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The Impact of Cefepime as First Line Therapy for Neutropenic Fever on *Clostridium difficile* rates among Hematology and Oncology Patients

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Abstract

After changing empiric treatment of febrile neutropenia from meropenem to cefepime, the effect on *C. difficile* infection (CDI) was investigated. The change was assessed using an autoregressive model. A significant increase in CDI rates occurred following the introduction of cefepime. There may be an association between increased cefepime usage and CDI.

Background

Clostridium difficile is a major cause of healthcare-associated infections. Infection prevention measures and antimicrobial stewardship programs have been associated with decreased *C. difficile* infection (CDI) rates.[1, 2]

Current Infectious Diseases Society of America (IDSA) guidelines for febrile neutropenia recommend an anti-pseudomonal cephalosporin, a carbapenem or piperacillin-tazobactam, as first line therapy.[3] Individual institutions may favor certain antibiotics based on availability, costs, ease of administration and local antibiogram.

We sought to evaluate the intervention of changing the institutional first-line antibiotic for febrile neutropenia on the rates of CDI in the hematology and oncology ward using a quasi-experimental design.

Methods

A retrospective investigation of antimicrobial usage and incidence of CDI on the oncology/hematology inpatient floor at Tufts Medical Center (TMC) was performed. TMC is an urban tertiary care, university affiliated hospital with 417 beds in Boston, MA.

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Prior to 2010, meropenem was the institutional choice as empiric initial therapy for neutropenic fever. After literature review, cost analysis and antibiograms, a change to cefepime was recommended by the antimicrobial subcommittee of the pharmacy and therapeutics committee; this occurred in July 2010.

Monthly antimicrobial usage data from January 2009 through December 2011 were obtained from the pharmacy information system and converted into defined daily dose (DDD; ATC/DDD version 2010), and expressed as DDD per 1000 bed-days. Case mix index data was collected for the same time period.

The number of hospital-acquired CDI cases was based on infection preventionist reports which are maintained using standard National Health and Safety Network definitions, which includes hospital onset cases only. The CDI rate was collected on a monthly basis and expressed per 1000 patient-days. The microbiology laboratory used two different testing methods during the specified time period. From January 2009 until January 2011, a toxin based qualitative enzyme immunoassay was used (Premier toxins A & B – Meridian biosciences, Cincinnati OH, USA). From January 2011 a DNA amplification assay (Illumigene *C. difficile* – Meridian Biosciences) was used. In the only study which compares the two tests directly, the tests have a reported sensitivity of 83.3% and 100% respectively compared to toxigenic culture.[4] A CDI case was defined as a positive test (by either method) in the presence of clinical diarrhea.

The effect of the intervention was assessed using an autoregressive model to estimate changes in the CDI rates before and after the antibiotic change, serial correlations between the data were evaluated. Individual effects of case mix index and other antibiotic use were examined and those that had statistically significant effect were included in the final model.

Results

Prior to the change in empiric therapy for neutropenic fever, the CDI rate on the hematology/oncology ward was 0.45/1000 patient days and DDD of cefepime was 290/1000 patient days, while the mean meropenem DDD was 180/1000 patient days. After the change, the mean CDI rate was 2.59/1000 patient days, the mean DDD of cefepime was 340/1000 patient days, and the mean DDD of meropenem was 109/1000 patient days.

Using an autoregressive linear model, we identified a significant upward trend in the CDI rate following change to cefepime from meropenem as the preferred agent for empiric neutropenic fever therapy. The rate increased by 0.3 units for every additional month post intervention ($p=0.008$). However, tests for serial correlations were non-significant, indicating independent residuals. Therefore, the data were analyzed using a linear regression model, and the results were similar to those obtained from the autoregressive model. There was a significant increase in the trend of the CDI rate ($p<0.001$) after the switch from meropenem to cefepime.

