Shannon Carty, PGY-2
ICCR IRB Project Proposal
April 9, 2008

Study Title: Observational Study to Determine the Effect of an Emergency Department "Adult Oncology Stat Antibiotic Protocol" on Clinical Outcomes in Adult Oncology Patients with Febrile Neutropenia.

A. Study Purpose and Rationale

Febrile neutropenia in cancer patients is a medical emergency. The relationship between degree of neutropenia and infection risk was first recognized in patients with acute leukemias (Bodey et al, 1966). Prior to routine administration of empiric antibiotic therapy, mortality rates for cancer patients with febrile neutropenia were as high as seventy percent. In 1971, Schimpff et al. demonstrated that empiric antibiotic therapy in patients with neutropenic fever improved mortality. Current studies indicate mortality rates in recent years range from 5-12% (Bow, 2005). Multiple clinical trials have studied different antibiotic regimens (reviewed in Falagas et al., 2008). Current IDSA guidelines (Hughes et al., 2002) recommend a variety of antibiotic regimens, including monotherapy with cefepime or ceftazidime, imipenem or meropenem, or combination therapy, including aminoglycoside plus antipsdeumonal penicillin, cephalosporin (cefepime or ceftazidime) or carbapenem, with vancomycin added if clinically indicated.

At Columbia University Medical Center, a clinical pathway was established for the treatment of cancer patients with febrile neutropenia based on IDSA guidelines. In this pathway, fever is defined as a single temperature greater than or equal to 38.3°C (101°F) or temperature greater than or equal to 38.0°C (100.4°F) for one hour, with neutropenia defined as absolute neutrophil count (ANC) less than 500 or ANC less than 1000 with predicted nadir less than 500. Recommended empiric antibiotic therapy includes pipracillin/tazobactem at anti-pseudomonal dosages with or without tobramycin for double coverage for pseudomonal infections for the first seventy-two hours with a clinical reassessment at that point and addition or adjustment further antibiotic coverage if clinically indicated, including vancomycin for MRSA infections and/or antifungal coverage with liposomal amphotericin B.

Other therapeutic interventions to reduce morbidity and mortality in febrile neutropenia have been studied. The role of prophylactic granulocyte colony stimulating factor (G-CSF or GM-CSF) has been studied in primary prophylaxis of chemotherapy-induced neutropenia. Randomized clinical trials demonstrated that primary prophylaxis reduced the duration of chemotherapy-induced neutropenia; however, febrile neutropenia, infection, hospitalization and antibiotic use were not consistently affected in all the studies (reviewed in Bhana, 2007). Several oncology societies, including NCCN and ASCO, have written guidelines for the use of prophylactic granulocyte stimulating factors. In all of these guidelines, risk assessment for febrile neutropenia is recommended with use of colony stimulating factor support recommended in patients at high risk (>20%), consideration of CSF support in patients with intermediate risk (10-20%) and no CSF support recommended in patients at low risk (<10%). Use of CSF support is also recommended in patients with prior episodes of febrile neutropenia or when use of dose-dense or dose-intense chemotherapy has been shown to have a survival

benefit. The role of prophylactic antibiotics to prevent febrile neutropenia has also been extensively studied (reviewed in Leibovici et al., 2006). In the SIGNIFICANT study (Cullen et al., 2005), the prophylactic use of levofloxacin was studied in patients receiving solid tumors or lymphoma in a randomized, double-blind, placebo-controlled trial. The use of levofloxacin was found to reduce the incidence of fever, probable infection and hospitalization in these patients, but no difference was found in infection-related or overall mortality. In the GIMEMA study, prophylactic treatment with levofloxacin in patients with solid tumors and acute leukemia was found to decrease the absolute risk of febrile neutropenic episodes by 20% (Bucavene et al., 2005). No difference in mortality was noted; however, a higher incidence of fluoroquinolone-resistant bacteria was isolated in patients receiving the levofloxacin. NCCN guidelines recommend antibacterial prophylaxis in patients with high risk of febrile neutropenia or other cancer-related infections.

Multinational Association of Supportive Care of Cancer (MASCC) risk index score has been validated to stratify cancer patients with febrile neutropenia into high risk and low risk for development of serious medical complications during the neutropenic fever episode (Uys et al, 2004). This risk index has been studied to risk stratify cancer patients with febrile neutropenia to different levels of treatment. Escalante et al. (2004) studied outpatient antibiotic treatment of patients with febrile neutropenia stratified to the low risk group. This study demonstrated that outpatient antibiotic treatment in low risk febrile neutropenic patients was safe and effective. Current guidelines recommend oral antibiotic therapy with ciprofloxacin with amoxicillin/clavulonate only for patients at low risk for medical complications and inpatient admission for intravenous antibiotic administration in patients at intermediate and high risk for serious complications (NCCN, 2008).

