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Febrile Neutropenia in Head and Neck Cancers: An Untold Story

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Abstract:
Purpose: Febrile neutropenia is an oncological emergency that has been rarely discussed in relation to head and neck cancers in literature. Given the profile of these patients, with severe dysfunction of the upper aerodigestive tract, there are various factors that may worsen the outcomes in these patients. The purpose of this study was to study the predictors, prognostic indicators, trends and microbiological profile in these patients; so as to establish a better understanding of the disease.
Methods: We conducted a case control study based on all chemotherapy cycles given in a tertiary care hospital for head and neck cancers, from 2015-2019.
Results: Febrile neutropenia occurred in 32 of 301 cycles. Case fatality ratio was 9.25%. Various risk factors like, tube feeding, diabetes, presence of tracheostomy, Gastro intestinal side effects, etc were identified. Microbiological profile and trends were studied in these patients
Conclusions: The occurrence of febrile neutropenia in head and neck cancer patients has been underestimated in literature. There are various additional risk factors for febrile neutropenia that are prevalent in head and neck cancer patients, which need to be taken into account.
Key words: *Head and neck cancer, Febrile Neutropenia, Prognostic Markers, Indicators.*

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I. Background:

Febrile Neutropenia is an oncological emergency which accounts for significant mortality once it has set in[1-2]. It is defined as single oral temperature>/ 38.3^0C, or temperature >/ 38^0C sustained for more than or equal to one hour; and ANC<500 cells/cu.mm or ANC expected to decrease <500 cells/mm3 in 48 hours.

However, there are very few articles in literature that have studied febrile neutropenia patterns in head and neck malignancies[3]. Head and Neck malignancies present with a wide array of associated morbidities, like tube feeding, tracheostomy, aspiration, etc; which may have an impact on the outcome of febrile neutropenia patients[4].

Owing to the fact that systemic therapy is not a first line treatment in any head and neck malignancy, and that most of these patients will either receive high dose NACT, or be terminal, as in case of palliative chemotherapy, or may receive concomitant radiation, the immunity and the vulnerability of these patients is very high, compared to many other solid tumors[5].

The objectives of this study are as follows:

1. To determine the incidence of febrile neutropenia in various chemotherapy regimens over the past 5 years in department of ENT.
2. To establish predictors and prognostic markers of febrile neutropenia in these patients.
3. To study the microbiological profile and sensitivity patterns in these patients.
4. To make recommendations based on the study.

II. Materials and Methods:

Study setting: The study was a case control study, based in the Department of ENT at Goa Medical College (GMC) which is a tertiary care hospital in the state of Goa, located along the west coast of India.

Ethics: The approval of the Institutional Review Board, Goa Medical College was taken before conducting the study.

Sampling: All patients received chemotherapy for head and neck malignancies over the past five years (January 2015- December 2019)were analysed.

In all patients who developed febrile neutropenia, detail assessment of various demographic data, course of treatment, co morbidities, hematological profile, microbiological profile, and outcomes were analysed.

The data was correlated with the clinical findings, as obtained from the case sheets.

The data wasanalyzed to determine any predictors, prognostic indicators, and antimicrobial patterns, using excel spreadsheet and SPSS.

III. Results:

The study was conducted in department of ENT, in Goa Medical College. All 67 patients and 301 cycles of chemotherapy, over the past five years (2015-2019) were analysed. Case fatality ratio was 9.25%. The demographic data is as shown in tables 1 and 2.

