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A single institutional review of pediatric *Bacillus* spp. bloodstream infections demonstrates increased incidence among children with cancer

David S. Shulman, MD¹, Preeti Mehrotra, MD², Traci M. Blonquist, MS³, Andrew Capraro, MD⁴, Leslie Lehmann, MD¹, Lewis B. Silverman, MD¹, Neeraj K. Surana, MD, PhD^{5,6,*}, Andrew E. Place, MD, PhD^{1,*}

¹Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA, USA

²Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

³Department of Biostatistics and Computational Biology, Dana Farber Cancer Institute, Boston, MA, USA

⁴Division of Emergency Medicine, Business Intelligence, Boston Children's Hospital, Boston, MA

⁵Division of Infectious Diseases, Department of Medicine, Boston Children's Hospital, Boston, MA, USA

⁶Division of Infectious Diseases, Department of Pediatrics, Duke University School of Medicine, Durham, NC, USA

Abstract

BACKGROUND: *Bacillus* species are known to cause severe infection in immunocompromised hosts. The incidence of *Bacillus* bloodstream infections and characteristics of infection among children with cancer or indication for hematopoietic cell transplantation (HCT) is unknown.

METHODS: We performed a retrospective medical record review of all cases of *Bacillus* bacteremia between January 1st, 2005 and December 31st, 2014 at Boston Children's Hospital. We report average incidences from 2012 to 2014. We performed a detailed review of infections among children with cancer or undergoing HCT and a case-control study to evaluate whether neutropenia at diagnosis carries higher risk of *Bacillus* infection for children with acute lymphoblastic leukemia (ALL).

RESULTS: 114 children developed *Bacillus* bacteremia during the study period, with an estimated incidence of 0.27/1,000 patients. Among children treated for cancer or undergoing HCT, there were 37 bloodstream infections (2.0/1,000 patients). Of the 37 oncology/HCT patients, oncologic diagnoses included ALL (18), acute myeloid leukemia (3), myelodysplastic syndrome (1), solid tumors (8) and 7 children were undergoing HCT. The incidence of infection among

*co-corresponding authors Andrew E. Place, MD, PhD, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215, USA., Phone: 617-632-2313, Fax: 617-632-5710, andrew_place@dfci.harvard.edu, Neeraj K. Surana, MD, PhD, Department of Pediatrics, Duke University, 2301 Erwin Road, Durham, NC 27710, Phone: 919-613-8742, Fax: 919-681-2089, neil.surana@duke.edu.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to report.

children with ALL was 34/1,000 patients and all cases of CNS infection (6) and deaths (3) occurred in this population. Neutropenia at time of diagnosis in children with ALL was not associated with risk of infection ($p=0.17$).

DISCUSSION: We report the first hospital-wide analysis of *Bacillus* infection and found that immunocompromised children experience a significant proportion of *Bacillus* infections. Children with ALL have a high incidence of infection and are at higher risk of CNS involvement and deaths.

INTRODUCTION

Bacillus species are spore-forming, gram-positive rods found ubiquitously in the environment. Non-anthraxis *Bacillus* species have a biphasic existence in the human host—a likely contaminant in immunocompetent individuals and a dangerous pathogen in immunocompromised hosts.^{1,2} *Bacillus cereus* is known to cause endophthalmitis, respiratory infection and post-traumatic skin infections in compromised as well as immunocompetent individuals.^{1,3–6} Bacteremia and subsequent central nervous system (CNS) infection has been described in immunocompromised hosts.^{1,2} Within pediatrics, case reports have focused on infections in neonates^{7,8} and children undergoing treatment for cancer.^{9–14}

While pediatric oncology and hematopoietic cell transplant (HCT) patients are thought to be at a higher risk for *Bacillus* infection, it is not known if the overall incidence of *Bacillus* bacteremia is higher in these groups compared to the general population of pediatric patients. Neutropenia is thought to contribute to this risk given the higher morbidity and mortality reported in immunocompromised hosts, however this has not been systematically studied. Among children with cancer, those with acute leukemia (particularly those with acute lymphoblastic leukemia (ALL) receiving induction chemotherapy) carry an increased risk of CNS infection once bacteremic.¹⁴ Two recent literature reviews of childhood and adult *Bacillus* CNS infections cite mortality rates of 42% and 66%, highlighting the need to further understand these infections and associated complications.^{11,15}

