Article published online: 2022-09-02

Original Article

Neuro-Oncology

Once-a-Day Ceftriaxone–Amikacin Combination as Empiric Antibiotic Therapy to Enable Outpatient Management of Febrile Neutropenia in Children—16-Year Experience from a Single Institute

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South Asian J Cancer 2022;11(4):370–377.

Abstract

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Background To enable outpatient department (OPD) management of febrile neutropenia (FN), we used once-a-day (OD) ceftriaxone–amikacin (CFT-AMK) as empiric antibiotic therapy. Our experience over 16-year period is presented.

Methods This was a retrospective study conducted from January2002 to December2017. Inclusion criteria were <18 years of age, undergoing cancer chemotherapy, and having FN. Exclusion criteria were FN after palliative chemotherapy, bone marrow transplantation, or at diagnosis of malignancy. Empiric CFT-AMK was used in all, except those having respiratory distress, hypotension, altered sensorium, paralytic ileus, or clinical evidence of peritonitis. Admission criteria were age <1 year, acute myeloid leukemia (AML) chemotherapy, poor performance status, need for blood transfusions, convenience, insurance, or persistent fever >48 to 72 hours after CFT-AMK. Outcomes analyzed were response (defervescence within 48–72 hours), OPD management, antibiotic upgrade, and mortality. AML diagnosis, >7 days to absolute neutrophil count $>0.5 \times 10^9$/L, poor performance status, and malignancy not in remission were considered high-risk FN criteria.

Results CFT-AMK was given in 877/952 (92.2%) FN episodes. Seventy-six percent had hematolymphoid malignancies. Response, antibiotic upgrade, and mortality were seen in 85.7 and 65.5% ($p < 0.0001$), 15 and 45.5% ($p < 0.0001$), and 0 and 2% ($p = 0.003$) of low- and high-risk patients, respectively. Treatment was started in OPD in 52%, of which

Keywords
- febrile neutropenia
- outpatient management
- ceftriaxone–amikacin

DOI https://doi.org/10.1055/s-0042-1745834 ISSN 2278-330X

How to cite this article: Kanvinde S, Mulay A, Deshpande A. et al. Once-a-Day Ceftriaxone–Amikacin Combination as Empiric Antibiotic Therapy to Enable Outpatient Management of Febrile Neutropenia in Children—16-Year Experience from a Single Institute. South Asian J Cancer 2022;11(4):370–377.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

21.6% required subsequent admission. Of those initially admitted, early discharge (hospital stay <5 days) was possible in 24.6%. Forty-one percent episodes were managed entirely on OPD. Overall, 80% of low-risk and 42% of high-risk episodes received treatment wholly or partially on OPD.

Conclusion Our results show empiric OD CFT-AMK allows OPD management for most of the low-risk and a proportion of high-risk FN following chemotherapy in children, without compromising clinical outcomes.

Introduction

Febrile neutropenia (FN) is a medical emergency and needs to be treated urgently with intravenous antibiotics. Recommended empiric therapy includes drugs such as ceftazidime (CTZ), piperacillin–tazobactam (PTZ), or carbapenems, all of which require thrice-a-day dosing and hence admission to hospital. Availability of indoor beds is often a problem in our institute. To facilitate outpatient department (OPD) management of FN, we have been using a combination of once-a-day (OD) ceftriaxone (CFT) and amikacin (AMK) as initial empiric therapy. This combination has been used widely in the 1990s with good results.[1–9] Subsequent increase in prevalence of antibiotic resistant organisms led to the use of other antibiotics as empiric therapy for FN.[10–16] We have continued to use this combination as empiric treatment for FN and present our experience over a 16-year period, regarding its utility to facilitate OPD management of FN.

Methods

This was a retrospective study, done in department of pediatric oncology, in our institute. We screened case files of eligible patients between January 2002 and December 2017 for the presence of FN. We included patients <18 years of age, undergoing cancer chemotherapy, and having FN in the study. FN was defined as occurrence of temperature $>100.4^{\circ}$F plus absolute neutrophil count (ANC) $<0.5 \times 10^9$/L anytime during the febrile period. FN episodes occurring in patients on palliative chemotherapy, those following bone marrow transplantation, and those occurring at the time of diagnosis of the malignancy were excluded. The latter were excluded as distinguishing infection from disease fever was not possible.