Though all literature and guidelines recommend the prompt initiation of antibiotic therapy, there are very few studies that investigate the timing of antibiotic initiation in patients with febrile neutropenia. A retrospective chart review at the University of Pennsylvania found that the average time from ED triage to initiation of antibiotic therapy was 170 minutes in oncologic patients presenting with febrile neutropenia (Perrone et al., 2004). A retrospective chart review done at the Dartmouth-Hitchcock Medical Center to evaluate a quality improvement project designed to decrease time from patient arrival to initiation of antibiotic therapy demonstrated time to antibiotic therapy was 70 minutes in the clinic, 107 minutes in the emergency department and 188 minutes in the inpatient unit prior to the institution of algorithm to streamline antibiotic administration to neutropenic fever patients, which resulted in almost a 65% reduction in time to antibiotics (Baltic et al., 2002). At New York Presbyterian Hospital/Cornell, Nirenberg et al. (2004) performed a observational, prospective study to determine emergency department waiting times for patients who present to the Cornell ED with neutropenic fever. For twenty-three episodes of febrile neutropenia presenting to the emergency department, this study found that the mean time from symptom onset to ED presentation was 21 hours, median time from triage to physician assessment was 75 minutes, and median time from presentation to antibiotic administration was 210 minutes (range 87-520m).

Based on this finding, the NYPH/Cornell Emergency Department instituted a protocol designed to reduce the time from triage to antibiotic time in oncology patients

who present to the emergency department with febrile neutropenia, entitled "Adult Oncology Fast Track Antibiotic Protocol." Briefly, the protocol was designed to identify cancer patients who are likely to be neutropenic and who present with fever or reported fever and to streamline the triage process with the goal of antibiotic administration within 60 minutes of ED arrival.

The Columbia University Medical Center Hematology-Oncology Division and the CUMC Emergency Department (ED) have created a similar protocol, entitled "Adult Oncology Stat Antibiotic Protocol" to improve time from ED arrival to antibiotic administration in adult oncology patients who present with febrile neutropenia. Preliminary data gathered from the CUMC ED indicate that patients arriving in the ED with neutropenic fever have a median time to antibiotics of 237 minutes with a range of 65minutes to 485 minutes). The protocol is designed to improve the timely administration of appropriate antibiotics in adult oncology patients who present to the ED with fever or reported fever and who are neutropenic or suspected to be neutropenic due to recent chemotherapy or bone marrow/stem cell transplant. Patients followed in the CUMC Oncology Division would be given a identification card to be given the triage nurse to identify themselves as patients who are at risk for febrile neutropenia and patients who are followed elsewhere to be identified as soon as possible so that the protocol can be initiated. The protocol recommends immediate vital signs and immediate phlebotomy to obtain 2 sets of blood cultures and routine labs, including complete blood count with differential, basic metabolic panel and coagulation profile, as well as urinalysis with urine culture and chest radiograph. The protocol calls for the administration of antibiotic therapy within 60 minutes, with antibiotics initiated prior to the results of the complete blood count in patients with leukemia, lymphoma, myeloma, blood/bone marrow transplant patients and hemodynamically unstable patients. In patients with solid tumor malignancies, the protocol allows for the delay of antibiotics until the results of the CBC are received. The protocol clarifies the appropriate antibiotic coverage for febrile neutropenia, which is consistent with the existing clinical pathway outline above.

Given the emergent nature of febrile neutropenia and the importance of empiric antibiotic therapy, prompt initiation of antibiotics is universally recommended by the current literature and current clinical guidelines; however, no studies have addressed whether protocols designed to improve timing of antibiotic initiation affect clinical outcomes. This study is designed to determine if the initiation of an emergency department protocol at Columbia University Medical Center will affect clinical outcomes in adult oncology patients who present to the emergency department with febrile neutropenia.

B. Study Design and Statistical Analysis

This study will be a retrospective, observational study. The two main arms of the study will include patients who presented to the ED with febrile neutropenia prior to protocol initiation and patients who presented to the CUMC ED with febrile neutropenia after the initiation of the ED protocol.

Patient data will be obtained using ICD-9 admission diagnoses, including those for aplastic anemia (284), disease of white blood cells (288), fever (280.6). Then chart

review will identify adult oncology patients who presented to the emergency department with febrile neutropenia who meet the inclusion and exclusion criteria.

Data will be collected regarding age, gender, specific malignancy type, recent chemotherapy regimens, co-morbid conditions, MASCC risk index, the use of prophylactic antibiotics, the use of prophylactic granulocyte colony stimulating factors, mean ANC on presentation, mean nadir ANC, time from ED triage to physician assessment, time from physician assessment to antibiotic ordering, time from antibiotic ordering to antibiotic administration. Clinical outcomes measured will include mortality, admission into the step-down or intensive care units within two weeks of admission, length of antibiotic therapy, length of hospital stay, and clinical or microbiologic source found for febrile neutropenic episode.

The primary outcome measurement is mortality. Based on the review of the medical literature, we estimated that the current mortality rate for oncology patients hospitalized with febrile neutropenia was approximately ten percent. In order detect a 50% reduction in mortality from 10% to 5%, we estimated that we would need 475 subjects in each arm of the study (before and after initiation of the ED protocol) to detect this difference with a statistical power of eighty percent and a five percent significance level using the Chi-squared test. Secondary clinical outcomes include admission into the step-down or intensive care units within two weeks of admission, length of antibiotic therapy, length of hospital stay, and clinical or microbiologic source found for febrile neutropenic episode.