Table 1. Demographic Data of patients developing febrile neutropenia

Stage	
I	1
II	7
III	5
IV	19
Cycle	
1	20
2	5
3	6
4	1
5	0
6	0
Primary	
Oral Cavity	16
Oropharynx	11
Hypopharynx	3
Nasopharynx	2

Table 2. Age and Febrile neutropenia

Parameter	**FebrileNeutropenia(FN)**	**No FN**	**p**
Age			1.15
<50	11	66	
>50	21	204	

Three regimens were studied, mainly TPF (Paclitaxel, Cisplatin, 5-FU), DC (Docetaxel, Cisplatin), and Cisplatin based chemotherapy. Out of 69 cycles with TPF regimen, 17(24.63%) of the cycles progressed to febrile neutropenia. Out of 56 patients with DC regimen, 9(16.07%) of the cycles progressed to febrile neutropenia. Out of 204 patients who received cisplatin based chemotherapy, only 6(2.9%) patients developed febrile neutropenia. There was a statistically significant difference in the outcome between multiple agent chemotherapy, against single agent chemotherapy (p=0.007).

Out of the 32 patients with febrile neutropenia, 6 patients were recurrent cases. However there was no statistically significant difference between patients who developed febrile neutropenia amongst the recurrence and the non recurrent groups.

The intent for chemotherapy were either Curative, Neoadjuvant and Palliative. Thirteen patients who developed febrile neutropenia had received chemotherapy for curative intent, 13 had received for neoadjuvant and 6 for palliative intent. There was no statistically significant difference between these three groups. Dose alteration (RDI=100% vs RDI =80%) did not have any statistically significant difference.

Performance status and presence of tube feeding had statistically significant differences, as shown in tables 3 and 4.

Table 3. Performance Status and Febrile Neutropenia

P.S	**FN**	**No FN**	**p**
0-1	19	169	0.015
2	13	200	

Table 4. Tube feeding and febrile neutropenia

Tube Feeding	FN	No FN	p
+	20	109	0.0002
-	12	200	

Pre chemotherapyHemoglobin, did not have any statistically significant results. A total of 13% patients with pre chemotherapy Hb< 12g% developed febrile neutropenia; whereas 6% patients with pre chemotherapy Hb>12g% developed febrile neutropenia.

Various co morbidities of patients with febrile neutropenia were studied. Out of all 242 patients with <2 co morbidities, 24(9.82%) developed febrile neutropenia. Out of all 61 patients with >2 co morbidities, 12 (19.67%) patients developed febrile neutropenia. This result is statistically significant (p= 0.033).

Presence of gastro intestinal side effects post chemotherapy had significant bearing on the development of febrile neutropenia. Out of 62 patients with G.I side effects, 14(22.5%) developed febrile neutropenia. Out of 242 patients without GI side effects, 22 (9.09%) developed febrile neutropenia.

There was No statistically significant association with Neutrophil:Lymphocyte ratio, Platelet:Lymphocyte ratio, andPre Treatment Eosinophilia. Effect of pre treatment Absolute neutrophil count is as shown in table 5.

Table 5. Pre treatment Absolute Neutrophil Count (ANC) and febrile neutropenia.

ANC	FN	No FN	p
<3000	17	82	0.001
>3000	15	187	

Trends in Febrile Neutropenia Patterns

Most of the cases of febrile neutropenia post chemotherapy clustered around the first two weeks as shown in Figure 1. The numbers would drastically fall post 3 weeks.

The trends in the absolute neutrophil count is shown in Figure 2.

Out of all patients, 26% had no sepsis; 35% were in sepsis; 23% in severe sepsis and 16% were in septic shock

