Resistant Enterobacter Cloacae In The ICU: Risk Factors and Prognosis.

Sean Pickering

A. Study Purpose

Enterobacter cloaceae (E. cloaceae) is becoming an increasingly difficult organism (bacteria) to treat in the intensive care units (ICU). The reason for this is that many of the drugs that were once used to treat this organism are no longer effective against it due to the fact that the organism has acquired genetically derived resistance mechanisms, over time. This represents a common problem with infectious agents.

In addition to this ability of bacteria, the widespread use of "broad spectrum" antibiotics has also contributed to the problem. We must therefore attempt to limit the use of these antibiotics as much as possible. One way is to use them only when necessary and to not use them when the presence of an organism is not likely to result in a bad outcome.

E. cloacae specifically is in the natural bowel flora of 40-60% of normal individuals. The risk factors for the development of highly resistant organisms, aside from the exposure to antibiotics, have not been clearly outlined.

Bacteria may either colonize or infect an individual. Colonization refers to when bacteria simply exist in an individual, essentially not affecting that individual in any negative way; while infection implies some deleterious effect. Prognostic factors, particularly effects on survival or length of stay, in patients either infected, colonized, or noninfected/noncolonized in ICUs have not been clearly outlined.

In the future, hypothetically there may be distinct features about cases that allow us to predict the likelihood of development of resistant E. cloacae. Given colonization with E. cloacae we may learn how to predict whether or not eradication of the organism is warranted to prevent worse outcomes. We may avoid having to use imipenem and other broad spectrum antibiotics to prevent further resistance patterns in the future.

Work in this area thus far has been extensive with regards to VREF, MRSA, and resistant acinetobacter. But little is known about E. cloacae due to its recent emergence. Entire families of antibiotics including penicillins and aminoglycosides are no longer effective. There is growing literature on the emergence of cephalosporin resistant E. cloacae and this is the focus of this study.

Thus, we would like to assess the risk factors for and outcome of colonization and/or infection with multiresistant E. cloacae.

B. Description Of Study Design And Statistical Analysis

This is a prospective study comparing cases of ICU patients in the adult units of CPMC. By reviewing cases of resistant E. cloacae over the past year we found that the rate of emergence of resistant E. cloacae would seem to indicate that a 2 year study would generate an appropriate number of cases for a meaningful result. During this period we will identify patients prospectively as infected, colonized, or noninfected/noncolonized with E. cloacae and follow their courses.

1. We will identify the criteria for colonization and for infection.
2. We will identify the microbiologic analysis technique.
3. Risk factor analysis will be a comparison between noninfected/noncolonized individuals and case patients using a univariate analysis. This will then be followed by multiple logistic regression analysis of the whole study population.
4. Prognostic factors will be determined by a multiple logistic regression analysis using nonsurvivor vs. survivor data. We will also attempt to create a small matched cohort study to evaluate attributable mortality and excess length of stay in the ICU.

Colonization will be defined as a positive rectal, nasal, or skin swab. This must be accompanied by a normal temperature and a white blood cell count (wbc)< 12,000/ hpf, Central line tip culture must have a bacterial count of <1 0,000 colony forming units (cfu)/ml; urine must have < 100,000 cfu/ml with < 10 wbc/hpf on micro; wounds must have no pus; protected brush specimens (bronch) must have <1 000 cfu/ml.

Infection will be defined as fever with several other criteria: urinary tract infection if > 100,000 cfu/ml with pyuria (> 10 wbc/hpf on micro); bacteremia, primary if no other source and secondary if another source is present; central venous line catheter tip with >1,000 cfu/ml; bronchitis if purulent sputum and negative chest film; pneumonia if bronchial fluid analysis or brush specimen with > 1,000 cfu/ml and a persistent infiltrate on chest film.

Microscopic identification and antibiotic susceptibilities. Swabs will be cultured on sheep agar, chocolate agar and Sabourand yeast agar, incubated at 37 degrees for 24-48 hours. Standard microdilution methods will be used to determine minimal inhibitory concentrations (MIC) of gentamicin, tobramycin, amicacin, ampicillin, Amoxicillin, piperacillin, cefazolin, cefuroxime, cefoxitin, ceftazidime, aztreonarn, imipenem, and ciprofloxacin. The organisms will then be processed in trays containing compounds. MICs will be read 18 hours after incubation at the lowest concentration inhibiting visible growth.

Riskfactor analysis. The univariate analysis variables for further regression analysis will include: age, sex, severity of underlying disease (nonfatal, fatal, or ultimately fatal (within 5 yrs)), APACHE II score, organ or system failure (cardiovascular, renal, liver, lung, bone marrow, brain), previous infection, previous antibiotic use, location before ICU admission, duration of stay (admission to entry). These will be expressed as a mean +/- standard deviation or as proportions of the total number of subjects. To identify risk of nosocomial acquisition we will compare infected, colonized, and noninfected/noncolonized with the above variables.

We would then perform a logistic regression analysis to determine independent risk factors for nosocomial acquisition.

Prognosis analysis. This will be based on the addition of another variable: survived vs. not survived to the end of hospitalization. This will be included in a regression analysis for determining independent risk factors associated with death. For attributable mortality and excess length of stay the cases will be compared to controls. These controls will be defined as subjects with similar age, duration of stay, and APACHE II score. They will not however, be colonized or infected with E. cloacae. The end point will be the subjects status at the end of the hospitalization. This will be a small cohort study.

C. Description Of Study Procedures

No study procedures will be used.

D. Study Drugs

No study drug will be used.

E. Medical Devices

No Medical devices will be used

F. Study Questionnaires
No questionnaires will be used

G. Study Subjects

Men and women admitted to all 4 adult ICUs will be entered. Because we are studying ICU acquired infections any positive culture before or within 24 hours of entering the unit will result in exclusion from the study. Samples will be taken initially and weekly thereafter. Due to the fact that there is variability among physicians regarding empiric treatment of E. cloacae colonization we will accept cases from a predetermined group of physicians who do not routinely treat colonization.

H. Confidentiality Of Study Data

Does not apply to this study

I. Location Of Study

All patients will be admitted to the CPMC NICU, MICU, CCU, and SICU. All microbiological analysis will take place in the CPMC micro lab.

J. Risks And Benefits

The benefits are: with the results of this study it may be determined definitively what risk factors are associated with nosocomial E. cloacae colonization and infection and the subsequent infections Morbidity and mortality may be better outlined. This may result in the reduced or increased, but perhaps more appropriate use of antibiotic regimens that are very broad and in time result in highly resistant strains of bacteria. These are benefits to society. There may not be any direct benefit to in this study for any one of the subjects.

The risks of participation in this study are minimal as all infected patients will be treated. Currently there is no standard of therapy for colonization with E. cloacae. The decision to eradicate the organism is usually varied depending on the case and physician. All patients infected will be treated with either imipenem or ciprofloxacin depending on the case.

K. Alternative Therapies

Treatment of infections with imipenem (or other drug to which that E. cloacae is sensitive) is the standard protocol. An alternative to not eradicating a colonizing organism is to eradicate it as mentioned previously.

L. Compensation And Cost

There is no cost nor compensation necessary.

M. Minors And Research Subjects

There will be no minors nor research subjects involved

N. Radiation Or Radioactive Substances

There will be no excess radiation and no radioactive substances involved.

O. References