Antibiotic Treatment

We started empiric antibiotic therapy in all patients with intravenous CFT 100 mg/kg and AMK 15 mg/kg, given separately as a 1-hour infusion, OD. Maximum dose of CFT was 4 g OD and for AMK was 750 mg OD.

However, those patients presenting with respiratory distress, hypotension, altered sensorium, paralytic ileus, or clinical evidence of peritonitis were treated with PTZ in place of CFT. Prior to 2004, CTZ was used in place of PTZ for the above indications. For those patients started on ceftriaxone–amikacin (CFT-AMK) who did not respond after 48 to 72 hours, we upgraded antibiotics to PTZ. Carbapenems were used in case of persistent fever after 48 to 72 hours of PTZ/CTZ (earlier in case of clinical deterioration). Vancomycin was added at the outset or subsequently in case of skin/soft tissue infections, venous access device related sepsis, or intra-abdominal infections. Additionally, antibiotics changes were based on the presence of microbiologically documented infections. Amphotericin was started empirically in case of persistent fever >4 to 5 days or if fungal infection documented. In those patients having recovery of counts, antibiotics were continued till afebrile for 48 hours with minimum duration of antibiotics of 5 days. In those showing no recovery of counts, antibiotics were continued till patient was afebrile for 5 days with minimum duration of antibiotics of 7 days.

Admission Criteria

It had been our policy to treat FN episodes preferably on OPD basis. However, the patients having the following characteristics were admitted immediately or on a priority basis: age <1 year, acute myeloid leukemia (AML) chemotherapy, poor performance status, or need for blood transfusions. Also, patients were admitted on request for insurance or convenience. Those remaining febrile after 48 to 72 hours and showing no evidence of marrow recovery were also admitted.

All patients treated on OPD basis were clinically assessed OD, while all admitted patients underwent clinical assessment twice daily. At the time of initial and subsequent assessments, patients were checked for presence of fever, focus of infection, general condition, and vitals. Those treated on OPD basis were instructed to come for admission immediately in case of any of the following symptoms: "tachypnea/difficulty in breathing," "drowsiness," "does not have the strength to sit up and prefers to lie down persistently," or "loose motions >3 episodes in 1 day." Patients having any of the above symptoms, those with deterioration in performance status and those having persistent fever after 48 to 72 hours without recovery of counts, were admitted for further management. Antibiotics were modified based on specific criteria mentioned earlier. Complete blood counts were checked daily or alternate day till ANC $>0.5 \times 10^9$/L. Blood cultures were collected at baseline, after 48 to 72 hours if still febrile and prior to antibiotic change.

Analysis

For the purpose of this analysis, high-risk FN has been defined as having any of the following criteria: (1) Duration of neutropenia > 7 days. We have considered actual and not anticipated duration of neutropenia. Also, to calculate duration of neutropenia, time taken from onset of fever to reach absolute neutrophil + monocyte count $> 0.5 \times 10^9$/L has been considered. (2) AML chemotherapy. (3) Malignancy not in remission. This includes all leukemias during induction and all solid tumors with bone marrow (BM) involvement following first cycle of chemotherapy (patients having acute lymphoblastic leukemia beyond day 22 induction and solid tumor patients beyond first cycle were not considered high risk based on this criteria, even if BM documentation of remission was not done). (4) Those presenting with poor performance status. The Lansky performance scale < or = 40 has been used to define poor performance status in our study. Patients having respiratory distress/hypotension/hypoxia/altered sensorium/peritonitis were also considered high risk. However, they were not treated with CFT-AMK but with initial PTZ-AMK. All others were considered to have low-risk FN.

We recorded response to empiric antibiotic therapy (defervescence within 48–72 hours), outpatient management, need for antibiotic upgrade after initial empiric therapy, and mortality as outcomes of initial empiric treatment.

