The Outcome of Febrile Neutropenic Episodes in Paediatric Oncology at the Wendy Fitzwilliam Paediatric Hospital

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ABSTRACT

Objective: *To evaluate the incidence, presentation, treatment and outcome of febrile neutropenic episodes of patients treated at the Wendy Fitzwilliam Paediatric Hospital (WFPH) in Trinidad and Tobago.*

Methodology: *Using a retrospective cohort method, the records of all the patients registered at the Paediatric Oncology Unit at The WFPH, receiving chemotherapy for haematological or solid tumour malignancies from May 2001 to April 2008 and having episodes of febrile neutropenia were analysed.*

Results: *Seventy one episodes of febrile neutropenia were analysed from the 36 patient records. Episode frequency ranged from 1 to 5. The mean duration of febrile neutropenic episodes was 5.01 days (± SD 5.2), with range from 1 – 25 days. Acute Lymphoblastic Leukaemia (ALL) accounted for 43.7%. The mean WBC for the study population was 0.88 x 10^9/L (± SD 0.61), with the mean absolute neutrophil count (ANC) at 0.16 x 10^9/L (± SD 0.23). Antifungal therapy was used in 6 cases and the incidence of blood culture positive sepsis was 8.5%. Complete resolution occurred in 65 episodes*

Conclusion: *Febrile neutropenia episodes treated at the WFPH have a very favourable outcome (91.5%). The further analysis of the relationships found in this study between the total white blood cell count at presentation and the duration of antimicrobial therapy, the duration of the febrile neutropenic episodes and outcome is needed.*

Keywords: Childhood cancer, febrile neutropenia

La Evolución Clínica de los Episodios Neutropénicos Febriles en la Oncología Pediátrica en el Hospital Pediátrico Wendy Fitzwilliam

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RESUMEN

Objetivo: *Evaluar la incidencia, presentación, tratamiento y evolución clínica de los episodios neutropénicos febriles de pacientes tratados en el Hospital Pediátrico Wendy Fitzwilliam (WFPH) en Trinidad y Tobago.*

Metodología: *Mediante un método de cohorte retrospectivo, se analizaron las historias clínicas de todos los pacientes inscritos en la Unidad de Oncología Pediátrica en WFPH, que recibieron quimioterapia para el tratamiento de neoplasias hematológicas o tumores malignos sólidos desde mayo de 2001 a abril de 2008 y tuvieron episodios de neutropenia febril.*

Resultados: *Se analizaron setenta y un episodios de neutropenia febril de las historias clínicas de 36 pacientes. La frecuencia de los episodios osciló entre 1 y 5. La duración promedio de los episodios neutropénicos febriles fue 5.01 días (± SD 5.2), con un rango de 1 a 25 días. La leucemia linfoblástica aguda (LLA) representó el 43,7% de los casos. El promedio del conteo de glóbulos blancos (WBC) para la población de estudio fue 0.88 X 10^9/L (± SD 0,61), con el promedio del conteo absoluto de neutrófilos (CAN) en 0.16 X 10^9/L (± SD 0.23). La terapia antifúngica fue utilizada en 6 casos y la incidencia de la sepsis confirmada por cultivo positivo de la sangre fue 8.5%. En 65 episodios (91.5%) hubo resolución completa con 6 muertes.*

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Conclusión: *Los episodios de neutropenia febril tratados en la WFPH tienen una evolución clínica muy favorable (91.5%). Se necesita profundizar en el análisis de las relaciones encontradas en este estudio entre el conteo total de glóbulos blancos en la presentación y la duración del tratamiento con antibióticos, la duración de los episodios neutropénicos febriles y la evolución clínica.*

Palabras claves: Cáncer infantil, neutropenia febril

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INTRODUCTION

Febrile neutropenia is a common problem in children being treated for oncological diseases. Epidemiological studies have demonstrated a high incidence of sepsis in paediatric patients receiving chemotherapy, shown to be approximately 12.8% in children age 1–9 years and 17.4% in children aged 10–19 years, making febrile neutropenia a worrying and serious complication in childhood cancer treatment (1). In Trinidad and Tobago, childhood cancers are diagnosed and treated at the Wendy Fitzwilliam Paediatric Hospital (WFPH), the only tertiary care Paediatric Hospital in the country. Since the introduction of the Paediatric Oncology Unit at the WFCH in Trinidad and Tobago in 2001, studies detailing the incidence of febrile neutropenia have not been undertaken.