We reviewed all blood cultures that grew *Bacillus* species over a 10-year period at a large pediatric hospital, with the primary aim of determining the incidence of *Bacillus* bloodstream infections among oncology and HCT patients, compared to the general hospital population. We then aimed to provide a more detailed description of *Bacillus* bloodstream infections among children undergoing treatment for cancer, or HCT, including a thorough characterization of these infections among the largest group, children with ALL. Finally, given duration of neutropenia may contribute to risk of *Bacillus* bacteremia, we performed a case-control study to determine whether duration of neutropenia is associated with risk of *Bacillus* bacteremia for children being treated for ALL.

METHODS

Patients

This is an, IRB-approved, retrospective cohort study of patients with *Bacillus* bacteremia identified by the Boston Children's Hospital (BCH) microbiology laboratory between

January 1st, 2005 and December 31st 2014. This includes patients of all ages receiving care at the Dana-Farber/Boston Children's Cancer and Blood Disorders Center. Patients with *Bacillus* bacteremia were identified by reviewing the microbiology condensed line list from the Microbiology Core Lab at Boston Children's Hospital. For the purposes of this manuscript the terms bloodstream infection and bacteremia are used interchangeably.

To estimate the incidence of blood cultures positive for *Bacillus* we identified all cultures positive for *Bacillus* and then identified the total number of blood cultures drawn during the study period. To estimate incidence of bacteremia, we performed a search of the electronic medical record and identified 44,397, 43,134, and 42,904 unique patients treated in either the emergency department or inpatient setting at BCH during 2012, 2013, and 2014, respectively, representing the total number of patients treated at our hospital during a predefined set of years. Next, we identified all unique patients with an oncology or HCT note, consisting of 2,750, 2,774 and 2,950 patients in 2012, 2013, and 2014, respectively, representing the total number of oncology/HCT patients at our center during these years. An estimate of non-oncology, non-HCT patients was calculated by subtracting the number of oncology/HCT-patients from the total number of BCH patients (41,647, 40,360, and 39,954 for 2012, 2013, and 2014, respectively). To estimate the incidence of bacteremia among patients with acute lymphoblastic leukemia we identified all cases of *Bacillus* bacteremia among patients with *de novo* ALL enrolled on the Dana-Farber Cancer Institute (DFCI) biology study 06-078 and DFCI therapeutic protocols 05-001 and 11-001 during the study period. The incidence of *Bacillus* bacteremia among HCT patients was determined by identifying all cases of *Bacillus* bacteremia occurring in the number of unique children who underwent HCT at our center during the study period.

Variables

Clinical data were retrospectively collected on patients with *Bacillus* bacteremia by review of medical records. For all patients, we collected data on diagnosis, presence of a central line, and whether they had a true, indeterminate or contaminated blood culture. For all oncology/HCT patients, we also collected data on patient demographics, patient symptoms, lab values at the time of bacteremia, treatment course, and outcomes. Neutropenia was defined as an absolute neutrophil count (ANC) less than 500 cells/ μ L. We defined blood culture results as representing a true bloodstream infection if the identification of *Bacillus* occurred following a change in the patient's clinical status, including but not limited to fever, tachycardia, abdominal pain, neurologic changes and/or hypotension, and a treatment course of antibiotics was given or the patient died acutely prior to receiving effective treatment; an indeterminate result was defined as cases where a treatment course of antibiotics was administered but there was no clear change in clinical status; and a contaminant was defined as a case where a treatment course of antibiotics was not given and the patient did not die as a result of a *Bacillus* bloodstream infection. The CDC definition of laboratory-confirmed bloodstream infection for a common commensal organism such as *Bacillus* requires two positive cultures and a temperature $>38.0^{\circ}\text{C}$, hypotension, or chills. We modified our definition given that we believe hypotension/chills are late signs of sepsis in pediatric patients, and we do not routinely draw multiple simultaneous cultures on children at time of fever. Determination was based on a multiple-physician reviewer system.

Mortality data was based on whether a *Bacillus* bacteremia was considered by the treating medical team to directly contribute to the patient's death.