Statistical Analysis

Categorical variables are described as proportions and continuous variables are described as mean (standard deviation) or median (interquartile range) as appropriate. Difference between two proportions were tested using chi-square test or Fisher's exact test as appropriate using OpenEpi online program. We determined independent predictors for need for antibiotics upgrade using univariate and multivariate logistic regression. We considered age group, sex, primary disease, disease status (remission vs. not), performance status, days of fever, ANC nadir, platelet nadir, monocyte count at baseline, duration of neutropenia, and site of infection as potential for inclusion in the model. Site of infection was categorized as unknown, upper respiratory tract (URT) and other known site(s) of infection. Statistical analysis was conducted using SPSS version 26.

Results

During the study period, we identified 952 episodes of FN. Eight hundred and seventy-seven (92.2%) episodes were treated with CFT-AMK. Seventy-six percent of CFT-AMK episodes were in patients having hematolymphoid malignancies. Fifty percent cases presented to hospital for treatment > 12 hours after fever onset. Forty-five percent of episodes did not have any clinical focus of infection. Treatment was started on OPD in 52% of these episodes. ►Table 1 shows baseline patient characteristics of 877 patients who were initially treated with CFT-AMK empirically.

Response to empiric CFT-AMK was seen in 76.9% episodes, being 85.7 and 65.5% in low- and high-risk FN episodes, respectively ($p < 0.0001$). Out of those who responded to initial therapy, 3/416 (0.7%) and 43/253 (17%) of low- and high-risk patients, respectively, developed recurrence of fever in the same neutropenia episode. Antibiotics were upgraded in 72 (15%) and 176 (45.5%) episodes in low- and high-risk groups, respectively ($p < 0.0001$). ►Table 2 shows reasons for antibiotic upgrade.

►Fig. 1 shows flow chart depicting FN episode outcome with respect to initial hospitalization status and response to

Table 1 Baseline characteristics of patients with FN treated with empiric CFT-AMK

Characteristics (data available)		
Age ($n = 877$)	< 1 y	48 (5.5%)
	1–10 y	722 (82.3%)
	> 10 y	107 (12.2%)
Sex ($n = 877$)	Male	560 (63.9%)
Underlying disease ($n = 877$)	ALL	514 (58.6%)
	AML	91 (10.4%)
	NHL	59 (6.7%)
	Solid tumors	213 (24.3%)
Focus of infection ($n = 858$)[a]	None	406 (47.3%)
	URT	203 (23.6%)
	LRT	31 (3.6%)
	GI	170 (19.8%)
	Skin + soft tissue	38 (4.4%)
	VAD	37 (4.3%)
	Others	8 (0.9%)
Risk stratification ($n = 871$)	High risk	386 (44.3%)
	Low risk	485 (55.6%)
Initial hospitalization ($n = 877$)	Yes	423 (48%)
Malignancy status ($n = 877$)	Active disease	150 (17.1%)
Performance status ($n = 865$)	Poor	35 (4%)
Fever to antibiotic gap ($n = 771$)	< 12 h	385 (49.9%)
	12–24 h	327 (42.4%)
	>24 h	59 (7.6%)
Median days to ANC $> 0.5 \times 10^9$/L (range) ($n = 836$)	Low risk	5 (3–7)
	High risk	10 (3– > 20)
ANC nadir $< 0.1 \times 10^9$/L ($n = 871$)	Low risk ($n = 485$)	278 (56.9%)
	High risk ($n = 386$)	291 (75.3%)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ANC, absolute neutrophil count; CFT-AMK, ceftriaxone–amikacin; FN, febrile neutropenia; GI, gastrointestinal; LRT, lower respiratory tract; NHL, non-Hodgkin lymphoma; URT, upper respiratory tract; VAD, venous access device.
[a]few patients had multiple foci of infection.

Table 2 Reason for antibiotic upgrade

Reason for antibiotic upgrade	Low-risk FN $N = 72$	High-risk FN $N = 176$	Total $N = 248$
Recurrence of fever in same neutropenia episode after initial response	3 (4.2%)	43 (24.4%)	46 (18.6%)
Worsening general condition[a]	3 (4.2%)	14 (7.95%)	17 (6.9%)
New focus of infection	8 (11.1%)	25 (14.2%)	33 (13.3%)
Culture result	5 (6.9%)	12 (6.8%)	17 (6.9%)
Persistent fever only	53 (73.6%)	82 (46.6%)	135 (54.4%)

Abbreviation: FN, febrile neutropenia.
[a]New development of tachypnea, hypotension, altered sensorium, paralytic ileus (or other evidence of intra-abdominal infection), or worsening performance status.