In the Caribbean literature, there are a few case reports on neutropenic patients, however, these are for adult patients with unusual febrile neutropenic complications (2, 3). This study is the first of its kind in the English-speaking Caribbean looking at the important outcomes of febrile neutropenic episodes and serving as a pioneer study into the establishment of incidence data for febrile neutropenia in children and the further analysis of paediatric oncology patients both in Trinidad and Tobago and the Caribbean.

SUBJECTS AND METHOD

The study was conducted at the WFPH using a retrospective cohort of oncology patients age 0–16 years with febrile neutropenia for the period May 2001 to April 2008. Febrile neutropenia was defined as a documented evidence of pyrexia taken as two axillary recordings of temperature of 37.5°C one hour apart or one single recording of greater than 38 °C and neutropenia at an absolute neutrophil count (ANC) less than 1 x 10^9 /L.

The cohort was established using data from the Paediatric Oncology Clinic register, the Dr Elizabeth Quamina National Oncology Registry and the Central Statistical Office of Trinidad and Tobago.

Data collected included, patient demographics and diagnosis, episode data, clinical presentation and laboratory findings, clinical therapy, microbiological data and outcome. Patients were treated as inpatients following the febrile neutropenia protocol in use (Fig. 1.).

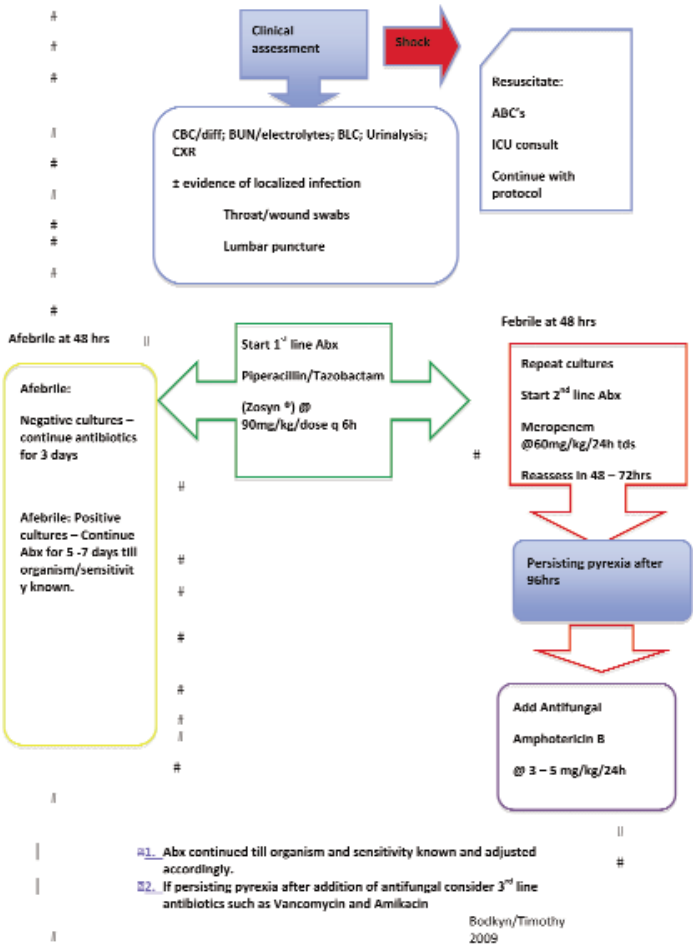

Fig. 1: Febrille Neutropenia protocol for Paediatric Oncology, WFPH

Patient confidentiality was ensured by following the Caldecott Guardian Principles. Approval was granted by the Ethics Committee of the Faculty of Medical Sciences before commencing data collection.

