INFECTIONS IN FEBRILE NEUTROPENIC CANCER PATIENTS WHO WERE UNDERGOING CHEMOTHERAPY AT THE MAKATI MEDICAL CENTER

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ABSTRACT
The immune system of children with malignancies is compromised by chemotherapy and by the cancer itself. In addition, frequent intravenous cannulation, indwelling catheters, malnutrition, prolonged exposure to antibiotics and frequent hospitalizations increase the risk for infection. Neutropenia may lead to an inappropriately low inflammatory response so that fever may be the only manifestation of infection. Management of this complication can vary widely, relating to different geographic patterns of infections and antimicrobial resistance, as well as, issues of treatment availability and cost attainment.
The objective of this study was to determine the etiology of infections in febrile neutropenic cancer patients aged 18 years and below who were undergoing chemotherapy at the Makati Medical Center.
Inpatient charts of 21 episodes of febrile neutropenia in 19 cancer patients undergoing chemotherapy were reviewed. The primary diseases were mostly acute leukemias (94.7%). Sites of documented infections were the respiratory tract (26.1%), skin and soft tissues (21.7%) oral cavity, ear and sinuses (19.6%), gastrointestinal tract (17.4%), bloodstream (8.7%) and the genitourinary tract (6.5%). Cultures from different sites of infection yielded *Escherichia coli (*36.4%) and *Staphylococcus* species (27.3%) to be the most common isolates. The overall mortality was 4.8%.
Although broad spectrum antibiotics were used as empiric therapy, the number of isolates obtained was too few to allow a standard recommendation on an appropriate antibiotic regimen.

INTRODUCTION

The diagnosis of cancer in a child places a significant medical, psychological and financial burden on the patient and his family. The approach to treatment, therefore, is multidisciplinary, including primary modalities such as chemotherapy, radiotherapy or surgery, combined with supportive care services. Aside from the disease itself, there are also complications arising from radiation and chemotherapeutic agents. The most common of these complications, and possibly the most lethal, is neutropenia.

Neutrophils are an essential part of the body's defense system, particularly against bacterial infections. As a response to a bacterial infection, neutrophils are one of the first inflammatory cells to migrate toward the site of inflammation by chemotaxis. Neutrophils react within an hour of tissue injury and are the hallmark of acute inflammation. Chemotherapy drugs may affect neutrophil production through myelosuppression, and this, in conjunction with immunosuppressive drugs, renders the patient at risk for infection.

Neutropenia is a condition in which the absolute neutrophil count (ANC) is more than two standard deviations below the mean, which may vary with race and age. The immune system of children with malignancies is compromised by chemotherapeutic drugs and by the direct effect of the cancer itself. In addition, frequent intravenous cannulation, indwelling catheters, malnutrition, prolonged exposure to antibiotics and frequent hospitalizations all increase the risk for infection in these children. Aerobic and anaerobic gram positive and gram negative bacteria, fungi, viruses and parasites may cause infections in these patients. The lack of neutrophils can lead to an inappropriately low inflammatory response so that fever may be the only manifestation of infection.[3]

Although empiric administration of broad-spectrum antibiotics at the onset of fever is the accepted standard approach to therapy for neutropenic patients, the inappropriate *use* of antibiotics is of special concern. Excessive use of these drugs may be associated with colonization by hospital-acquired organisms, the emergence of resistant strains, exposure to adverse effects, and unnecessary expense.[2] Despite virtually identical rates of response, time of clinical response and estimated cost of care *vary* significantly *between* regimens. An early discharge strategy based on our definition of the time point of clinical response may further reduce the cost of treating non-low-risk patients with febrile neutropenia.[5] It is in this context that this retrospective paper was created in order to allow the appropriate evaluation and treatment approach based on hospital experience.

The *objectives* of the study *were* to determine the *etiologic agents and sites* of *infection in* patients *aged 18 years and below* with febrile *neutropenia* who were undergoing chemotherapy at the Makati Medical Center, as well as their clinical response and outcome.

MATERIALS AND METHODS

Study Design

This is a hospital-based descriptive study, reviewing in-patient charts of cancer patients aged 18 years old and below admitted for chemotherapy at the Makati Medical Center between January 1, 2003 to June 30, 2009

Methodology, Scope and Limitation

Study patients with an absolute neutrophil count *(ANC)* of <500/cu mm were identified. Cases were obtained from MMC pediatric consultants' data records and through the MMC Records Section patient database using ICD codes for malignancies. These were narrowed down further to patients with a new onset of fever during the neutropenic period.

Host factors such as age, sex, type of disease, symptoms and physical examination findings were reviewed. *Sepsis* work-up data (culture and sensitivities of various specimens), radiographic and imaging results prior to, and

during, antibiotic treatment were identified. Clinical outcome based on antibiotics given were recorded and analyzed. Clinical outcome was assessed by the resolution of symptoms and fever as well as survival related to infection.

