IMPACT OF ANTIBIOTIC MINIMUM INHIBITORY CONCENTRATION ON MORTALITY IN PATIENTS WITH SUSCEPTIBLE PSEUDOMONAS AERUGINOSA OR KLEBSIELLA PNEUMONIAE BACTEREMIA EMPIRICALLY TREATED WITH B-LACTAMS

Riley J Williams II, Pharm.D.
PGY-2 Infectious Diseases Resident
Oklahoma City VA Medical Center

LEARNING OBJECTIVES
BACKGROUND

- Bacteremia is among the top 10 leading causes of death in the United States
  - Nosocomial infections carry a high risk of mortality (~27%)
  - Certain organisms, such as *Pseudomonas aeruginosa*, have mortality rates as high as 62%
- Beta-lactam antibiotics serve as first-line, empiric treatment for bacteremia
  - Broad spectrum
  - Bactericidal

BACKGROUND

- Uncertainty exists for minimum inhibitory concentration (MIC) breakpoints
  - Breakpoints set by Clinical and Laboratory Standards Institute (CLSI)
    - Recently revised for Enterobacteriaceae and *Pseudomonas*
  - Based on limited *in vitro* and *in vivo* (animal) studies
    - Pharmacokinetic and pharmacodynamic outcomes
  - Previous clinical studies have demonstrated increased mortality for bloodstream infections caused by susceptible organisms with elevated MICs and treated with beta-lactams
STUDY AIMS

- Elucidate whether mortality from susceptible 
  Pseudomonas aeruginosa or Klebsiella pneumoniae 
  bacteremia is influenced by the MIC of the β-lactam 
  antibiotic used for treatment (particularly initial, empiric 
  treatment)
- Hypothesis: mortality from bacteremia caused by such 
  organisms will increase as MIC rises within the 
  susceptible range
- Ultimate objective is to guide empiric and targeted 
  antibiotic selection for the treatment of Gram negative 
  bacteremia

STUDY DESIGN

- Three concurrent, retrospective studies
  - MIC trends study
  - Pseudomonas bacteremia mortality study
  - Klebsiella bacteremia mortality study
- Studies will utilize data from the Veterans Affairs 
  Informatics and Computing Infrastructure (VINCI) 
  database
  - Contains information for patients at all VA 
    medical centers in the US
STUDY 1

- Assess trends in MICs and susceptibility rates for bloodstream isolates of *P. aeruginosa* and *K. pneumoniae* across the nation’s VA Medical Centers
  - Temporal
  - Geographic
  - Facility demographic
- Will assess the following antibiotics:
  - ceftriaxone, cefotaxime, ceftazidime, cefepime, aztreonam, piperacillin/tazobactam, ertapenem, imipenem, meropenem, moxifloxacin, ciprofloxacin, levofloxacin, gentamicin, tobramycin, and amikacin

STUDIES 2 & 3

- Retrospective analyses of mortality in bacteremia
- Study population drawn from VINCI data 2007 to 2013
- Inclusion criteria
  - bacteremia due to *P. aeruginosa* or *K. pneumoniae*
  - susceptibility data including (MIC) is available
  - receipt of appropriate β-lactam antibiotic within 24 hours after collection of the positive blood culture and given for at least 72 consecutive hours
- Exclusion criteria
  - polymicrobial blood cultures
  - isolates that are intermediate or resistant to the initial antibiotic
  - receipt of a concomitant β-lactam antibiotic to which the infecting organism is susceptible or intermediate within the first 72 hours of therapy
STUDIES 2 & 3

• Data to collect:
  • Demographic characteristics
  • Hospital course (i.e. dates of admission, discharge)
  • Comorbidities
  • Source of bacteremia
  • Laboratory data
  • Microbiologic data
  • Medication administration data
  • Severity of illness (modified Pitt Bacteremia Score)

STUDIES 2 & 3

• Primary Endpoint
  • Thirty-day all-cause mortality from the date of collection of the first positive blood culture

• Secondary Endpoints
  • Mortality at discharge
  • Duration of bacteremia
  • Length of stay after first positive blood culture
  • Readmission rate within 30 days of discharge
STATISTICAL ANALYSIS

- Baseline demographic characteristics and clinical outcome will be compared between patients within each MIC stratum for a given empiric antibiotic
  - Kruskal-Wallis test for continuous variables
  - χ-squared or Fisher’s exact test for dichotomous variables
- Univariate variables will be determined associated with the primary outcome
- Multivariate analysis will be conducted to identify independent variables associated with the primary outcome, including univariate variables with p < 0.10
- The a priori alpha for all statistical analyses will be set at p < 0.05

REFERENCES