SPSS 16.0 was used to analyse the data. Mann Whitney and Kruskal Wallis tests were used to determine the relationships between multiple variables. One-way ANOVA with Bonferroni post hoc testing was used to compare means between groups. Independent t testing was used to compare means in some instances where one-way ANOVA could not

be used. Statistical significance was assessed at the $p < 0.05$ level.

RESULTS

Of the 118 records reviewed, 36 were eligible, yielding 71 episodes. The outcome was favourable in 91.5%. The episode frequency per patient ranged from 1 to 5 with 15 patients (41.7%) having 1 episode only, 9 (25%) patients having 2 episodes, 10 (27.7%) patients with 3 episodes, 1 (2.8%) patient with 4 and 1 (2.8%) patient with 5 episodes. The mean duration was 5.01 days ± SD 5.2 (range being from 1–25 days). The mean age of the study population was 7.32 years (± SD 4.07) with the male: female ratio at 1.1:1.

Acute Lymphoblastic Leukaemia (ALL) accounted for 43.7% of the episodes (Fig. 2). Pyrexia alone was the commonest presenting complaint (67.6%) followed by mucositis (18.3%) and respiratory complaints (12.7%). Mean WBC was 0.88 x 10^9/L (± SD 0.61) with the mean ANC 0.16 x 10^9/L (± SD 0.23).

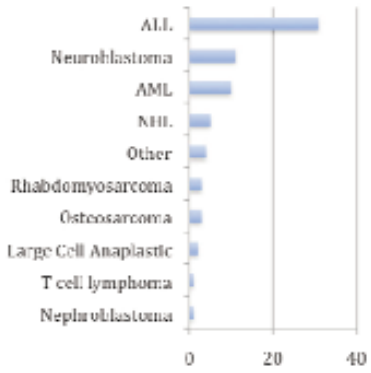

Fig. 2: Bar chart showing the distribution of diagnoses in the febrile neutropenic episodes

Fig.1: Febrile Neutropenia protocol for Paediatric oncology, WFPH

Piperacillin-tazobactam was used as the first line antibiotic in 70.4% episodes; 31% required second line antibiotic therapy with 8.5% requiring antifungal therapy. Antifungal usage correlated significantly with the duration of the episode ($p < 0.0005$), the WBC ($p = 0.023$) and the ANC ($p = 0.010$) at presentation.

Culture positive sepsis was seen in 8.5% of the episodes (Table 1). There was no significance between the culture positive and culture negative groups for WBC, ANC and temperature. Independent t testing of the mean WBC from the resolved episodes *versus* the episodes ending in death revealed significance ($p = 0.003$).

Correlation of the WBC to the duration of episodes revealed a R- value of negative (-) 0.321 with $p = 0.006$. When WBC was correlated to the ANC, the R- value was positive (+) 0.732 with $p < 0.0005$ (Fig. 3). Correlation applied to the total duration of antibiotic therapy to the ANC and the WBC, both revealed negative R values of -0.41. The ANC correlated significantly with $p = 0.01$ but the WBC's relationship on the total duration of antibiotic therapy was highly significant with $p < 0.0005$. The outcome of the febrile neutropenic episodes also correlated negatively with WBC (R = -0.308) and showed significance ($p = 0.009$). Absolute neutrophil count did not correlate with any significance to both outcome and the duration of the febrile neutropenic episodes.

Positive blood cultures

Case	Age	Diagnosis	Organism	Sensitivity	Outcome
1	8	AML	α-Haemolytic Streptococcus	Pip/Tazo Gentamycin Chloramphenicol Co-amoxiclav	Resolved
2	5	AML	E coli	Pip/Tazo Imipenem	Died
3	5	AML	Enterobacter gergoviae	Ceftazidime Gentamycin Tobramycin	Resolved
4	4	Neuroblastoma	Staph aureus	Vancomycin	Resolved
5	15	Neuroblastoma	Staph aureus	N/A	Died
6	15	Large cell anaplastic	MRSE	Oxacillin Vancomycin Cotrimoxazole	Resolved