Case-Control Study

A case-control study in patients with ALL undergoing induction therapy was performed to determine whether ANC at time of diagnosis was associated with risk of *Bacillus* bacteremia. We included patients who were enrolled onto or treated as per Dana-Farber Cancer Institute protocols for *de novo* ALL including protocols DFCI 05–001¹⁶ and DFCI 11–001. Initial treatment on these regimens consisted multi-agent induction for all patients, including prednisone (or methylprednisolone), vincristine, doxorubicin, pegaspargase, low-dose intravenous methotrexate and intrathecal chemotherapy. Presenting ANC was defined as the highest ANC recorded prior to initiation of oncologic treatment. Patients with B-cell ALL treated on DFCI 05–001 or 11–001 without bacteremia during induction and who achieved a complete remission were used to select a matched control group to those with *Bacillus* bacteremia in a 4:1 ratio. Propensity score nearest neighbor matching was used to select the control sample matched on age at diagnosis, gender, protocol, and protocol defined initial risk group, which includes diagnostic white blood cell count (WBC). The original matching was performed with 13 *Bacillus* cases, regardless of timing of bacteremia, resulting in a total sample size of 65 (13 cases and 52 controls). Medical record data was unavailable for 5 patients in the control group. Two cases with a post-induction bacteremia were removed from this analysis. The final analytic sample included 11 cases and 47 controls, and the groups remained balanced by matching criteria.

Statistical Analysis

The incidence of *Bacillus* positive cultures and *Bacillus* bacteremia was calculated for each year between 2012 and 2014 and then averaged. Categorical and continuous variables were compared by group using the Fisher's exact test and Wilcoxon rank sum test, respectively.

RESULTS

Incidence of *Bacillus* bacteremia at a large pediatric center

The incidence of blood cultures growing *Bacillus* and patients with *Bacillus* bacteremia are summarized in Table 1. Of the 114 positive blood cultures, 77 were non-oncology patients of which 27 (35%) were considered a true bacteremia, 13 (17%) were indeterminate, and 37 (48%) a contaminant. Forty-seven (61%) of the non-oncology patients with a positive blood culture had central access at the time the blood culture was drawn. The remaining 37 positive blood cultures were from children undergoing oncologic treatment or bone marrow transplant. Thirty-four (92%) of these cultures were considered a true bloodstream infection, 2 (5%) were indeterminate, and 1 (3%) was considered a likely contaminant. Thirty-four (92%) had a central venous line in place. Three (8%) patients died as a result of the *Bacillus* bacteremia in the oncology and HCT patient cohort. For 2012–2014, the average incidence rate of blood cultures positive for *Bacillus* spp. was 0.27/1,000 patients for all patients treated in the emergency room and/or as an inpatient at our center. The incidence of positive cultures was 0.16/1,000 for non-oncology patients and 2/1,000 for oncology and HCT patients.

Bacillus bacteremia among oncology and HCT patients

Given the higher incidence of bacteremia among children being treated for cancer or undergoing HCT, we describe these cases in greater detail. Patient characteristics for the 37 oncology/HCT patients with a *Bacillus* positive blood culture are summarized in Table 2. Of these children, 22 (59%) had a hematologic malignancy (18 ALL, 3 AML, 1 MDS), 8 (22%) had a solid tumor (4 neuroblastoma, 1 optic pathway glioma, 1 Ewing sarcoma, 2 glioblastoma), and 7 (19%) had received HCT. Of the seven HCT-patients, diagnoses included relapsed T-cell ALL, relapsed B-cell ALL, aplastic anemia, β -thalassemia, Fanconi anemia, severe combined immunodeficiency, and hemophagocytic lymphohistiocytosis. The two children with ALL undergoing HCT were categorized as HCT patients for the purpose of this study given proximity to preparative regimen, marrow infusion and concomitant HCT-related immunosuppression. Among the 37 oncology patients, 22 (59%) patients were neutropenic at the time of bacteremia with a median ANC of 60 (range 0–17,000) cells/ μ L. The median duration of neutropenia, for patients with available sequential blood counts (18/22), prior to bacteremia was 12.5 days (range 1–24 days). Six of 37 patients had two blood cultures that were positive for *Bacillus* during their episode of bacteremia and the remaining patients had one positive culture. No patients had recurrent *Bacillus* bacteremia following treatment for their initial *Bacillus* infection.