Operational Definitions

The ANC is the product of the white blood cell count (WBC) and the fraction of polymorphonuclear cells (PMNs) and band forms reported in the differential analysis. Neutrophilic metamyelocytes and younger forms are not included in this calculation. The formula is as follows:

$$\text{ANC} = \frac{\text{WBC (cells/microL) x \% (PMNs + bands)}}{100}$$

Febrile neutropenia was defined as temperature greater or equal to 38.0C, in combination with an *ANC* of 500/cu mm or less.

Cancer patients 18 years of age and below who were admitted at the Makati Medical Center from January 1, 2003-June 30, 2009 for chemotherapy; with absolute neutrophil counts less than 500/cu mm and with a new onset of fever (≥38.0C) during the course of the chemotherapy were included in the study.

Patients with neutropenia in conditions not related to malignancies and chemotherapy or had fever which occurred prior to the onset of the neutropenic period or prior to the onset of chemotherapy were excluded.

Data Collection

In-patient charts of study patients were reviewed and the following data were taken: name, age and gender; type of cancer; initial *ANC* during the febrile neutropenia episode; severity of new onset fever during the neutropenic stage; *sepsis* workup done and results, including microorganisms isolated in cultures, and drug susceptibility; antibiotics used during the febrile episode; and clinical response.

Statistical Analysis

Nominal data were tabulated and measures of central tendency were obtained.

RESULTS

Patient Profile

A total of 21 cases of febrile neutropenia among 19 cancer patients on chemotherapy were identified. Ages ranged from 1-17 years with a mean of six years. There were nine males and ten females. Majority of the primary diseases were acute leukemias (94.7; a single solid tumor case, liver sarcoma (5.3%) was seen (Table1). Infections were more prevalent in the *0-5* years old age group (52.6%) compared to the *6-12* years old (36.8%) and 13-to-17 years old (10.6%) age groups.

During febrile neutropenic periods, average initial *ANC* was 223/cu mm. Of the 21 episodes of febrile neutropenia, nine had initial *ANC* of 300-500/cu mm, seven were in the 100-299/cu mm range and five in the <100/cu mm range. Length of fever ranged from three-to-16 days, with a mean of 5.9 days, and temperature ranged from 38.0C to 41.0C, with a mean of 38.2 °C.

Infections

Of the 21 hospital admissions, there were 46 documented infections; 13 of these (28.3%) were present during the time of admission, while the other 33 (71.7%) manifested with signs and symptoms after the third hospital day.) Of these, the most common sites were the respiratory tract (26.1%) and the skin and soft tissues (21.7%). Four patients had bacteremia (8.7%) (Table 2). Respiratory infections included acute bronchitis, comprising 13.0% of all infections, and 8.7% had radiologic findings of pneumonia. Chest x-rays showed diffuse infiltrates in

Table 1. Type of *m*alignancy *a*ccording to *s*ex and *a*ge (N=19)

Underlying Disease	**Male**				**Female**			
Age of Patient (years)	**0-5**	**6-16**	**13-18**	**Total**	**0-5**	**6-16**	**13-18**	**Total**
Acute leukemias n=18 (94.7%)				8(42.1%)				10 (52.6%)
Acute lymphocytic leukemia	3	3	0	6(31.5%)	4	3	1	8 (42.1%)
Acute myelogenous leukemia	1	1	0	2(10.5%)	1	0	1	2 (10.5%)
Solid Tumors n=1 (5.3%)								
Liver *s*arcoma	1	0	0	1(5.3%)	0	0	0	0(0%)
TOTAL	**5**	**4**	**0**	**9 (47.4%)**	**5**	**3**	**2**	**10 (52.6%)**

Table 2. Sites of clinically and microbiologically documented infections and mean duration of antibiotic use, by infection type and site (N=46)

	Blood	**Sputum**	**Urine**	**Abscess**	**TOTAL**
Gram negative n=7 (63.6%)					
E. coli	1 (9.1%)		2 (18.2%)	1 (9.1%)	4 (36.4%)
Klebsiella spp.	1 (9.1%)				1 (9.1%)
Enterobacter spp.		1 (9.1%)			1 (9.1%)
Serratia spp.				1 (9.1%)	1 (9.1%)
Gram Positive n=4 (36.4%)					
Staphylococcus aureus	1 (9.1%)			1(18.2%)	2(18.2%)
Staphylococcus hominis	1 (9.1%)				1 (9.1%)
Group D *Streptococcus*			1 (9.1%)		1 (9.1%)
TOTAL	**4 (36.4%)**	**1 (9.1%)**	**3 (27.3%)**	**3 (27.3%)**	**11 (100%)**