C. Study Procedure

This study is an observational study of patients before and after the initiation of the protocol in the emergency department for oncology patients presenting with febrile neutropenia designed to determine if such a protocol affects clinical outcomes. The study will be performed using review of medical charts in patients that meet the inclusion criteria and are not excluded based on the exclusion criteria. Demographic data and data regarding clinical outcomes will be recorded in a database. Statistical analysis of the data will be performed using the above methods.

D. Study Drugs: not applicable

E. Medical Device: not applicable

F. Study Questionnaires: not applicable

G. Study Subjects

a. Inclusion criteria:

(1) Oncology patients greater than or equal to age 18

(2) Admission through the CUMC Emergency Department

(3) Presentation with febrile neutropenia after recent chemotherapy

(4) Triaged using the “Adult Oncology Stat Antibiotic Protocol” in the CUMC Emergency Department

b. Exclusion criteria:

(1) No evidence of neutropenia on admission laboratory values

(2) Febrile neutropenic patients who were not triaged using the "Fast Track Oncology Protocol" in the ED

H. Recruitment of Subjects

This study is a retrospective, observational study and will only include patients already admitted to the hospital under the aforementioned clinical conditions. Therefore, patients will not need to be recruited specifically for the study.

J. Potential Conflict of Interest: not applicable

K. Location of the Study

This study will be performed at New York Presbyterian Hospital/Columbia University Medical Center. The patients will have been admitted through the Emergency Department and hospitalized at Milstein Hospital.

L. Potential Risks

Since this is a retrospective, observational study involving a review of medical records, this study involved minimal risks to the subjects of the study.

M. Potential Benefits

The potential benefit of this study would be the confirmation that a protocol such as the one described above might influence clinical outcomes and the implementation of such protocols at other emergency departments. However, there will be no clinical benefit to the subjects of this study.

N. Alternative Therapies: not applicable

O. Compensation to subjects: Compensation will not be provided to subjects.

P. Costs to subjects:

The study subjects will not incur any additional costs as a result of participating in the study.

Q. Minors as Research Subjects: not applicable

R. Radiation or Radioactive Substances: not applicable

References:

ASCO. American Society of Clinical Oncology 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. Jan 2008.

Baltic T, Schlosser E and Bedell MK. Neutropenic Fever: One Institution's Quality Improvement Project to Decrease Time From Patient Arrival to Initiation of Antibiotic Therapy. Clin J Oncol Nurs. 2002 Nov-Dec;6(6):337-40.

Bhana N. Granulocyte colony-stimulating factors in the management of chemotherapy-induced neutropenia: evidence based review. Curr Opin Oncology 19: 328-335, 2007.

Bodey GP et al. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med. 1966 Feb: 64 (2): 328-40.

Bow EJ. Management of the febrile neutropenic cancer patient: lessons from 40 years of study. Clin Microbiol Infect. 2005 Oct;11 Suppl 5:24-9.

Bucaneve et al. Levofloxacin to Prevent Bacterial Infection in Patients with Cancer and Neutropenia. New Engl J Med 2005: 353: 977-987.

Cullen M et al. Antibacterial Prophylaxis after Chemotherapy for Solid Tumors and Lymphomas. N Engl J Med 2005: 353: 988-98.

Escalante CP et al. Outcomes of treatment pathways in outpatient treatment of low risk febrile neutropenic cancer patients. Support Care Cancer. 2004 Sep; 12 (9) 657-62.

Falagas ME, Vardakas KZ, and Samonis G. Decreasing the incidence and impact of infections in neutropenic patients: evidence of meta-analyses of randomized controlled trials. Curr Med Res Opin. 2008 Jan; 24(1) 215-35.

Hughes WT et al. 2002 Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer. Clin Infect Dis. 2002 Mar 15;34(6):730-51.

Leibovici L et al. Antibiotic prophylaxis in neutropenic patients: new evidence, practical decisions. Cancer. 2006 Oct 15; 107 (8): 1743-51.

NCCN. Myeloid growth factors. NCCN Clinical Practice Guidelines in Oncology. V1.2008.

Nirenberg A, Mulhearn L, Lin S, Larson E. Emergency department waiting times for patients with cancer with febrile neutropenia: a pilot study. Oncol Nurs Forum. 2004 Jul 13;31(4):711-5.

Perrone J, Hollander JE, Datner EM. Emergency Department evaluation of patients with fever and chemotherapy-induced neutropenia. J Emerg Med. 2004 Aug; 27 (2): 115-9.

Schimpff S, Satterlee W, Young VM, Serpick A. Empiric therapy with carbenicillin and gentamicin for febrile patients with cancer and granulocytopenia. N Engl J Med. 1971 May 13;284(19):1061-5.

Uys A, Rapoport BL and Anderson R. Febrile Neutropenia: a prospective study to validate the Multinational Association of Supportive Care of Cancer (MASCC) risk-index score. Support Care Cancer (2004) 12: 555-560.