We also assessed the incidence of *Bacillus* bacteremia specifically in patients with ALL and in those who received a HCT given these patient groups represented the most common underlying diagnosis of patients with *Bacillus* bacteremia. Out of 350 patients with *de novo* ALL enrolled at our center on DFCI protocols 06–078, 05–001 and 11–001 during the study period, 12 (34/1,000 patients) had a positive *Bacillus* blood culture. Of the 526 patients who received a HCT during the study period, 7 (13/1,000 patients) had a positive *Bacillus* blood culture.

CNS involvement by Bacillus occurs in patients with ALL and Bacillus bacteremia

CNS involvement is a known complication of *Bacillus* bacteremia. In our cohort, CNS imaging was performed in 23 of the 37 oncology/HCT-patients (11 CT; 12 MRI). Six patients (16%) were found to have CNS complications including brain abscess (n=3), hemorrhagic brain abscess (n=1), subdural fluid with infarct (n=1) and frank brain hemorrhage (n=1). Two patients had CSF cultures sent at next planned lumbar puncture for chemotherapy administration at 5 and 18 days following positive blood culture. Both cultures were negative and the remaining four patients did not have CSF cultures sent for testing. All CNS infections occurred in children with ALL undergoing induction chemotherapy (6/11; 55%). One child with brain hemorrhage died of their infection and the other five recovered without long term neurologic deficits.

Vancomycin and meropenem remain the most common treatments for Bacillus bacteremia in Oncology/HCT-patients

Prior to the first positive culture, 26 (70%) oncology/HCT patients were actively receiving one or more antibiotic(s) (cefepime, 7; ceftazadime, 4; trimethoprim-sulfamethoxazole, 9; atovaquone, 3; vancomycin, 1; cefazolin, 1; piperacillin-tazobactam, 2; gentamicin, 1). Vancomycin was ultimately used as treatment for 29 (78%) patients. One patient was unable

to tolerate a full course of vancomycin due to acute renal insufficiency and required meropenem to complete their treatment course. Four of the 29 patients who received vancomycin also received meropenem as part of their treatment course. One patient received a 14-day course of clindamycin for treatment. The median duration of antibiotic treatment for children with true bloodstream infection treated at least 7 days (n=33), was 14 days (range 7–42). Four of the 37 oncology/HCT patients with positive cultures did not receive a treatment course of antibiotics as one patient was deemed to have a contaminated culture and not a true bloodstream infection and three died acutely of their infection. Four of the 6 patients with CNS involvement were treated with antibiotics for 42 days, one received a 37-day course and one died acutely of infection that included brain hemorrhage detected on CT scan. For the 28 patients without CNS involvement who received a treatment course of antibiotics, 23 (82%) were treated no longer than 14 days.

Characteristics of *Bacillus* bacteremia among children with ALL

Given that children with ALL had the highest incidence of bacteremia and were the only children to have CNS infection, we report further details on the nature of bacteremia seen in this patient population. Of the 18 children with ALL who developed *Bacillus* bacteremia, all had B-cell ALL and 2 had relapsed disease. In this cohort, 11 patients developed *Bacillus* bacteremia during induction (median of day 16, range 1–23), 3 during consolidation (post-induction intensification), 2 during maintenance, 1 during re-induction after relapse, and 1 during maintenance after relapse.

Among the 16 patients with *de novo* ALL, on the day of the first positive blood culture the median WBC count was 0.57×10^3 cells/uL (range 0.08 – 7.16) and the median ANC was 5 (range 0 – 5220) cells/ μ L. Twelve (75%) patients were neutropenic at the time of positive culture and for these patients the median number of days of neutropenia leading up to the positive blood culture was 14 days (range 1–24).

Neutropenia at diagnosis is not associated with an increased risk of developing *Bacillus* bacteremia among children with ALL

Among a homogeneous population of patients with B-cell ALL, we attempted to determine whether being neutropenic at time of initial diagnosis was a risk factor for *Bacillus* bacteremia. Eleven children developed a *Bacillus* bacteremia during their induction course and were compared to 47 matched controls receiving induction who did not develop bacteremia (Table 3). The median presenting ANC for those developing a *Bacillus* bacteremia was 180 (range 0–3,770) cells/ μ L compared to 650 (range 0–13,610) cells/ μ L in uninfected controls (p=0.30). Of patients who were neutropenic at presentation (n=24), 7 (29%; 90% CI 15–48%) developed *Bacillus* bacteremia compared to 4 (12%; 90% CI 4–25%) of those who were not neutropenic (n=34).