CFT-AMK. In 454 (52%) of the 877 episodes treated initially with CFT-AMK, treatment was started on OPD. Among the patients treated initially on OPD, subsequent admission was required in 21.6% episodes (17% of low-risk and 33.6% of high-risk FN episodes). Of the 423 episodes where patients were admitted at the outset, early discharge (hospital stay < 5 days) was possible in 24.6% episodes (39.6% of low-risk and 15.5% of high-risk episodes), with further treatment

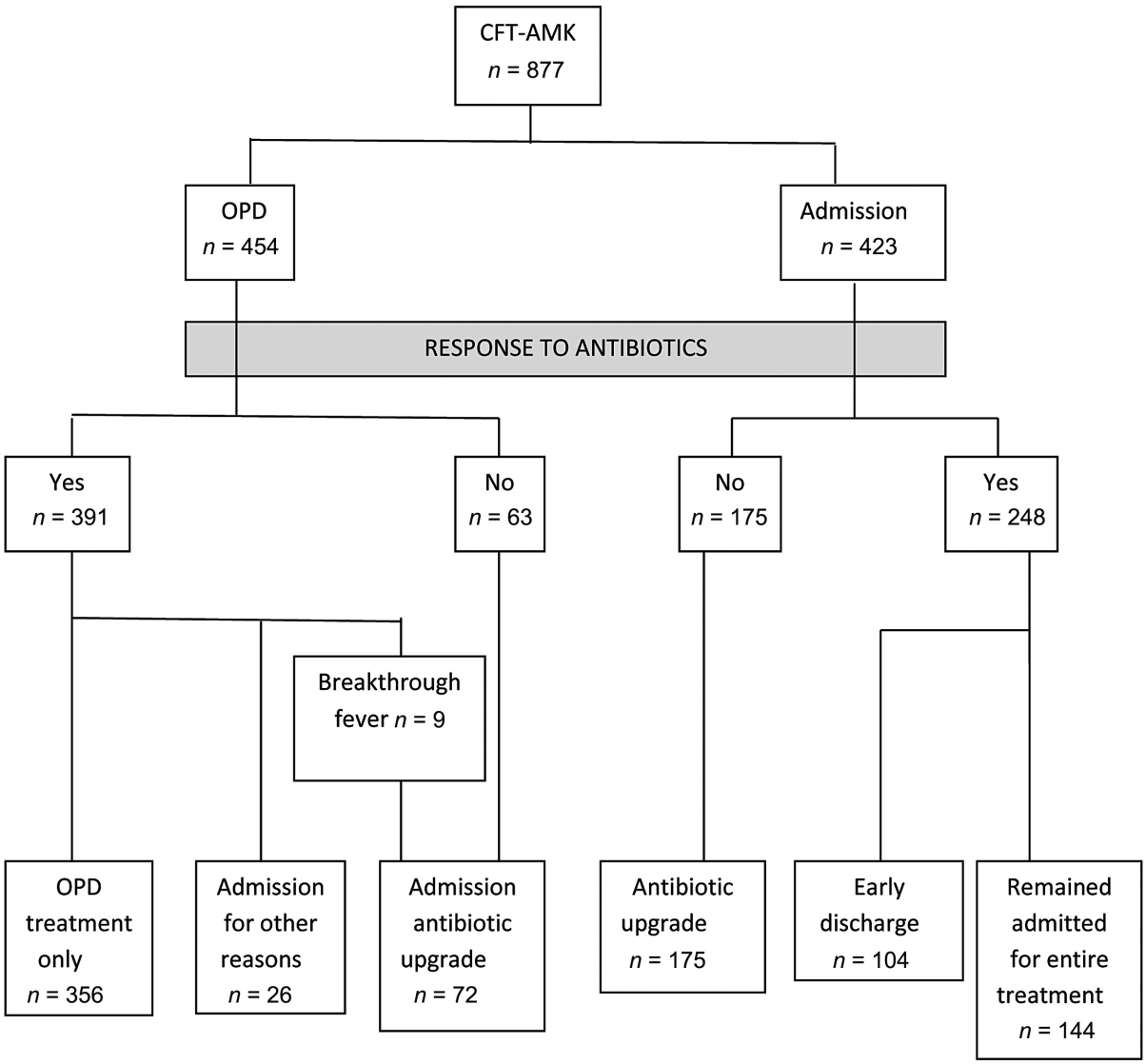

Fig. 1 FN episode outcome based on initial hospitalization status and response to ceftriaxone–amikacin (CFT-AMK). OPD, outpatient department.

