Non-infected ICU patients treated empirically for C difficile infection:
A good test population for refuting antibiotic prophylaxis for nosocomial diarrhea?

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Study Purpose and Study Rationale:

Clostridium difficile is a common nosocomial pathogen, particularly among ICU patients, whose clinical characteristics often include important risk factors for C difficile infection, such as severe underlying disease and treatment with antimicrobials[1]. Rates of C difficile infection have risen rapidly over the past decade, reflecting emergence of isolates with increased pathogenicity, replicative capacity, and antibiotic resistance, the appearance of community-acquired disease, and the increasing use of immunosuppressive therapies on elderly and debilitated patients[2]. A recent CDC survey of New Jersey hospitals showed a greater than 2-fold increase in C difficile infection rates during the 5 year period from 2000-2004 with corresponding increasing trends in rates of complications from C difficile infection, including shock, toxic megacolon, colonic perfoation, or colectomy, C difficile outbreaks, recurrent infection, and all-cause mortality within 30 days of infection[3]. In the ICU, studies have reported 0.4-100 cases of infection per 1,000 patient-days per 1,000 admissions, but rates may be higher in outbreak settings and regional variation may also be seen; approximately half of these patients have been shown to acquire the infection in the ICU[4].

C difficile affects a large proportion of ICU patients, tends to spread rapidly among this high-risk population, and associated with significant morbidity, increased length of hospital stay, and increased health care costs in this population[1,4]. Control of C difficile infection in the ICU has centered on minimization of antibiotic use, development of infection control committees, and prevention of infection transmission via prompt isolation of infected patients, hand hygiene, and thorough cleaning procedures[5,6]. There is currently no evidence supporting the use of antibiotic prophylaxis for C difficile infection, although prior reports of C difficile prevention have focused on theoretical objections to prophylaxis, such as the inability of antibiotics to eradicate Clostridium spores and the increased risk of infection after use of antibiotics, even those found to be effective in treating infected patients[7]. One small randomized-controlled trial of 30 patients in a VA hospital found to be asymptomatic carriers of C difficile randomized patients to receive 10 days of oral Vancomycin, Metronidazole, or placebo, and followed serial fecal samples for up to 2 months to see whether C difficile could be successfully eradicated in these patients. In the Vancomycin group only, C difficile was non-detectable in stool samples during and for a short period following treatment; however, in most of these patients C difficile excretion recurred by the end of the study, whereas patients treated with placebo were more likely to have cleared the organism by the end of the study[8].

No studies are available confirming inefficacy of antibiotic prophylaxis for C difficile infection in patients not known to be carriers of the organism, and given the risk of increased, rather than decreased, rates of C difficile infection following use of many classes of antibiotics, a prospective study of antibiotic prophylaxis for C difficile is unlikely to be done. However, given that there are physicians who continue to use antibiotic prophylaxis for C difficile it may be worthwhile to find alternative ways to demonstrate increased harm from treating uninfected patients with antibiotics for C difficile.

In our experience, there is a subpopulation of ICU patients who are treated empirically for C difficile in the absence of laboratory-confirmed infection. These patients tend to have signs or symptoms conferring clinical suspicion for C difficile, including watery diarrhea, fever, or leukocytosis, although such markers for infection are also common in the general ICU population; they may commence treatment on the same day that stool studies are sent to the laboratory but before results are available confirming or refuting infection. Some of these patients ultimately fail to have laboratory-confirmed infection, although they typically receive several days of antibiotic therapy active against C difficile. Given that these noninfected patients essentially receive courses of antibiotics which would likely be used in prophylactic regimens for C difficile, they may form a natural test group for examining the rate of C difficile infection after exposure to prophylactic antibiotics to C difficile.

Our hypothesis is that ICU patients empirically treated with antibiotics for C difficile but who are laboratory test negative for C difficile infection by stool studies sent within 24 hours of the onset of antibiotic treatment ultimately develop higher rates of infection with C difficile than the remainder of the ICU population.

