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Prevalence of Infectious Complications in Children with Cancer

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Abstract

Background: Infections are the most common complications during chemotherapy. The trends have been changing over time due to use of multi-agent intensive chemotherapy. Procedure: We looked over our data to see what complications we get in our patients. The data was collected on patients treated in King Fahad Medical City from July 2009 to Dec 2015. Results: We found that 86 patients had one episode only while 92 had 2 or more episodes reaching up to 11 episodes in 1 patient. We found positive cultures in 17.3% of episodes with staphylococcus as common gram positive and Klebsiella pneumoniae as common gram negative bacteria, respiratory viral infections in 13.8% and GI infections in 9%. We found Candida albicans as the most common fungus while other yeasts followed. Acute lymphoblastic leukaemia was the most common diagnosis. The episodes were associated with neutropenia of <500 in 61.2% while 58.8% were associated with duration of neutropenia of >7 days in 1st episode and 56.8% in cases with repeated episodes. We had 2 deaths one from recurrent infections with CNS (Central Nervous System) damage and one from Pulmonary infections causing pulmonary haemorrhage. We had one with persistent neurological sequele from prolonged fungal infection. Conclusions: Neutropenia of <500 and duration of >7 days came out to be significant risk factors for infection across all diseases. We have an acceptable level of morbidity and mortality due to good supportive services. We need prospective studies to get an up-to-date picture of our practice. We need prophylactic antibiotics and antifungals for high-risk patients like AML.

Keywords

Infections, Cancer, Children

1. Introduction

Infections have caused significant problems in patients with neutropenia over time as the survival improved in cancer due to better and intensified treatments [1]. Life-threatening complications due to bacterial infections have been reported in a significant percentage of febrile episodes in children with cancer [2] [3]. From 1960s to 1980s, aerobic Gram-negative bacilli were the major cause of infection in the neutropenic patient [1]. Schimpff *et al.* [4] have reported that aerobic Gram-negative bacilli were involved in approximately 60% - 80% of the microbiologically proven infections, with P. aeruginosa being a leading isolate and S. aureus was the most important gram-positive isolate. Later, in the mid-80s, the spectrum of organisms causing infection began to change. A steady increase in Gram-positive infections occurred until presently, 60% - 70% of bacteremia's with a single organism identified are caused by Gram-positive cocci [5] [6] [7]. Coagulase-negative staphylococci and S. aureus are the predominant organisms. This change from Gram-negative to Gram-positive organisms is due to many factors important among them include aggressive chemotherapeutic regimens causing more severe mucositis, protracted course of neutropenia, almost uniform use of centrally placed catheters, use of Histamine receptor 2 antagonists and use of prophylactic antibacterial agents with relatively weak coverage of Gram-positive organisms [8]. In addition to this the move from Gram-negative to Gram-positive organisms, other Gram-positive organisms have become important causes of infection [5] [9].

Respiratory viruses have become a frequently observed source of infection in about half of the patients with respiratory tract infections in children undergoing chemotherapy [10].

Koskenvuo *et al.* [11] documented the presence of respiratory infection in 44% of the cases of children and adolescents with leukaemia and fever, and Srinivasan *et al.* [12] observed rates of 75% in their study.

Another important cause of mortality in children with cancer is the invasive fungal infection, especially haematological disorders, who undergo high dose chemotherapy or bone marrow transplant [13] [14] [15]. One of the most common infections is invasive aspergillus's but we also see other non-Aspergillus fungi being increasingly reported [16]. This increase in the incidence of invasive fungal infections in children appears to have increased over the past few decades, due primarily to the prolonged survival of children with immune deficiency syndromes [17] [18] [19].

There are few studies from Middle East and Saudi Arabia showing the same trends but the number is very small and one study looked at only bacterial isolates [20] [21].

Prophylactic antibiotics and antifungals have been shown to reduce the number of episodes of febrile neutropenia and severity of infections especially in cases on intensive chemotherapy and in post-transplant patients [22].