DISCUSSION

Bacillus causes rare but serious infections in children. We present the first hospital-wide analysis of *Bacillus* bacteremia and the largest cohort of *Bacillus* cases at a tertiary children's hospital. The overall rate of positive *Bacillus* cultures at our institute is estimated

at 0.27 per 1,000 cultures, which is similar to what is reported in the recent literature.¹⁷ Our data demonstrate that children being treated for cancer or undergoing bone marrow transplant make up the largest proportion of patients with *Bacillus* bacteremia with an estimated incidence 12.5-times higher compared to the overall hospital rate. In addition, the proportion of true bacteremia (i.e., not indeterminate or contaminant) was higher among oncology/HCT patients compared to non-oncology patients.

In our study, *Bacillus* bacteremia occurred in patients with a variety of underlying oncologic diagnoses at different phases of treatment. However, patients undergoing treatment for ALL had an incidence of *Bacillus* bacteremia that was 212-times higher than the rate of bacteremia among non-oncology patients, a finding that strongly suggests these patients have a higher risk for *Bacillus* bacteremia. Among patients in this study with *de novo* ALL who developed a *Bacillus* bacteremia 11 of 16 were receiving induction chemotherapy, which is a previously identified risk factor for *Bacillus* CNS infection among patients with ALL.^{11,14} All patients with ALL treated at our center during the study period received an intense multi-agent induction regimen including anthracycline chemotherapy. This regimen typically results in profound neutropenia and gastrointestinal mucositis. Gastrointestinal translocation is likely the most common avenue for *Bacillus* entry into the bloodstream in these patients. Interestingly, the rate of bacteremia among patients with ALL was nearly twice that of patients undergoing HCT, who also endure a period of neutropenia and profound immunocompromised state. Most patients in our center receive oral vancomycin-polymyxin B during HCT, an oral antimicrobial medication with activity against intraluminal *Bacillus*, which might contribute to this difference in *Bacillus* bacteremia rates.

Not only do children with ALL in induction make up the largest group of patients with *Bacillus* bacteremia, they also account for all of the deaths and CNS infections in our cohort. Induction chemotherapy for ALL and neutropenia are known risk factors for *Bacillus* CNS infection,¹⁴ and in our cohort 55% of children who developed bacteremia during induction were found to have CNS infection. Given the rate of CNS involvement in patients with acute leukemia and that some of these infections included frank brain hemorrhage and abscesses, CNS imaging should be strongly considered for children with leukemia who develop *Bacillus* bacteremia. In our study, neutropenia at diagnosis was not associated with an increased risk of developing a *Bacillus* bacteremia, highlighting the need to be vigilant for this infection in all newly diagnosed patients with ALL.

There are several limitations to this study. First, there is the possibility of reviewer bias in determining whether positive cultures represented true bloodstream infection, a risk that we have attempted to mitigate by utilizing a multiple reviewer system. The comparison between culture data obtained from oncology/HCT patients versus non-oncology/HCT patients is inherently challenging given the increased suspicion for serious infection in heavily immunosuppressed patients. Similarly, given that CSF cultures are not routinely obtained at the time of identifying *Bacillus* in the bloodstream, CNS involvement was not culture-proven in our cohort. However previous reports have demonstrated a propensity for *Bacillus* to involve the CNS and in our cases there was no other clear alternative etiology. We utilized an advanced medical record search to estimate the population of unique patients seen at our center over a 3-year period in order to generate incidence data. While this number is an

estimate, we feel it closely represents the entire oncology population and provides the best available means of providing an incidence of bacteremia among these groups of patients. Further, the search results included patients on active treatment and those in off-therapy follow-up. The off-therapy follow-up patients have a significantly lower risk of infection than those on therapy. However, this underestimates the degree to which bacteremia risk is higher for active oncology/HCT patients compared to the general pediatric hospital population. The incidence calculation for patients with ALL and HCT represents a population that does not include long-term follow-up patients and represents a more accurate estimate of incidence in these populations. Finally, given that this is a single-center study, the possibility exists that hospital-specific practices or environmental contamination could have influenced the results of this study.