Figure 1 Onset of neutropenia post chemotherapy

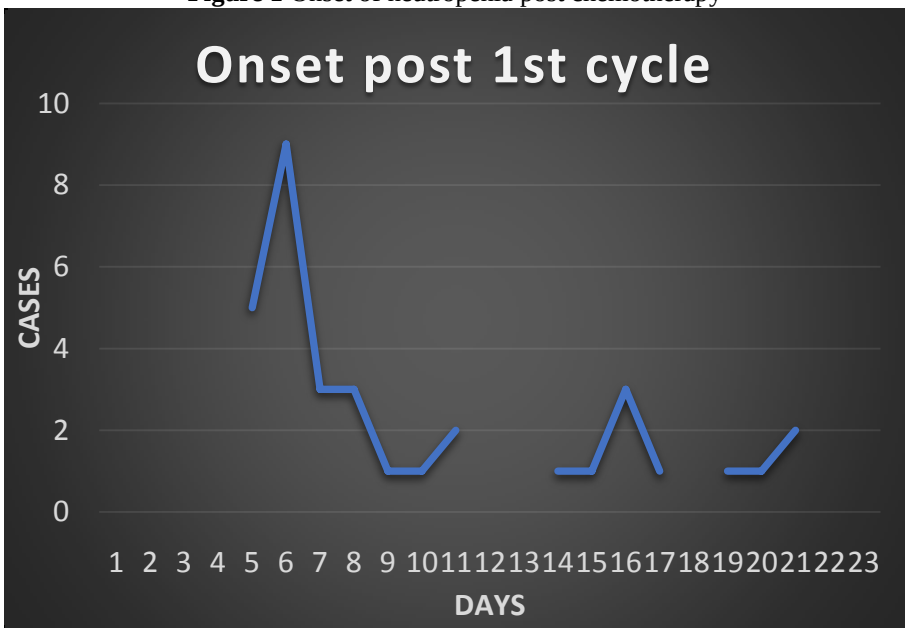
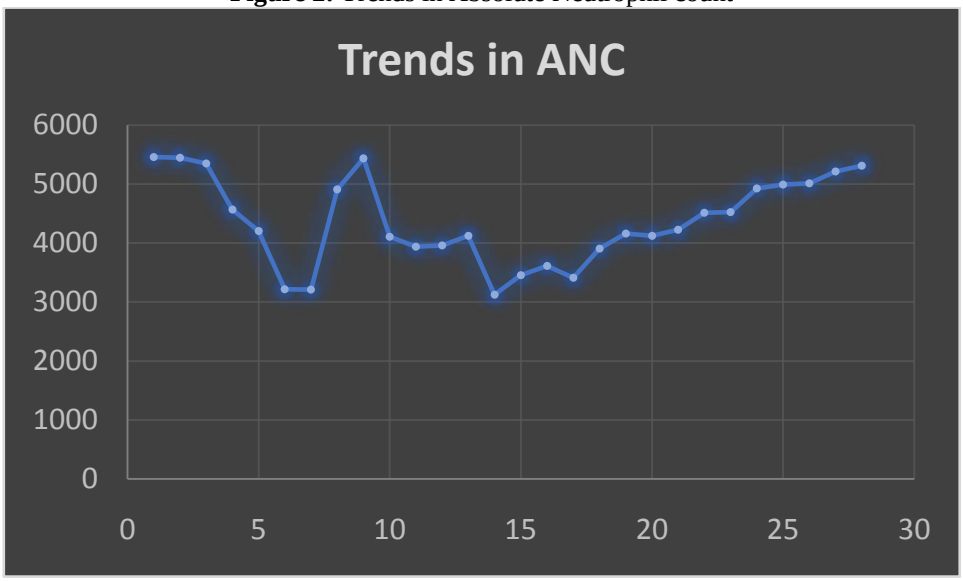


Figure 2: Trends in Absolute Neutrophil count



Prognostic markers

The various prognostic indicators have been summarised in table 6.

Table 6. Prognostic Indicators

Parameter	Recovered	Succumbed to toxicity	p value
Co morbidities			
<2	5	13	0.094
>2	7	5	
DM			
+	1	11	0.0018
-	13	7	
Tube Feeding			
+	4	16	>0.01
-	12	2	
Performance Status			
0-1	11	8	0.049
2	3	10	
ANC			
<3000	5	12	0.0042
>3000	12	3	
Tracheostomy			
+	11	2	>0.001
-	5	6	

Microbiological Profile

The organisms cultured in these patients, from various body fluids is summarised in figure 3. The most common organisms being Pseudomonas Aeruginosa and MRSA.