Study Design and Statistical Procedures:

We will perform a prospective cohort study of all patients admitted to the CPMC medical ICU from the date of study onset until recruitment is completed. For all patients admitted to the ICU and who remain in the ICU for greater than 24 hours, a basic panel of data will be collected, including age, sex, ethnicity, primary diagnosis, and APACHE II score. Initiation of treatment for C difficile will be identified at the pharmacy level by use of oral Metronidazole or Vancomycin; pharmacists will be instructed to notify the study team when either of these antibiotic preparations are requested by clinicians in the ICU. Study coordinators will then collect additional information about flagged patients, including result of laboratory test for C difficile sent within 24 hours of initiation of therapy, as well as other clinical information for use in characterizing the empirically treated population, including use of any antibiotic within the previous 30 days, presence or absence of fever, presence or absence of leukocytosis, presence or absence of diarrhea, use of antacids since ICU admission, presence of comorbid illnesses, and length of treatment. All patients included in the study will be followed for 30 days following discharge from the ICU or until hospital discharge, whichever occurs first, with data collection primarily via analysis of the electronic medical record. No data will be obtained from involved clinicians or at the bedside, although information may be obtained from the paper chart as needed after the patient has been discharged from the hospital. Rotating clinical faculty, house staff, PAs, RNs, and other staff involved in patient care will not be made aware of the study to minimize bias.

All patients admitted to the ICU who have an ICU stay longer than 24 hours will be included in the study. Patients who are treated with oral Metronidazole or Vancomycin with clinical documentation of concern for C difficile infection but that do not have laboratory-confirmed C difficile infection from a stool sample sent within 24 hours of initiation of antibiotic therapy will comprise the exposure group. All other ICU patients, including patients not receiving oral Metronidazole or Vancomycin therapy for any reason and patients with C difficile infection confirmed prior to initiation of therapy or by stool sample sent within 24 hours of initiation of therapy, will comprise the non-exposure group.

Our primary outcome measure of interest is the rate of C difficile infection in the exposure group vs nonexposure group during the 30 day period following admission to the ICU or until date of hospital

discharge. Secondary outcome measures will be rates of complications from C difficile infection, including shock, toxic megacolon, colonic perfoation, colectomy, or death, and all-cause mortality in the exposure group vs nonexposure group, although the number of patients experiencing these outcomes is likely to be small.

Statistical analysis will be performed on all patients included in the study. Basic demographic information about the study population will be analyzed suing T-test and chi-square models. Prevalence of C difficile infection will be reported for the entire ICU population as well as for the exposure and non-exposure groups, and compared between the exposure and non-exposure groups (our primary outcomes) using chi-square analysis, with reporting of 95% confidence interval. Secondary outcomes will also be analyzed using chi-square analysis, with reporting of 95% confidence interval. For patients receiving empiric antibiotic therapy for whom additional clinical data is gathered, continuous variables will be summarized using mean values with reporting of standard deviations or medians with reporting of interquartile ranges and categorical variables will be summarized using frequencies; these values will be compared between groups using t-tests and chi-square analysis, respectively.

We expect rates of ICU-acquired C difficile infection in the non-exposure group to be similar to previously published rates of ICU-acquired C difficile infection in the general ICU population. Assuming a rate of ICU-acquired C difficile infection of 2%, we will need 249 patients in the non-exposure group and 62 patients in the exposure group to detect a 10% increase in the rate of post-exposure C difficile infection, with power of 80% and alpha of 0.05.

Study Procedures:
No procedures will be used during the course of this study.

Study Drugs or Devices:
No drugs or devices will be used during the course of this study.

Study Questionnaires:
The use of questionnaires is not planned for this study.

Study Subjects and Recruitment:
All patients admitted to the medical ICU at CPMC for greater than 24 hours will be included in the study.

Confidentiality of Study Data:
Once data collection has been completed for each study subject, all patient identifiers will be removed from that patient's data set and data identified by number only. Patient-linked numbers will be kept until study completion in a secure location accessible by the study coordinator only. Recruitment will take place from the time of study onset until the appropriate number of patients have been included in each group.

Potential Risks:
Patients included in this study are at minimal risk. Patients may be placed at risk if confidential health information is distributed beyond appropriate study personnel, although as stated above measures will be taken to minimize distribution of patient information. Given this study places patients at minimal risk, that all personnel involved in patient care will not be notified that the study is underway and thus that the study will not alter the natural course of patient treatment, we hope to meet exclusion criteria for obtaining patient consent for patients included in this study. As some patients would be sure to object to inclusion in a research study, this will facilitate including all patients treated in the ICU during the study and allow our prevalence measurements to be more accurate.

Potential Benefits:
Although patients are unlikely to derive individual benefit by their participation in the study, they may contribute to clinical knowledge of C difficile infection in the ICU setting and thus benefit future ICU patients.

References:

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