The primary objective of this study was to collect data about our patients to

see the trends of infections in our set up because we do not have many studies form Middle East and specifically from Saudi Arabia. Also, we wanted to see the effect of the strength of chemotherapy on the trends and to recognize those patients or diseases that will benefit from prophylactic antibiotics and antifungals. This will also help us plan our antibiotic and antifungal policies and reduce the burden on the healthcare system by reducing infection rate and admission rate so reducing hospital days.

2. Aims and Objectives

Primary:

To study the prevalence of infections during chemotherapy in our centre as compared to other centres and devise ways to improve it.

Secondary:

To see the effect of degree and duration of Neutropenia on the rate of infection

Inclusion Criteria:

- All patients from 0 - 14 years who received chemotherapy at KFMC presenting with fever or positive culture in cases with suspected sepsis.

Exclusion Criteria:

- Patients who have comorbidities which predispose to infections e.g. immunodeficiency, down syndrome.
- Non-malignant conditions requiring chemotherapy, *i.e.* Aplastic anaemia, Congenital and autoimmune Neutropenia, etc.

3. Materials and Methods

The data was collected on patients treated (completed treatment) in King Fahad Medical City from July 2009 to Dec 2015. Any patient presenting with a fever of 37.8˚C on 2 occasions 30 minutes apart or one episode of 38˚C or a positive culture reported in a child with suspected sepsis presenting with other symptoms *i.e.* diarrhoea, vomiting, flu, etc. Neutropenia was defined as ANCas < 1500 (mild), <1000 Moderate, <500 as severe and <200 as very severe. Duration of Neutropenia of <7 days as mild, 7 - 14 days moderate and >14 days as prolonged. The common antibiotics used were Piptazobactam, Amikacin, Vancomycin, Meropenem, Clindamycin, etc. Patients were screened for fungal infections after 5 days of unresolved fever with CT chest, abdomen and pelvis and in some cases with chest x-ray and Ultrasound of the abdomen. The collection of data was from patient files, Hospital Information Management system, CORTEXX (hospital management system) and patient road maps. Specific forms were used for the collection of data by one person and then uploaded on spreadsheets by another so to make sure data is checked by 2 people. Deficient data was rechecked with patient file. The data was analysed, and results compiled which was then compared with other international groups. A comparison was done to see the effect of different chemotherapy regimens on the incidence of infections to formulate a prophylactic antibiotic regimen for those at high risk of infections.

Statistical Analysis Procedure

All categorical variables gender, primary diagnosis, site of infections, etc. is presented as numbers and percentages. Continuous variables like age, duration of antimicrobials are expressed as Mean ± S.D. Pearson's Chi-square/Fisher's exact test is applied according to whether the cell expected frequency is smaller than 5. Independent sample t-test/ANOVA is used to determine the mean duration (days) of antimicrobials in contrast to chemotherapy regimen. In addition, 95% confidence interval of differences is estimated. P-value < 0.05 is considered as statistically significant. All data was entered and analysed through statistical package SPSS version 22.

4. Results

A total of around 754 patients were treated from 2009 to 2015. Files of 178 patients were analysed who presented with 480 episodes but the data was not complete in about 75 episodes so 405 episodes were analysed (Table 1).

Age ranged from 3 - 168 months with a mean of 69.5 +/− 43.3 months. Male to female ratio is 60:40 respectively (Table 2).

42.5% of episodes happened at home while 57% happened in the ward and one each in Emergency room and PICU (Table 3).

86 patients had one episode, 45 had two, 25 had three, while the rest had four or more episodes going up to 11 episodes in one case. Ave episodes per patient were 2.8 in Burkett's lymphoma, followed by 2.6 in ALL, 1.7 in AML, 1.6 in Hodgkin's disease and 1.54 in Medulloblastoma. We had to remove line in 5.2% (17). ALL comprises 68.5% of cases followed by AML with 5.5%, Burkett's lymphoma 4.2%, Medulloblastoma 4.2%, Hodgkin's disease 4% and the rest other diseases (Table 4).