Figure 3. Microbiological Profile

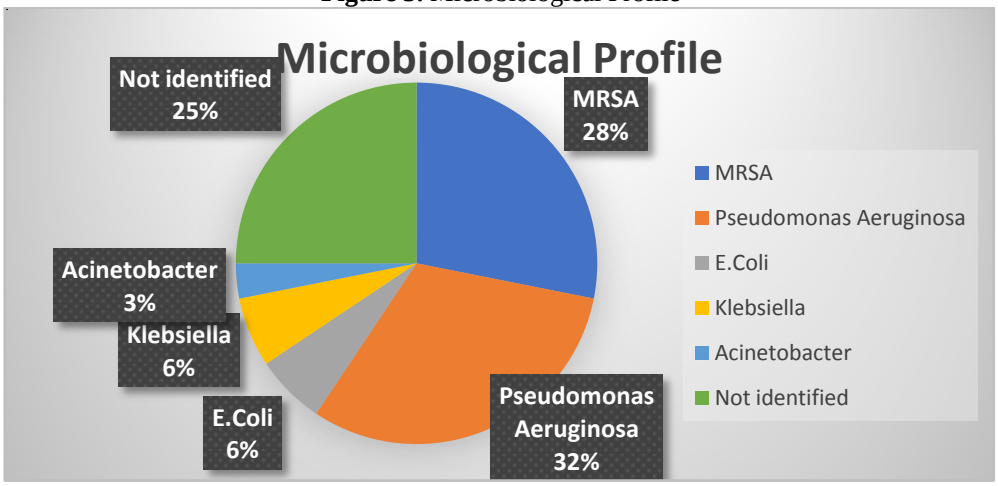
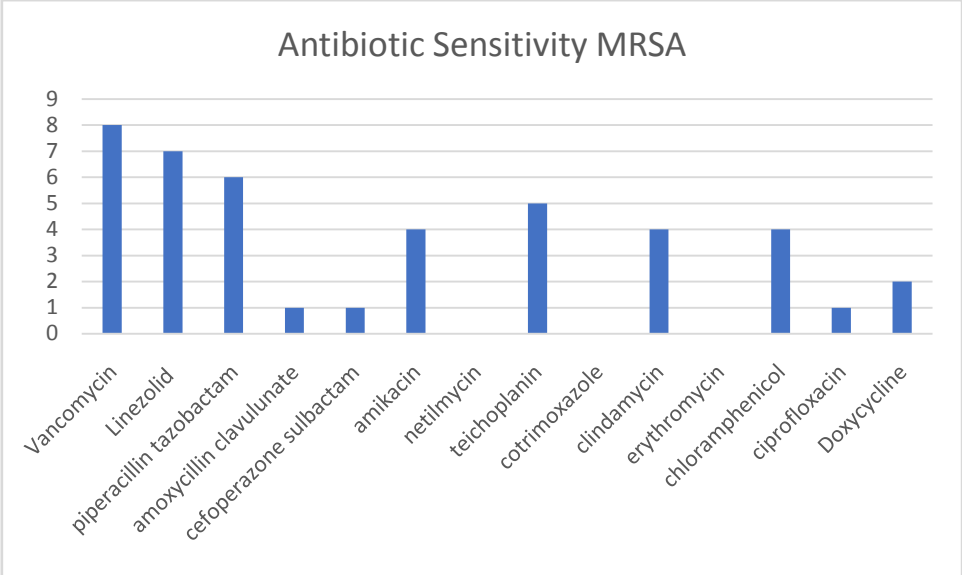
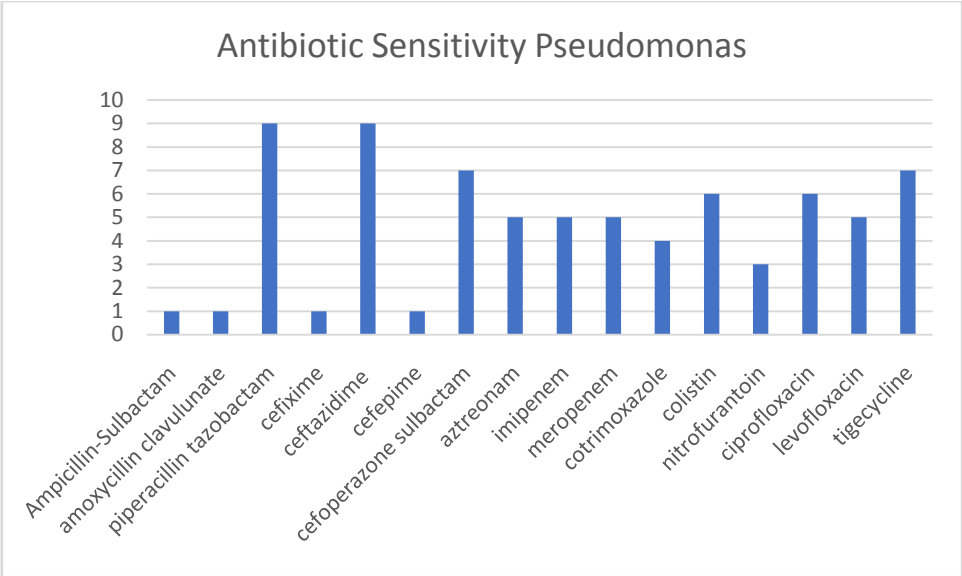