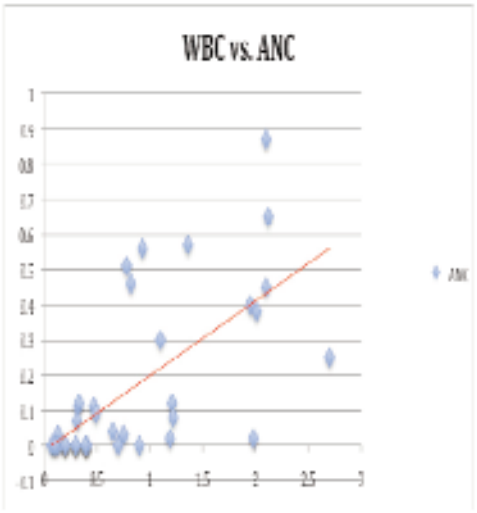

Fig. 3: Scatter plot of WBC (x axis) *vs* ANC values with trend line.

DISCUSSION

Studies on febrile neutropenia at Paediatric Oncology Centres in Developing Countries (POCDC) are lacking, but febrile neutropenia remains a major cause of hospitalization apart from admissions for chemotherapy administration (5). In previous studies of febrile neutropenia in children, criteria were established which aided clinicians in caring for these

patients based on their presentation and their laboratory indices (1, 6).

One of the criteria established in the management of febrile neutropenia is the absolute neutrophil count at presentation, with ANC counts < 0.2 x10^9/L being associated with a high risk of infection and bacterial sepsis (7). In more recent studies, the value of the absolute monocyte count has been shown to correlate highly with the duration and outcome of febrile neutropenic episodes (6, 8, 11).

While larger American and European centres push toward identifying the individual components of the white cell count that contribute to the duration of febrile neutropenic episodes such as the absolute monocyte count, in POCDC, clinicians often have to work without these laboratory indicators. Investigating the relationship between the total WBC coupled with other clinical parameters may prove useful to predict the duration and outcome of febrile neutropenia.

In this study population, the WBC correlated negatively with the duration of antibiotic therapy ($p < 0.0005$). This relationship serves as an important prognostic factor in management of febrile neutropenic episodes in POCDC. With the total WBC correlating highly with the duration of antibiotic therapy, predictive models can be made for the antibiotic management of these neutropenic episodes using the total WBC count, especially where POCDC may not have the advanced laboratory technology to provide differentials on the total WBC count. Further studies into this relationship may provide additional clinical evidence for implementing a new protocol for POCDC. In this study, a positive linear relationship is seen between ANC and WBC values where increasing WBC values correspond to increasing ANC values and vice versa. Since this linear relationship had a correlation coefficient of 0.732 and a p value < 0.0005, the WBC value can be confidently used to predict severity of neutropenic episodes based on the value at presentation.

At our centre, antifungal therapy is initiated after 96 hours of persistent pyrexia despite a step-up to second line antibiotic therapy (Fig. 1). No case of culture positive fungal sepsis was seen in this study population. This finding may be accounted for by the low use of highly myelosuppresive treatments such as bone marrow transplantations in addition to the other factors such as low central line usage and emerging intense protocols as mentioned above. Bone marrow transplant as a modality of treatment often warrants antifungal prophylaxis as it is associated with severe fungal sepsis (9, 10). Additionally, the lack of TPN and low central line usage may also account for less fungal sepsis being seen. During the study period analysed, long lines and central lines were not readily available for insertion with this trend somewhat reversing toward the end of the study period.

The presence of less bacteraemia in the study population compared to international figures may be accounted for by the lack of multi-drug resistant organisms usually seen in developed countries. While the organisms found may be similar, the virulence of the multi-drug resistant species is much higher and they fail to respond to appropriate antimicrobial therapy.