Table 1. Summary of the whole study.

Total Episodes	483
Incomplete data	78
Episodes analysed	405
Total patients screened	178
Bacterial infections	72
Viral infections	56
Fungal infections	5
PICU admissions	21
Inotropes	9
Non-invasive vent	12
Invasive vent	13
Mental retardation	1
Deaths	2
Central line present	329
Central line removed	17

Table 2. Demographic data.

Demographics	Male	Female	Total
Age	70.7 +/− 42.0 months (3 - 168)	68.0 +/− 45.3 months (4 - 161)	69.5 +/− 43.3 months (3 - 168)
M:F	101 (56.7%)	77 (43.3%)	178 (100%)

Table 3. Location of episodes.

Episodes/Location	No. (%age)
Home	172 (42.5%)
Ward	231 (57%)
PICU	1 (0.2%)
ER	1 (0.2%)

Table 4. Number of episodes per patient with diagnosis.

Episodes/Dx	No. of Episodes/Patient (Total)	No./Patient (Average)
ALL	274/101	2.6/patient
AML	22/13	1.7/patient
Burkett's	17/6	2.8/patient
Medulloblastoma	17/11	1.54/patient

Blood stream was the common infection site with 17.3% (70), followed by Respiratory tract with 13.8% (56), Gastroenterology 9.1% (37), skin and soft tissue 2.5% (10) and urinary tract, musculoskeletal and CNS 1% (4) of cases. The yield from blood cultures was 15.8% and the most common organism was Coagulase negative staphylococcus 3.7%, MRSA 2.2%, Klebsiella 2%, staphylococcus aureus 1.7%, Acinetobacter and enterococcus 1%, followed by other like E. coli, citrobacter, enterbacter seratia and streptococcus species. We also got fungal infections and the leading cause was Candida Albicansin 1.7%, followed by other yeast 1.2%.

Neutropenia of 1000 - 1500 was found in 28% of episodes, 500 - 1000 in 12.1%, 200 - 500 in 37.5% and <200 in 22.5% of episodes (**Figure 1**). In 59% of episodes the ANC was <500 in 1st episodes while in repeated infections it was 61% which was significant with a P value of 0.001. The duration of neutropenia of <7 days was observed in 42.3%, 7 - 14 days in 19.2% and >14 days in 38.4% of episodes (**Figure 2**). Blood cultures were positive in 63.4% cases with duration of Neutropenia exceeding 7 days and 75.6% in cases with ANC of <500. Respiratory infections were more common with duration of <7 days in 55.8% and with ANC of <500 at 66%. Skin infections were equally distributed.

21 patients went to PICU needing inotropes in 9 cases and oxygen in 12 cases. 13 cases needed intubation and ventilation. We had two deaths, one from streptococcus pneumonae with concomitant influenza A and B leading to pulmonary

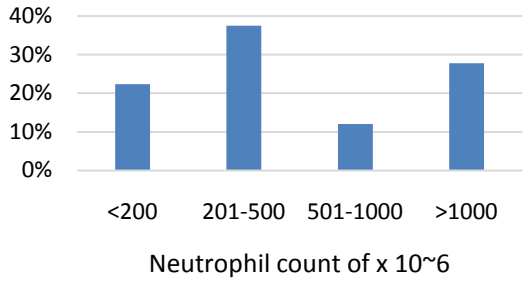

Figure 1. Infection rate with degree of Neutropenia.

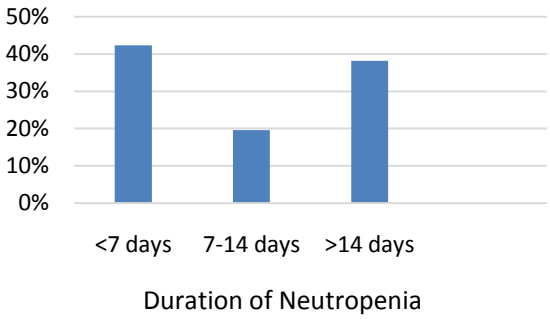

Figure 2. Infection rate with duration of Neutropenia.

haemorrhage. The second case was a case with T cell ALL who had recurrent infections, last one been CNS infection. One patient has long term neurological sequele due to prolonged CNS fungal infection.