Table 3.Bacterial spectrum of isolates, according to body fluid source (N=11)

	Blood	**Sputum**	**Urine**	**Abscess**	**TOTAL**
Gram negative n=7 (63.6%)					
E. coli	1 (9.1%)		2 (18.2%)	1 (9.1%)	4 (36.4%)
Klebsiella spp.	1 (9.1%)				1 (9.1%)
Enterobacter spp.		1 (9.1%)			1 (9.1%)
Serratia spp.				1 (9.1%)	1 (9.1%)
Gram Positive n=4 (36.4%)					
Staphylococcus aureus	1 (9.1%)			1(18.2%)	2(18.2%)
Staphylococcus hominis	1 (9.1%)				1 (9.1%)
Group D *Streptococcus*			1 (9.1%)		1 (9.1%)
TOTAL	**4 (36.4%)**	**1 (9.1%)**	**3 (27.3%)**	**3 (27.3%)**	**11 (100%)**

Table 4. Antibiotics *used* in the *t*reatment of *i*nfections *among f*ebrile *n*eutropenic *p*atients

Antibiotic n=22	**1st line drug N (%)**	**2nd line drug N (%)**	**3rd line drug N (%)**	**Total N (%)**
Cefepime	8 (17)	1 (7.7)	1 (20)	10 (15.4)
Mycostatin	8 (17.)	0(0)	0(0)	8 (12.3)
Amikacin	6 (12.8)	0(0)	0(0)	6 (9.2)
Cefuroxime	4 (8.5)	0(0)	1 (20)	5 (7.7)
Fluconazole	3(6.4)	1(7.7)	0(0)	4 (6.1)
Co-Amoxiclav	3 (6.4)	0 (0)	0(0)	3 (4.6)
Piperacillin-Tazobactam	1 (2.1)	1(7.7)	1 (20)	3 (4.6)
Clindamycin	2 (4.2)	1(7.7)	0(0)	3(4.6)
Ceftazidime	2(4.2)	1(7.7)	0(0)	3 (4.6)
Ampicillin	3 (6.4)	0(0)	0(0)	3(4.6)
Imipenem	0(0)	2 (11.8)	1 (20)	3(4.6)
Vancomycin	0(0)	2 (11.8)	1 (20)	3(4.6)
Meropenem	2(4.2)	0(0)	0(0)	2 (3.1)
Cotrimoxazole	0(0)	1(7.7)	0(0)	1 (1.5)
Ceftriaxone	1(2.1)	0(0)	0(0)	1(1.5)
Ticarcillin-Clavulanic Acid	0(0)	1(7.7)	0(0)	1(1.5)
Oxacillin	1(2.1)	0(0)	0(0)	1(1.5)
Amoxicillin	0(0)	1(7.7)	0(0)	1(1.5)
Metronidazole	1(2.1)	0(0)	0(0)	1(1.5)
Cefixime	0(0)	1(7.7)	0(0)	1(1.5)
Erythromycin	1(2.1)	0(0)	0(0)	1(1.5)
Levofloxacin	1(2.1)	0(0)	0(0)	1(1.5)
Total	47 (72.3)	13 (20.0)	5 (7.7)	65 (100)

different lobes. There were no reports of loculations or consolidations.

Phlebitis was the top cause of skin infections, while one child with a peri-anal abscess grew *E. coli*, *Serratia* and oxacillin resistant *Staphylococcus aureus in* culture (Table 3). Two patients had cellulitis, one *at* the left side of the neck, and one *at* the right ankle, which were both not related to an intravenous catheter.

Among the oropharyngeal infections, three cases of gingivostomatitis and one case of herpangina were *seen*. Infections in the gastrointestinal tract included seven *with* diarrhea and one with *Clostridium difficile* colitis.

There were three cases of urinary tract infection, one of which showed a urinalysis with pyuria and bacteriuria but with a urine culture showing no growth. The other two grew >100,000 CFU *E. coli* on culture. No follow-up imaging studies such as ultrasound and DMSA scans were done.

Seventeen blood cultures were taken, with thirteen (76.5%) showing no growth. Bacteremia was documented in four cases: one each of *Staphylococcus aureus*, coagulase negative *Staphylococcus*, *E. coli* and *Klebsiella spp.* The patient with *Klebsiella* bacteremia presented with cough, colds, and diarrhea upon admission. *Escherichia coli* caused bacteremia in a patient with diarrhea and perianal pyoderma, with both urinalysis and urine culture showing evidence of a urinary tract infection. Among the *gram-positive* organisms isolated, *Staphylococcus spp.* isolates were not related to phlebitis or intravenous access.