Table 3 Outcome as per initial hospitalization status

	Low risk	High risk	Risk stratification not available	Total
Initial OPD	326	122	6	454
Subsequent admission	56	41	1	98
Death	0	0	0	0
Initial admission	159	264	0	423
Early discharge	63	41	0	104
Death	0	8	0	8

Abbreviation: OPD, outpatient department.

continued on OPD. There were no deaths in those treated initially on OPD, or in those who were discharged early. ►Table 3 shows outcome of FN episodes based on initial hospitalization status. Overall, 356 episodes (40.6% of all CFT-AMK episodes) were managed entirely on OPD. Those episodes where at least 2 days of OPD treatment was possible, either initially or after early discharge, were considered to have partial OPD treatment. Among the low-risk episodes, 389 episodes (80.2%) received treatment entirely ($n = 270$) or partially ($n = 119$) on OPD, while among the high-risk episodes, 162 (41.9%) episodes received treatment either entirely ($n = 81$) or partially ($n = 81$) on OPD.

Comparison of the data over three time periods (Period 1: 2002–2007; Period 2: 2008–2012; Period 3: 2013–2017) was done. Proportion of FN episodes treated initially on OPD were 34, 38, and 68%, respectively, in the three time periods. There was no difference in the proportion of patients requiring antibiotic change following initial CFT-AMK in the three time periods, which was required in 26, 31, and 27%, respectively ($p > 0.05$).

Using multivariate logistic regression model (►Table 4), AML chemotherapy, ANC nadir, platelet nadir, monocyte count at baseline, and known focus of infection other than URT were found to be significant independent predictors of

Table 4 Logistic regression showing independent predictors of antibiotic upgrade

		Univariate		Multivariate	
		OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Gender—male		0.90 (0.66–1.22)	0.50	–	
Diagnosis	Solid tumor	Ref			
	NHL	1.18 (0.61–2.27)	0.62	1.25 (0.55–2.85)	0.60
	ALL	1.01 (0.70–1.47)	0.96	0.79 (0.47–1.33)	0.38
	AML	5.33 (3.14–9.04)	<0.001	2.40 (1.16–4.81)	0.018
Disease status—active disease		2.70 (1.88–3.88)	<0.001	1.16 (0.67–2.02)	0.59
Performance status—poor		4.03 (2.01–8.06)	<0.001	2.13 (0.75–6.02)	0.16
Age group	<1 y	Ref		–	
	1–10 y	1.04 (0.54–2.00)	0.91	–	
	>10 y	1.25 (0.59–2.67)	0.56	–	
Duration of fever prior to antibiotics	<12 h	Ref		Ref	
	12–24 h	0.66 (0.48–0.92)	0.014	0.90 (0.59–1.38)	0.90
	>24 h	0.88 (0.50–1.56)	0.67	1.84 (0.83–4.08)	0.13
ANC nadir		0.000 (0.000–0.001)	<0.001	0.012 (0.000–0.299)	0.007
Duration of neutropenia		1.12 (1.08–1.15)	<0.001	1.03 (0.99–1.07)	0.16
Platelet nadir		0.974 (0.967–0.980)	<0.001	0.985 (0.979–0.992)	<0.001
Monocyte count at baseline		0.011 (0.002–0.077)	<0.001	0.14 (0.03–0.80)	0.027
Site of infection	URTI	Ref		Ref	
	Unknown	1.35 (0.85–2.16)	0.20	0.91 (0.52–1.58)	0.73
	Other known site	5.36 (3.39–8.49)	<0.001	4.18 (2.40–7.28)	<0.001

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ANC, absolute neutrophil count; CI, confidence interval; NHL, non-Hodgkin lymphoma; OR, odds ratio; URTI, upper respiratory tract infection.

need for antibiotic upgrade after initial empiric CFT-AMK treatment. There was no statistically significant difference in response to initial CFT-AMK between solid tumor and non-AML hematological malignancy patients.