The patients were treated according to our febrile neutropenia protocol with Piptazobactam and Amikacin as the first line with addition of Vancomycin if still febrile by day 72 hours and no positive culture followed by Voriconazole/ Amphotericin B as antifungal if still febrile by day 5 without source of infection. Antibiotics were modified according to culture and sensitivity if a culture became positive. Line was removed if recurrent positive culture of same organism or any fungal infection.

5. Discussion

The treatment of cancer has been transformed in the last 50 years due to improvement in supportive care services. Infections have always been a major threat to cancer patients because of neutropenia associated with chemotherapy. As time has passed, emergence of resistance in bacteria and fungi has become a major problem in treating high-risk cases that need intensive multiagent chemotherapy and those undergoing transplant. The purpose of this study was to see what our major problems are and how are we doing as compared to others. In 2001, HM Meir *et al.* [23] from Jeddah presented similar data in acute lymphoblastic leukaemia with Respiratory infection as the common presentation, 24% had only one episode as compared to 59% in our study. We found blood stream as the most common site of infection and we had similar results with the Coagulase Negative Staphylococcus as the most common organism. RA Am-

mann *et al.* [24] in 2003 from Switzerland had similar findings of 37% presenting with an infection in 285 episodes as compared to our 45%. A similar data was presented in 2004 by S Mahmoud *et al.* [25] from Pakistan with 44% positive cultures from 62 episodes with blood as the most common site 24% as compared to our 16%. A recent study from Qatar was published by N AlMulla *et al.* [26] with the same pattern of organisms as our study with Staphylococcus as the most common gram positive and Klebsiella as the most common gram negative organism. H Ashour and A Alshareef [27] from Cairo reported the same organisms (G negative) in 2009. SS Purewal *et al.* [28] also reported similar findings from India in 2011. TC Yeh [29] from Taiwan reported in 2014 that prophylactic antibiotics prevented severe infections in high-risk cases thus suggesting a role for prophylactic antimicrobials in these situations.

Sarah Georgaudou *et al.* [30] from MD Anderson in USA in 2011 reported cases of fungal infections with a difference to our series where they reported aspergillus as the most common while we found Candida and yeasts as the most common organism probably due to different weather conditions or ethnicity. It is apparent from the examples above that we are similar in the way of bacterial infections and the source of infections but different in our fungal organisms.

We have two deaths from infection related complications which is 0.5% of all the episodes and is excellent as compared to international data as reported by David *et al.*, 2014 from UKALL 2003 trial as 2.4% and SK Basu *et al.*, from Edinburgh as 3%. It may be partly to the number of less complicated patients as we were building our patient number and we did not have many relapsed patients.

There are some limitations of this study due to the retrospective nature of the study, lack of consecutive case reporting and a lot of missing information, so it may not be representative but none the less presents the overall picture. Therefore, I have decided to extend this study and collect consecutive prospective data so that we can get a clearer picture and make our recommendations on that.

6. Conclusion

Infections are still a big problem in cancer patients on chemotherapy and we need to look for other ways to improve our antimicrobial coverage and select cases with high risk and give them prophylactic antibiotics during neutropenic episodes. We need prospective data on our patients to get a clearer picture of the risks facing our patients. We need more education for the patients and their families to bring the child quickly to the hospital and make sure these patients are seen immediately to prevent simple infection progressing to a severe one.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

CT	Computed Topography
CNS	Central Nerves System
AML	Acute Myeloid Leukaemia
ANC	Absolute Neutrophil Count
PICU	Paediatric Intensive Care Unit
ALL	Acute Lymphoblastic Leukaemia
MRSA	Methicillin Resistant Staphylococcus Aureus