In summary, *Bacillus* bloodstream infections cause significant morbidity and mortality in the pediatric oncology/HCT population. In our study, children with acute lymphoblastic leukemia carried the highest risk of infection and suffered all CNS infections and deaths. Thus *Bacillus*-directed antibiotics may be considered in the empiric treatment of fever and neutropenia until *Bacillus* bacteremia is ruled out (negative culture) during early phases of ALL therapy. Further studies in children with acute leukemia may benefit from cross-institutional collaboration to capture a larger, more homogeneous patient population in a prospective fashion that can further elucidate risk factors for *Bacillus* bacteremia.

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Table 1:Incidence of *Bacillus* bacteremia among patients in a single large pediatric hospital

Incidence of positive blood cultures (2005–2014)			
Group	Blood cultures growing <i>Bacillus</i>	Total blood cultures drawn	Incidence (per 1,000 cultures)
All cultures	114	155,491	0.73
Incidence of <i>Bacillus</i> bacteremia (2012–2014)			
	Blood cultures growing <i>Bacillus</i>	Number of unique patients	Incidence (per 1,000 patients)
Positive cultures among all patients			
2012	18	44,397	0.41
2013	8	43,134	0.19
2014	10	42,904	0.23
Average Incidence			0.27
Positive cultures among non-oncology patients			
Year			
2012	8	41,647	0.19
2013	5	40,360	0.12
2014	6	39,954	0.15
Average Incidence			0.16
Positive cultures among oncology patients			
Year			
2012	10	2750	3.6
2013	3	2774	1.1
2014	4	2950	1.4
Average Incidence			2.0

Table 2:Characteristics of *Bacillus* bacteremia among oncology/HCT patients

Patient characteristic	N (%) (n=37)
Gender	
Male	16 (43)
Female	21 (57)
Age at diagnosis in years, median (range)	4 (0.5–18.6)
Diagnosis	
ALL	16 (43)
Relapsed ALL	2 (5)
AML	3 (8)
MDS	1 (3)
HCT	7 (19)
Solid tumor	8 (22)
Clinical characteristics at time of positive blood culture	
Neutropenic (ANC < 500 cells/ μ L)	22 (59)
Abdominal pain	17 (46)
Fever	34 (92)
CNS Involvement	
Yes	6 (16) *
No	17 (46)
Imaging not done	14 (38)
WBC $\times 10^3$ cells/ μ L, median (range)	0.88 (0.06–70.0)
ANC (cells/ μ L), median (range)	60 (0–17,000)

* All patients were receiving induction therapy for ALL

ALL – acute lymphoblastic leukemia; AML – acute myelogenous leukemia; ANC – absolute neutrophil count; CNS – central nervous system; HCT – hematopoietic cell transplant; MDS – myelodysplastic syndrome; WBC – white blood cell count

Table 3:Patient characteristics of children with B-cell ALL who developed *Bacillus* infections and matched controls

	No <i>Bacillus</i> infection N (%)	<i>Bacillus</i> infection N (%)	p-value
Number of patients	47 (100)	11 (100)	
Age at Diagnosis (median (range))	5.9 (2.1–16.8)	5.1 (2.5–17.5)	
< 10 years	31 (66)	7 (64)	p = 1.0
10 years	16 (34)	4 (36)	
Gender			
Female	23 (49)	7 (64)	p = 0.51
Male	24 (51)	4 (36)	
NCI Risk Group			
Standard Risk	24 (49)	5 (45)	p = 1.0
High Risk	23 (51)	6 (55)	
WBC at Diagnosis			
< 50 K/ μ L	37 (79)	7 (64)	p = 0.43
50 K/ μ L	10 (21)	4 (36)	
ANC at Diagnosis			
< 500 cells/ μ L	17 (36)	7 (64)	p = 0.17
500 cells/ μ L	30 (64)	4 (36)	

ANC – absolute neutrophil count; NCI – National Cancer Institute; WBC – white blood cell