One of the two urine cultures showed significant growth, while the single stool culture done showed no growth. Both peri-anal abscess and sputum culture yielded microorganisms. A number of *gram-negative* infections were isolated (63.6%), the most common of which was *E. coli* (36.4%). *Klebsiella, Enterobacter* and *Serratia* were also found but were cultured from different sites. *Gram-positive* organisms identified were of the *Staphylococcus* species (27.3%) (Table3). Several of these cultures had more than one organism isolated.

Antibiotic Treatment

Gram-positive infections were all susceptible to vancomycin. Gram-negative organisms were more sensitive to broad-spectrum antibiotics (Table 4). Isolates obtained were too few to allow a reasonable recommendation for appropriate antibiotic regimens to use.

The length of antibiotic therapy varied, which depended on the severity of the illness

and presence of multiple infections. The length of treatment ranged from 8-14 days. Ten of these infections resolved with the use of empiric antibiotics; however, 11 required switching to a second drug based on culture results and the lack of improvement in symptoms. Broad-spectrum antibiotics were used as empiric treatment for most patients (Table 4).

Clinical Response

There was a high survival rate observed in the population of this study (95.2%) when treated with intravenous antibiotics. Two of the 19 patients, however, were not fully evaluated for response to treatment; one patient was transferred to another institution, and another was discharged due to financial constraints. There was one mortality, which was due to pneumonia and acute respiratory distress syndrome (4.8%).

DISCUSSION

Management of febrile neutropenia can vary widely, relating to different geographic patterns of common infectious organisms and of antimicrobial resistance, as well as issues of treatment availability and cost. The Infectious Disease Society of America guidelines recommend prompt initial therapy in all patients, with three empiric options: one approach includes combination therapy with ceftazidime and vancomycin; other options for empiric therapy include monotherapy (ceftazidime, imipenem, meropenem or cefepime) and combination therapy (with an aminoglycoside and an anti-pseudomonal beta lactam).[1]

This study found the most common malignancies to be leukemias. In a study done by Billote, et al. (1996), febrile neutropenic patients aged five-to-68 years had their primary sites of malignancy being hematologic (71%), with acute leukemia being the most common; it was followed by solid tumors (12.7%). More than half (58.2%) had received cancer chemotherapy within the three weeks prior to the onset of febrile neutropenia; 14.5% were on immunosuppressive agents. The isolated pathogens were) *gram-negative* bacilli (51.5%), most of which were from the family *Enterobacteriaceae*; gram-positive cocci (24.2%); *Candida albicans* (9.1%); and parasites/amoeba (15.2%). The sites of the documented infections were the respiratory tract (35.4%), skin and soft tissues (20.8%), oropharyngeal mucosa (10.4%), urinary tract (8.3%), gastrointestinal tract (8.7%), and peritoneum (2.1%).

Among the 46 documented infections in this study, 17 blood cultures were obtained as well as other body samples. Two out of three urine cultures showed growth of *E. coli*, while the one stool culture done was negative. Culture from the peri-anal abscess was also done. Although there were 12 documented respiratory infections, it was observed that only one sputum culture was done, which reflects the difficulty in obtaining respiratory samples from children.

The usual empiric antimicrobial treatments were broad-spectrum antibiotics. A key point in the antibiotic treatment of febrile neutropenic children is to keep the infections in focal sites out of the bloodstream in order to decrease morbidity and mortality. Bacteremia can result in overwhelming sepsis, shock, and multiple organ failure, aside from causing serious morbidity and mortality. Length of treatment using antibiotic was hard to determine because signs and symptoms tended to overlap and there were instances where there were more than one infection at one time. Fever was observed to resolve even if the absolute neutrophil counts were still low (<500/cu mm) in the presence of antibiotic therapy. In this light, although there is no current consensus on when to stop antibiotics, it was observed that these were discontinued when the fever had resolved and the clinical infection had been adequately treated despite persistent neutropenia. The number of isolates obtained in this study was too few, however, to

recommend a standard antibiotic regimen for empiric use during febrile neutropenia episodes. This study, however, found a good response to empiric broad-spectrum antibiotics, as reflected by the high survival and low mortality rates.

CONCLUSIONS AND RECOMMENDATIONS

Febrile neutropenia in a cancer patient undergoing chemotherapy is a major risk for infection. In this study, 90.5% percent of patients had identified infections. The respiratory, integumentary, oropharyngeal and gastrointestinal tract were almost equally likely to be the sites of infection; bacteremia *was* seen in 8.7%. In this study population, *E. coli* and *S. aureus* were the most common isolates. The number of isolates obtained from body fluids in this study did not constitute enough data to allow a reasonable recommendation on the best antimicrobial regimen to employ. Broad-spectrum antibiotics were used as empiric *treatment* in a majority of cases. There *was* a high survival rate (95.2%).

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