All other antibiotics used on the ward and case mix index were included in the models. However, there were no significant associations between other individual antibiotics or case mix index and *C. difficile* rate. There was no change in the rate of MRSA or VRE infection during the same time period, and no major changes in infection control practices were made until after the increase in CDI rates was recognized.

The hospital-wide CDI rate increased as expected from 0.61/1000 patient days while the EIA toxin test was utilized and 0.84 after the introduction of the DNA amplification assay (figure 2) $p=0.06$.

Discussion

Cephalosporins have long been implicated as a risk factor for the acquisition of CDI. Broad spectrum antibiotics are thought to disturb the microflora of the gastrointestinal tract, allowing pathogenic bacteria such as *C. difficile* to overgrow. This may occur to a lesser extent with antimicrobials like meropenem, which have activity against *C. difficile* and therefore may inhibit its growth.[5, 6]

Studies done on the risk factors for CDI in an endemic setting have shown that the administration of a fourth generation cephalosporin is an independent risk factor for the acquisition of CDI[7]. Similarly, in outbreaks of CDI, cefepime has been associated with an increased odds ratio (OR 2.1) of developing CDI[8] and restriction of cephalosporin administration has been associated with the control of epidemic CDI.[9] In a comparative study of cefepime and piperacillin/tazobactam in neutropenic patients, CDI was more often observed among the patients receiving cefepime (2.3% vs. 6.8%, p=0.012)[10].

While this study suggests that there may be an association between increased cefepime use and *C. difficile* rates on a hematology-oncology ward, it has a number of limitations. Being a quasi-experimental study, there may have been other unrecognized factors which affected the CDI rates, such as changes in infection control practices. The stable rates of hospital-acquired MRSA and VRE suggest that no significant changes in practice occurred. The change in diagnostic methodology most certainly impacted CDI rates, however comparison with the hospital as a whole shows that the CDI rate on the hematology/oncology floor was disproportionately higher than rates in the rest of the hospital (figure 2). Furthermore the increase in CDI rate in the hematology/oncology ward was substantially higher than would be expected had the difference been due to the change in testing methodology alone.

This study shows that there may be an association between increased cefepime use for empiric neutropenic fever and CDI rates. This finding may have significant clinical implications and warrants further investigation.

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- The empiric therapy for neutropenic fever was changed from meropenem to cefepime.
- Time series analysis used to assess any change in C. difficile rates.
- There was an association between the switch to cefepime and C. difficile rates.