Figure 7 and 8 show the antimicrobial sensitivity patterns in MRSA and Pseudomonas respectively





IV. Discussion:

Febrile Neutropenia, secondary to myelosuppression, in patients receiving Chemotherapy is a condition resulting in significant morbidity, and even mortality[6]. The incidence and case fatality rate are higher in our study, compared to various other studies. This could be attributed to the fact that most of these studies have been done in trial settings[7-8]. This is because, the patients recruited in trial studies, tend to be younger, with few co-morbidities, better performance status and are monitored more meticulously.

Goa, like various other places in India has a high rate of oral malignancies. This is attributed to the significant consumption of alcohol and tobacco, like many other places in the Indian subcontinent; thus contributing to field cancerization. This is reflected in the demographic data. Furthermore, as far as Indian population is concerned, more patients developing these malignancies tend to be elderly[9]. This too, has been reflected in the study.

Similar to other studies[7-8], we have found that the effect of performance status, co morbidities, multidrug chemotherapy, low pre treatment absolute neutrophil count, has increased risks of developing febrile neutropenia. We have found that patients being tube fed, have higher chances of developing febrile neutropenia; and is prognostically poorer. This can be explained due to silent aspiration, and aspiration pneumonitis that is prevalent in this group of patient[10]. Gastrointestinal adverse effects too, have a similar effect. This can be attributed to the fact that gastric adverse effects tend to derange the mechanical protective effect of the mucosa. This predisposes these patients to systemic infections[11].

Presence of diabetes, is a risk factor, as well as a poor prognostic indicator for febrile neutropenia. This is because of the high susceptibility to various systemic infections[12]. Presence of tracheostomy also has a poorer prognostic outcome in these patients. The possible explanation could be that tracheostomised patients usually tend to have advanced disease, and significant silent aspiration could have occurred prior to the chemotherapy, which increases vulnerability to the infections.

The trends and microbiological profile of these patients are similar to that documented previously in literature[4].

V. Conclusions

The risk and outcomes of febrile neutropenia in patients with head and neck cancers has been underestimated in literature. There is a significant mortality and morbidity associated with the same.

Presence of tracheostomy, diabetes, tube feeding, etc have a significant baring on the outcomes of these patients. These factors need to be kept in mind while formulating an institutional framework for patients with head and neck cancers, on chemotherapy.

Owing to the microbiological profile and the high chances of sepsis in these patients, high antibiotics should be preferred when starting empirical therapy.

More studies need to be conducted in order to understand the disease and take necessary steps to minimize the morbidity and mortality in these patients.

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