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Use of Polymyxin B in patients with severe sepsis receiving concurrent RRT therapy

A. Statement of Study Purpose and Rationale

The development of antibiotics over the last 50 years has been one of the greatest life-saving achievements in modern medicine. In turn, with their liberal use, the resultant emergence of multidrug-resistant gram negative bacterial species has occurred (1, 2). The limitation of therapeutic options has reopened the door to the use of older antibiotics such as the polymyxins, which are active against gram-negative bacteria, namely *Acinetobacter, Pseudomonas and Klebsiella* species.

Polymyxins were originally discovered in 1947. They are a group of cationic polypeptide antibiotics, classified from A-E, with only class B and E (inhaled colistin) utilized in clinical practice (3). Concerns about the adverse effects of polymyxin use arose with the observation of ototoxicity, nephrotoxicity and neuromuscular blockade in patients who were treated with the antibiotic (4). These were thought to be dose dependent, however, the appropriate pharmacokinetic and pharmacodynamic studies were not performed at that time. Thus, standards of administration were not established. Polymyxin was eventually replaced by antibiotics thought to have a less significant toxicity profile.

The recent re-emergence of the use of polymyxin for treatment of multidrug-resistant gram negative bacteria has prompted researchers to take a closer look at the drug's efficacy in hopes of establishing criteria for dosing administration and adequate clinical response. More specifically, there is little data in the literature that addresses the use of intravenous polymyxin B in patients with renal failure who require renal replacement therapy with conventional hemodialysis or continuous venovenous hemodialysis. Many institutions have internal guidelines on the use of polymyxin B in the above-mentioned situations, however, these lack substantial physical data.

In patients with concurrent acute renal failure who are undergoing continuous venovenous hemodialysis, the quantity of drug and the duration over which it is removed from the body remains unclear. Old reports had attempted to quantify the amount of drug that was removed from the blood via conventional hemodialysis and peritoneal dialysis (as CVVHD was not available for use at that time). These suggested that the amount of drug that is removed from the blood via dialysis is relatively small. Patients undergoing peritoneal dialysis were estimated to lose approximately 1mg (10,000U) of polymyxin per hour in a study by Goodwin (5).

CUMC anti-infective dosing recommendations for adults undergoing renal replacement therapy currently suggests a one time loading dose of 2.5-3mg/kg followed by doses at 1mg/kg administered every 3-5 days (6). Currently, there is no commercially available assay available to monitor frequent blood levels of polymyxin. Effectiveness is determined on an individual basis by evaluating clinical improvement. In addition, with the development of novel dialysis membranes, it is even more difficult to assess the exact

rate of drug clearance. Due to the improvement in permeability of the dialysis membrane, it can be assumed that the rate of drug removal in patients undergoing CVVHD is faster than predicted. If polymyxin is to be given every three days as recommended, the drug may be removed from the body much earlier than the next scheduled dose, allowing for bacterial growth and potential development of resistance. Therefore, it is possible that the frequency of drug administered is too far apart, leading to inadequate treatment of MDR gram negative bacteria, and a continued state of sepsis requiring a prolonged stay in the intensive care unit.

Our hypothesis states that by administering intravenous polymyxin in patients who are severely septic and undergoing CVVHD every 36 hours instead of every 72 hours after an initial loading dose has been given, the drug will remain in the body for longer periods of time, thereby increasing its effectiveness and translating into clearance of bacteremia and overall clinical improvement as measured by an overall decrease in the duration of ICU length of stay.

B. Description of Study Design and Statistical Analysis

Study Aims: To assess whether altering the frequency of administration of IV polymyxin B in patients requiring CVVHD with severe sepsis from MDR gram negative bacteria is associated with overall decreased ICU length of stay.

Study Design:
Randomized, double-blind, longitudinal, prospective, interventional study of 100 patients. We will identify all the patients with severe sepsis from multidrug-resistant gram negative bacteria and acute renal failure placed on CVVHD in one of the four ICUs at Columbia University Medical Center. Assuming that the length of stay for these critically ill patients will range from 7-21 days in the ICU, we will be powered 80% to detect a decrease in ICU length of stay by two days in the treatment group, assuming a p-value of 0.05.

The two arms will be distinguished by the frequency of administration of IV polymyxin B. An initial loading dose of the drug will be administered to all patients. Treatment difference will occur when 50 patients will receive subsequent doses of IV polymyxin B every 72hrs and 50 patients will receive the dose every 36hrs.