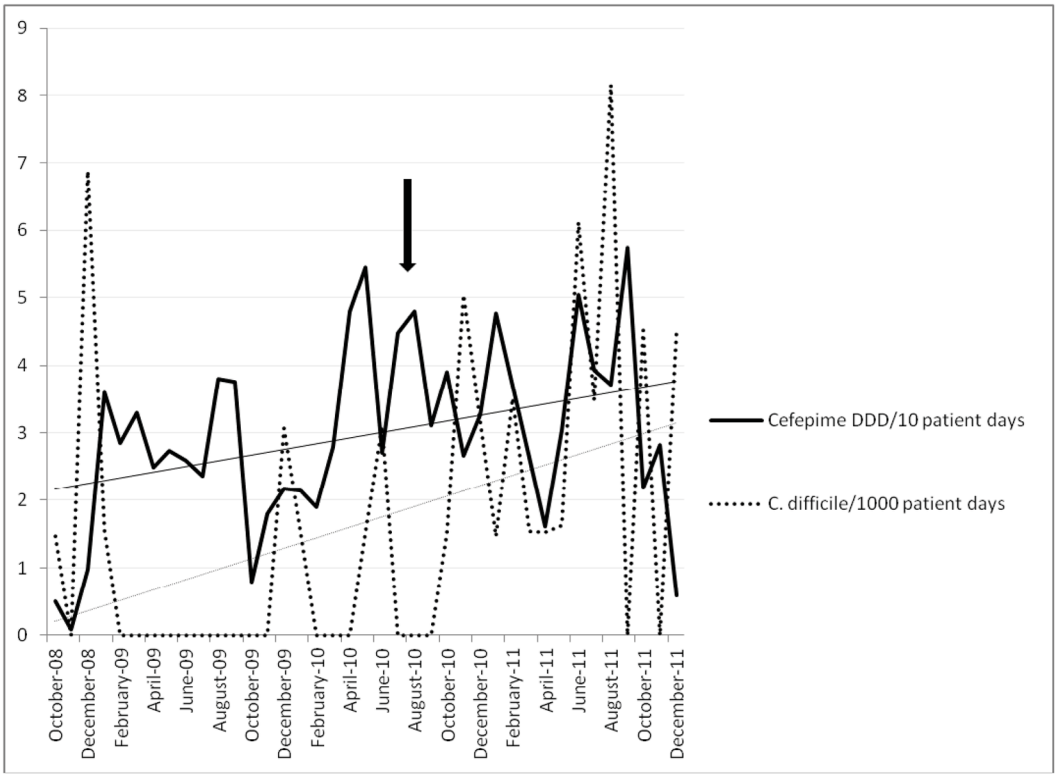

Figure 1.

C. difficile rate/1000 patient days pre- and post- intervention and DDD of cefepime/10 patient days pre- and post- intervention. Arrow indicates date of change to cefepime as empiric therapy.

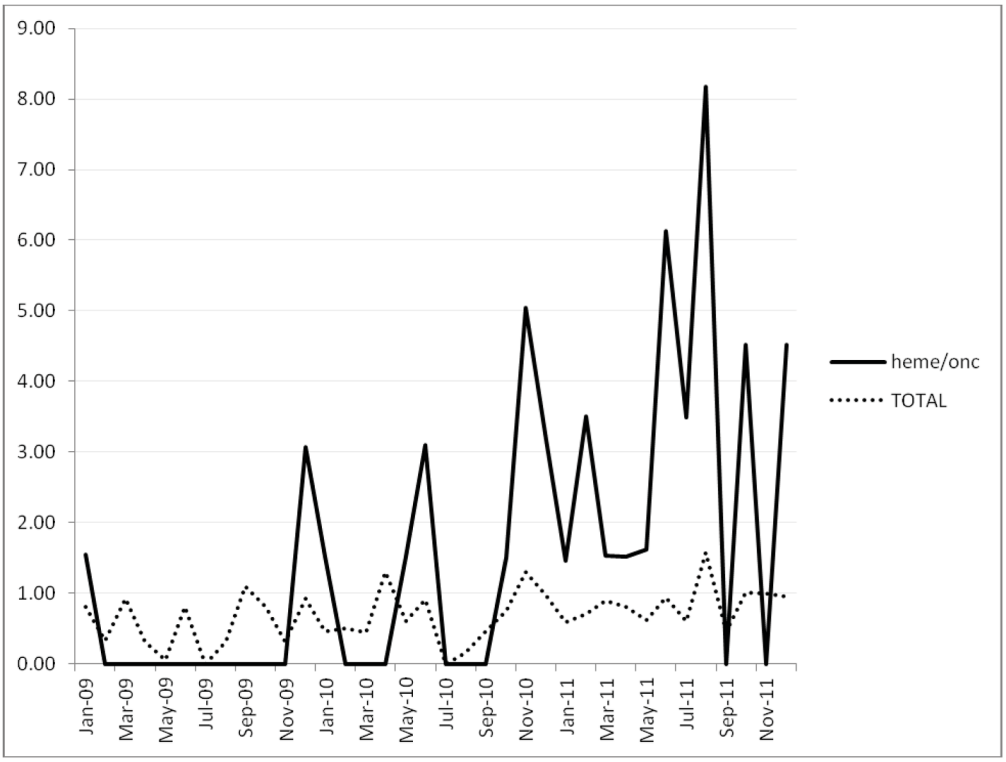

Figure 2.
C. difficile rates per 1000 patient days in heme/onc ward and the hospital as a whole.