns was performed, and the criteria of Tenover et al. were applied (Tenover et al. 1995). Only closely related strains, i.e. ≤3 bands difference, were considered for transmission events (McLaughlin et al. 2013).

2.4. Horizontal VRE transmissions

Patients newly infected or colonized with VRE and present in a high-risk unit (i.e., a unit with a known high rate of VRE transmission) during the study period were considered for inclusion. Pre-defined high-risk units included the medical intensive care unit, two physically and clinically distinct hematology/oncology units (e.g., a primarily solid tumor oncology medicine unit [hematology/oncology 1] and a primarily hematologic malignancy medicine unit [hematology/oncology 2]), and the stem cell transplant unit. VRE prevalence on these units is prospectively monitored at our institution by the Healthcare Epidemiology and Infection Prevention department (HEIP). VRE isolates from patients within these units identified during the study period that were A) closely related (i.e., ≤3 bands difference) (McLaughlin et al. 2013; Tenover et al. 1995), B) present inter-patient, and C) temporally related were further reviewed to determine the presence of a horizontal transmission event (Esterly et al. 2014). Patient electronic medical records for the index admission (i.e., the admission where a VRE transmission occurred) were reviewed by the HEIP staff to determine potential sources of VRE transmission. Contemporarily hospitalized patients were considered as possible source patients for a transmission event if they were 1) colonized or infected with VRE, 2) co-localized on the same unit as the transmission event, 3) and crossed-over temporally within the same unit as the transmission event. Medical record and microbiology database review were performed to identify the presence of overlapping caregivers and shared equipment. Bed traces were completed to determine patient geographic proximity and identify timeframe of horizontal transmission. Patients were excluded if they were less than 18 years of age at the time of transmission. VRE transmissions were standardized with a denominator of 1000 days present (DPs) for each study month and location. As such, each transmission event was also represented in the denominator.

Patient level data for each transmission event were collected to assess differences in patient characteristics between evaluated locations. Variables included: patient age, sex, *Enterococcus* species, length of hospital stay during the index admission, number of antibacterial agents received during the index admission, the number of individual patients who may have transmitted VRE (i.e., number of potential source patients per transmission event), and number of admissions to our institution in the 12-month period preceding the transmission event.

2.5. Antimicrobial consumption

Antimicrobial consumption data were collected as follows: clinical decision support software (Theradoc; Premier Inc., Salt Lake City, UT) was used to package data for submission to the CDC National Healthcare Safety Network (NHSN) Antimicrobial Use and Resistance (AUR) Module (Mignard and Flandrois 2006). Data were extracted from https://sams.cdc.gov and represented all administered doses in the specified location generated from bar-code medication administration records. Antimicrobial consumption was quantified as patient antimicrobial days (ADs), as defined by the CDC: "The aggregate sum of days for which any amount of a specific antimicrobial agent administered to an individual patient as documented in the electronic medication administration record and/or bar coding medication record" (Mignard and Flandrois 2006). Patient ADs were collected for a pre-specified list of commonly utilized antimicrobial agents including cefepime, ceftazidime, piperacillin-tazobactam, ampicillin-sulbactam, aztreonam, carbapenems (aggregation of meropenem and imipenem), ciprofloxacin, moxifloxacin, and intravenous (IV) vancomycin. ADs were standardized with a denominator of 1000 DPs for each study month to adjust for consumption fluctuation between months and between evaluated inpatient locations (Ibrahim and Polk 2014). As such, each patient represented in the numerator was also represented in the denominator. Input data for the regression analysis for each location consisted of monthly values for standardized consumption of each specific antibiotic and monthly values for the standardized number of VRE transmission events, 24 months in total. Antibacterial agents with a mean consumption rate of <10 ADs/1000 DPs per month by location were excluded from analysis to minimize outlier data effects on associations.