Further investigation of the relationships demonstrated in this study is needed, looking at larger numbers of febrile neutropenic cases. Development of the relationships of the WBC to the duration of antimicrobial therapy, the duration of febrile neutropenic episodes and survival, can allow for POCDC to establish a protocol that may predict the duration of hospital stay and survival if correlated and analysed along with other parameters affecting the duration of hospital stay such as the presence of mucositis, the pre-morbid weight, the nutritional status at presentation and the number of days to presentation after intravenous chemotherapy (1).

The use of more intensive and aggressive treatment regimens and the increasing use of central lines may also prove to change the course, frequency and outcome of febrile neutropenic episodes in our population. To this end, a prospective study can be designed looking at the factors contributing to future episodes of febrile neutropenia and how the new trends in treatment, overall management and outcome compare with this initial study.

In summary, febrile neutropenic episodes treated at the WFPH have a favourable outcome especially for a paediatric oncology centre in a developing country. The low incidence of fungal sepsis and the lack of multi-drug resistant bacterial organisms add favourably to the highly positive outcome of these episodes. The further analysis of the relationships found in this study between the total white blood cell count at presentation and duration of antimicrobial therapy, the duration of the febrile neutropenic episodes and outcome is needed, with similar studies being performed in other developing centres. Confirmation of this relationship in other centres may see the introduction of new protocols in the management of febrile neutropenic episodes where WBC and other clinical parameters may be successfully introduced into a predictive model for the management of febrile neutropenic episodes in POCDC.

REFERENCES

1. Mendes AVA, Sapolnic R. New Guidelines for the clinical management of febrile neutropenia and sepsis in paediatric oncology patients. J Pediatr (Rio J). 2007; **83 (2Suppl): S** 54–63.
2. Lashley P, Callender D. Aspergillosis in a patient with acute lymphoblastic leukemia. West Indian Med J 1991; **40:** 37–40.
3. Brady West D, Richards L. Cancrum oris (noma) in a patient with acute lymphoblastic leukemia. A complication of chemotherapy induced neutropenia. West Indian Med J 1998; **47:** 33–4.
4. Phillips B, Selwood K, Lane SM. Variation in policies for the management of febrile neutropenia in Untied Kingdom Children's Cancer Study Group centres. Ach Dis Child 2007; **92:** 495–8.
5. Basu SK, Fernandez ID, Fusher SG. Length of stay and mortality associated with febrile neutropenia among children with Cancer. J Clin Oncol 2005; **23:** 7958–66.
6. Klassen R, Goodman TR. Low risk prediction rule for pediatric oncology patients with fever and neutropenia. J Clin Oncol 2000; **18:**1012–19.

7. Acquino VM, Tkaczewski I, Buchanan GR. Early discharge of low risk febrile neutropenic children and adolescents with cancer. Clin Infect Dis 1997; **25:** 74–8.
8. Rackoff W, Gonin R, Robinson C. Predicting the risk of bacteraemia in children with fever and neutropenia. J Clin Oncol 1996; **14:** 919–24.
9. Hughes T. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Infectious diseases Society of America guidelines. Clin Infect Dis 2002; **34:**730–51.
10. Cagnoni PJ. Liposomal Amphotericin B versus conventional Amphotericin B in the empirical treatment of persistently febrile neutropenic patients. J Antimicrob Chemother 2002; **49 Suppl**. **S1:** 81–6.
11. Baorto EP, Aquino VM, Mullen CA.Clinical parameters associated with low bacteraemia risk in 1100 pediatric oncology patients with fever and neutropenia.Cancer 2001; **92:** 909–3.
12. Central Statistical Office of Trinidad and Tobago National Census 2000– 2002.
13. Bodkyn C. Incidence of childhood cancer in Trinidad and Tobago. SIOP Abstract book 2008; **J033:** 183.
14. Cancer in Trinidad and Tobago. A report on Cancer 2000–2002. A report of The Dr. Elizabeth Quamina Cancer Registry: The National Cancer Registry of Trinidad and Tobago. Cancer in Trinidad and Tobago 1995–1999. A report of the Dr Elizabeth Quamina Cancer Registry: The National Cancer Registry of Trinidad and Tobago.