Exploring the Role of Antibiotics on VRE Colonization and Infection

Dr. James McKinnell, Dr. Loren Miller, Dr. Arnold Bayer
K30 Fellow
Harbor-UCLA/University of Alabama
Background

- *Enterococcus* Spp. are the third most common nosocomial bloodstream infection.

- According to the NNIS, the percentage of isolates with vancomycin resistance has increased from <1% in 1990 to nearly 30% in 2003.
Background

- There are 45,000 cases of VRE-BSI in the US every year

- **VRE-BSI** has an attributable mortality of 30% and accounts for $1.5 billion in US healthcare costs
Exposure of *Enterococcus* spp. to vancomycin leads to genetic mutations that afford resistance to glycopeptides
Antibiotics VRE

- Hospital epidemiology studies show little correlation between vancomycin use and rates of VRE colonization or infection.

- In contrast, multiple investigations show good correlation with cephalosporin use.
WHAT!!! Did he just say that VRE is more related to cephalosporin use and NOT Vancomycin use??!!?!?!!!

- Animal Data
- Multiple Hospital Epidemiology Studies
Model for VRE Bacteremia

Colonization Pressure: VRE Carriage in Stool, VRE Infections

Self-Contamination

Environmental Contamination

Patient-to-Patient Transfer

Bacteremia

Bacteremia
Two-Hit Hypothesis for VRE Colonization

Normal Intestinal Flora

Hit #1
VANCOMYCIN

VRE Carrier
1) Selection of VRE isolates
2) Normal Flora inhibits VRE
3) VRE may remain for years

Hit #2
BROAD SPECTRUM ANTIMICROBIALS
Gram Negative Rods, Anaerobes, Fungi

VRE Fecal Colonization
1) Alteration of Intestinal Flora
2) Overgrowth of VRE
Can you link antibiotics and Colonization?

- “Antibiotic Exposure” is a risk factor for VRE colonization in patients admitted to the intensive care unit

- Animal Data indicate that cephalosporins with high biliary excretion (e.g. ceftriaxone) are more likely to lead to colonization with VRE
So, Can you link Antibiotics with actual infection?

- There have been more than 10 epidemiologic studies that associate antibiotic use, particularly cephalosporins, with subsequent development of invasive VRE infections.

- There have been 9 studies that non-selectively restricted cephalosporins and reduced VRE infection rates.
So, why not restrict cephalosporins?

- Non-selectively restricting cephalosporins is impractical for most hospitals

- Surprisingly, VRE-BSI risk has not been quantified for individual cephalosporins
The overall hypothesis of this proposal is that a causal pathway links individual cephalosporins with VRE colonization which, subsequently, leads to more invasive infections (A+B).
**Specific Aims**

- **Aim 1:** Explore the association between individual antibiotics and VRE colonization (A)

- **Aim 2:** Assess the relationship between exposure to specific antibiotics and VRE-BSI (C)

- **Aim 3:** Characterize the putative pathway between antibiotic exposure, colonization pressure, and VRE-BSI rates (A+B or C)
Aim 1: Antibiotics and Colonization

- Monitor Patients for VRE Gastrointestinal Colonization
  - MICU, NICU, SICU
  - Admission Swab
  - Surveillance Swab
- Collect Demographic Information
  - Electronic Extraction
  - Chart Review
- Collect antibiotic treatment history
  - Prior to ICU
  - During ICU

Diagram:
- Admission to ICU Baseline Screening
  + Colonized Prior to Intensive Care
  - Not Colonized on Admission
    - Weekly Unit Surveillance
      + Incident Colonization
      - Never Colonized
    - Discharged Prior to Surveillance Screen
Aim 1: Antibiotics and Colonization

- Compare Colonized Prior to ICU with Not Colonized on Admission
  - Descriptive Analysis

- Compare Incident Colonization with Never Colonized
  - Case-Control
  - Match for LOS, ICU, Ventilator, colonization pressure

- Analyze Incident Colonization
  - Time to Event Analysis
Aim 2: Antibiotics and Infection

- **Hospital**
  - Antibiotic Use and Rates of VRE-BSI

- **Ward**
  - Antibiotic Use and Rates of VRE-BSI

- **Patient**
  - Compare Antibiotic Treatment History between those with VRE-BSI, those with VSE-BSI, and those without VRE-BSI
Negative Binomial Regression: Ceftriaxone Use Correlates with Rates of VRE-BSI  \( P = 0.005 \)
Aim 3: A+B or C?

- Use dual datasets from Aim 1 (antibiotics->colonization) and Aim 2 (antibiotics->infection) to synthesize a global model linking antibiotic exposure, colonization, and VRE-BSI.

- Mediation analysis? to measure the impact of increased colonization on the association between antibiotics and VRE-BSI.
Thank you for your time. I would GREATLY APPRECIATE your feedback.