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What Are the Risks That Predispose a Patient to Being Colonized with *Klebsiella pneumoniae* Producing Carbepenemases? A Case-Controlled Retrospective Study.

A. Study Purpose and Rationale

Klebsiella pneumoniae is a gram-negative saphrophytic bacteria that is a member of the family Enterobacteriaceae. It is known to colonize the GI tract, hands and nasopharynx and classically has been associated with a severe form of pneumonia, especially in alcoholic, immunocompromised and diabetic patients (1). Naturally, *Klebsiella pneumoniae* does not harbor extensive antibiotic resistance given a minimal number of chromosomal resistance genes. Despite this, *Klebsiella pneumoniae* has been known to be a prolific hoarder of antibiotic resistance plasmids. Initially in the 70s and 80s *Klebsiella pneumoniae* frequently harbored aminoglycoside resistance and more recently, *Klebsiella pneumoniae* has been infamous for producing extended spectrum beta-lactamases. This often left carbepenems as the last major class of antibiotics known to be effective against multi-drug resistant *Klebsiella pneumoniae*. This was true until the late 90s when the first reported case of *Klebsiella pneumoniae* producing a carbepenemase was reported out of North Carolina. Soon after reported cases were noted on every continent, with the Northeast United States as an epicenter (2). The extensive spread of *Klebsiella pneumoniae* producing carbepenemases (KPCs) becomes especially concerning given the possibility of plasmid spread to additional species (reported cases of *E. coli* and other gram negatives producing carbepenemases) (2-4).

Carbepenemases are broken up into four different classes (A-D) based on the Ambler system. Classes, A, C and D are serine beta-lactamases, while type B is a metallo-beta lactamase. Type A is the most common carbepenemase and is frequently seen in New York City (5). CUMC has been particularly affected by KPCs with anywhere from 10-15 cases in the hospital at a given time. Cases include bacteremia, pneumonia, urinary tract infections, and wound infections (3). Once infected mortality rates have been reported anywhere between 25-70% (2-4). Important reported risks include being severely ill / having multiple co-morbidities, an immunocompromised status (including those receiving solid organ transplants), and previous exposure to flouroquinolones and cephalosporins (3). More in-depth information about the epidemiology of KPCs has not been completely fleshed out as the research consists of mostly case reports, case series and small meta-analyses.

One important epidemiological factor that has not been fully explored is KPC colonization. A previous study out of Greece in 2012 revealed that 12.5% of patient's entering an ICU in a tertiary care medical center were colonized with KPCs (noted via rectal swab). Risk factors for colonization included a previous ICU stay,

COPD, previous lengthy hospitalization and use of certain antibiotics (6). Further studies have revealed that once colonized the risk for developing a subsequent KPC infection approaches 10% (7). A pilot surveillance study was done at CUMC where rectal swabs were taken on approximately 300 patients entering one of the ICUs. Of these patients close to 100 were noted to be colonized with KPCs. The estimated 30% colonization rate is substantially higher than previous reports, but is consistent with the observation that NYC is an epicenter for KPC infections. Given the risk for development of a KPC infection once colonized it becomes important to identify possible risk factors for colonization. Therefore, the purpose of this study will be to identify what patient characteristics are associated with being colonized with KPCs at CUMC. The major hypothesis being that the risk factors associated with KPC infection at CUMC will also be associated with KPC colonization. This includes an immunocompromised status, multiple co-morbidities, previous exposure to broad-spectrum antibiotics, and a previous lengthy hospital stay.

B. Study Design

This will be a case controlled retrospective study. Swabs were previously collected from patients entering an ICU at CUMC and grown in chromogenic agar. Following identification of *Klebsiella pneumoniae* susceptibility testing for various antibiotics was performed identifying those isolates that were KPCs. For this study all the patients colonized with KPCs will be identified from this pool of swabs. The KPC positive cases will be matched by time of entry with two patients who were not colonized with KPC upon entry to a CUMC ICU. Following identification and matching characteristics and demographic information from each case and control will be obtained through a retrospective chart review. This will include age, sex, ethnicity, co-morbidities, days of hospitalization in the previous six months, history of recent ICU stay, and antibiotic exposures during the previous six months.

- Statistical Analysis: Univariate alalysis for each categorical variable will be performed with Fisher exact tests or chi square tests depending on the number of patients in each group. Univariate analysis for continuous variables (length of hospitalization etc.) will be performed with a T test. Odds ratios and confidence intervals will be calculated for all variables. Variables that have a p value of less than 0.2 can then be used for a multivariable logistic regression model (8).

- Power Analysis: From the initial pilot surveillance study we can assume that the overall level of colonization with KPCs in patients entering an ICU at CUMC is 30%. If we assume that a given variable is seen in 40% of cases and 20% of the controls then there would need to be 66 patients in the case group and 133 patients in the control group to reach significance with a p value of 0.05 and a power of 0.80. If a variable was seen in 35% of the cases and 25% of the controls then there would need to be 258 patients in the case group and 516 patients in the control group to reach significance.

C. Study Procedure
Through collaboration with the clinical microbiology laboratory at CUMC the medical record numbers of the ICU patients who had rectal swabs taken will be obtained. All the patients with positive rectal swabs for KPCs will be placed in the case group. These cases will be matched with two times the number of controls (those with negative rectal swabs for KPCs) based on time of entry into the ICU. With the use of CUMC's medical record system, eclipsys, all the patient information detailed above will be gathered and subsequently analyzed. Since rectal swabs have already been obtained no further patient participation will be needed.

D. Study Drugs
There will be no use of drugs in this study.

E. Medical Device
There will be no use of a medical device in this study.

F. Study Questionnaies
There will be no study questionnaires used in this study.

G. Study Subjects
Subjects in this study will be those patients who had a rectal swab taken upon entry to a CUMC ICU.

- Inclusion in the case group: ICU patients who were previously identified as colonized with a KPC via rectal swab will be included in the case group.

- Inclusion in the control group: Consecutive ICU patients previously identified as not being colonized with a KPC via rectal swab will be assigned to the control group. Two times the number of KPC cases will be included in the control group.

H. Recruitment of subjects
Cases have already been recruited via the pilot surveillance study done at CUMC. No further study subjects will be recruited to complete this study.

I. Confidentiality of Study Data
Once the cases and controls are identified from the clinical microbiology laboratory, all subjects will be de-identified, after which only medical record numbers will be used.

J. Potential Conflict of Interest
There is no conflict of interest with this study.

K. Location of this Study

The collection of the swabs took place at the various ICUs of CUMC. The processing of the swabs took place at the clinical microbiology laboratory of CUMC. Data analysis will take place at the laboratory of Anne-Catrin Uhlemann, (In the Physicians and Surgeons Building) the principal investigator of this study.

L. Potential Risks
There will be no potential risks to the subjects of this study.

M. Potential Benefits
There will be no immediate potential benefits to the subjects of this study.

N. Alternative Therapies
N/A

O. Compensation to Subjects
There will be no compensation provided to the subjects in this study.

P. Costs to Subjects
There will be no costs incurred by the subjects in this study.

Q. Minors as Research Subjects
N/A

R. Radiation or Radioactive Substances
N/A

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