Primary endpoint:
Duration of length of stay in the ICU

Secondary endpoints:
Clearance of positive bacterial cultures
Duration of utilization of CVVHD
Improvement in APACHE II score

A secondary analysis of the data will be performed to identify alternate predictive clinical indicators of duration of stay in the ICU such as number of organ failures and the

requirement for pressor support. Linear regression models will be used to evaluate differences among treatment groups in age, gender and initial APACHE II score.

C. Description of Study Procedures

We will identify study participants by asking staff members to alert the investigator of patients in the ICU setting who require CVVHD and who carry the diagnosis of severe sepsis. Participants and/or their appointed health care agent will be given an explanation of the risks and benefits of participation and will be asked to sign a consent form.

Patients who are eligible to participate in the study will be randomly assigned to treatment with either IV polymyxin 1mg/kg every 72hrs or 1mg/kg every 36hrs. Both groups will initially receive a one time loading dose of 2.5mg/kg once the presence of multidrug-resistant gram negative bacteria has been identified via positive blood cultures. Duration of ICU length of stay will be measured from one to twenty-eight days. Patients will be followed until the day of hospital discharge.

D. Study Drugs/Medical Devices

Intravenous Polymyxin B sulfate preparation in 50mg (500,000U) vials, diluted with 300 to 500mg D5W. Initial loading dose of 2.5mg/kg (25,000U/kg) followed by 1mg/kg (10,000U/kg) doses at treatment intervals.

E. Study Questionnaires

There will be no questionnaire administered to participants

F. Description of Study Subjects

Inclusion Criteria:

1. Adults age 18 and older
2. Severe sepsis as defined by the consensus definition of the American College of Chest Physicians
3. Acute renal failure requiring initiation of continuous venovenous hemodialysis
4. Positive growth of multidrug-resistant gram negative organisms (*Pseudomonas, Klebsiella, Acinetobacter* spp.)

Exclusion Criteria:

1. Age less than 18
2. Pregnancy
3. History of sensitivity to polymyxin
4. Patients undergoing CVVHD for non-renal indications

G. Recruitment of Subjects

Patients will be recruited from one of four Columbia University Medical Center intensive care units. All patients undergoing CVVHD will be identified via the dialysis unit, which maintains data of all patients who receive dialysis while in the ICU. The investigator will then evaluate these patients for study eligibility.

H. Confidentiality of Study Data

All patient information will be collected and stored using a unique patient code. Data will be stored in a locked cabinet. Computer analysis will be performed on coded information only. Access to this information will be granted solely to the principal investigator and the co-investigators.

I. Potential Conflict of Interest

None

J. Location of Study

Columbia University Medical Center

K. Potential Risks

Potential risks to the patients participating in this study include ototoxicity, neurotoxicity and nephrotoxicity (4). Studies published between 1962 and 1977 reported an incidence of nephrotoxicity between 20%-35% in patients with preexisting acute or chronic renal disease, however, in most of the reported cases the total daily dose of polymyxin administered was significantly higher than the recommended current dose (7). More recent analysis of data from 1995 to 2005 found the incidence of nephrotoxicity to range between 10% and 19%. In addition, a comparison between the use of polymyxin and imipenem/cilastatin for ventilator- associated pneumonia due to *Acinetobacter baumanii* found that nephrotoxicity occurred in 24% and 42% of patients, respectively (8). Neuromuscular toxicity, most commonly in the form of paresthesias, had been reported to occur approximately 27% in patients receiving intravenous polymyxin according to studies published nearly 30 years ago. In addition, there had been case reports of episodes of respiratory apnea related to the intramuscular administration of polymyxin in patients with cystic fibrosis. However, within the last 15 years, there have been no documented reports of neuromuscular blockade or apnea as induced by polymyxins. Allergic reactions have been noted to occur in approximately 2% (9). Mild itching and rash are other potential side effects of this medication.

L. Potential Benefits

Patients face significant morbidity and mortality rates associated with severe sepsis from multidrug-resistant gram negative bacteria. Study participants may or may not benefit from participation of this study. Improvement in clinical outcomes, as well as decrease in overall cost of care are potential benefits of this study. This study will also benefit society

by providing more insight into the appropriate dosing interval of the studied drug in patients undergoing dialysis. The study findings will be important in defining future standards of care for more effective administration of intravenous polymyxin.

M. Alternative Therapies

None

N. Compensation to Subjects

None

O. Costs to subjects

None

P. Minors as Research Subjects

Minors are not included in the study

Q. Radiation or Radioactive Substances

Not Applicable

References:

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