Mortality occurred in eight (0.91% of all) episodes, being 2% of high-risk episodes. There was no mortality in any of the low-risk episodes or those high-risk episodes treated initially on OPD.

A total of 706 blood cultures were sent in 603 episodes, either at baseline or at subsequent time points. Results are not available in 69 episodes. Positive cultures were detected in 88/534 (16.5%) episodes. Gram-negative organisms were detected in 44, gram positive in 29, and fungal in 13 episodes (mixed bacterial/fungal growth was seen in two episodes). Antibiotic sensitivities were not consistently documented on case records and were available in 19/44 Gram negative isolates (carbapenem resistance was noted in 4/19, extended-spectrum beta-lactamase–producing *E. coli*/*Klebsiella* in 11/19).

During the study period, 70 episodes fulfilled criteria for treatment with PTZ-AMK from the outset. Thirty-five out of them (50%) required further antibiotic changes. There were six (8.57%) deaths in this group.

Discussion

The use of OD CFT-AMK combination for empiric treatment of neutropenic fever was used in the 1990s, with good efficacy and lower costs as compared with other antibiotics such as CTZ, which required thrice daily dosing.[1–9] However, with changing bacterial flora in the pediatric cancer population and increasing prevalence of multidrug-resistant organisms, many centers prefer to use other antibiotics for empiric treatment of FN.[10–16] Our data, spanning a 16-year period in a single institute, have demonstrated the persistent utility of this CFT-AMK combination, especially to facilitate OPD management of FN.

Eighty-six percent of low-risk episodes and 65% of high-risk episodes responded to the CFT-AMK combination. Fifty-five percent of high-risk episodes did not require change in antibiotics during the entire episode, thereby indicating the acceptable efficacy of this combination in carefully selected patients. Though we did not use CFT-AMK as initial treatment if there was evidence of serious infection such as hypotension, tachypnea, intra-abdominal infections, or altered sensorium, 92% of all FN episodes in the study period could be treated with CFT-AMK. Also, ~75% FN episodes in our study occurred in patients having hematolymphoid malignancies. There was no statistically significant difference in outcomes between FN episodes in non-AML hematolymphoid and solid tumor patients.

One important reason for continuing to use this combination, in addition to its lower cost, was its ability to be administered OD on OPD. This enabled us to treat a significant portion of our patients having FN on OPD basis, thereby freeing indoor beds for chemotherapy administration and for sick patients. Reduction in hospital stay was beneficial for patient compliance, cost of treatment, and potentially reduced the risk of getting hospital acquired infection. Even if a bed was available, the patients were given a trial of OPD treatment, provided they consented for the same and subsequently admitted only if required. The increase in proportion of patients initially treated on OPD basis (68 vs. 36–38% in the past) in the most recent time period (2013–2017) reflects not just our increased confidence in advising the same but also improvement in daycare protocols in our institute to facilitate OPD management and increased patient acceptance.

Current practice is to manage low-risk FN on OPD basis, either upfront or after a short inpatient stay.[9,12,13,16–22] In our study, even in the low-risk episodes, ANC nadir $<0.1 \times 10^9$/L was documented in 57% episodes. In spite of this, we treated 57% of our low-risk patients entirely on OPD, while another 22% received partial OPD care, either as initial empiric therapy or as step-down treatment. What is also noteworthy is that in our study, ~21% of high-risk episodes were also completely managed on OPD. In addition, early discharge was possible in another 15% of admitted high-risk episodes. This indicates that using our empiric antibiotic strategy, the option of OPD management is feasible even for some high-risk FN episodes, without compromising outcomes. Further studies would be necessary to better identify high-risk FN patients who could be successfully treated on OPD. High-risk non-AML patients, having good performance status, with no or URT focus of infection may be potential candidates for an OPD trial. On the other hand, our study indicated that patients having a non-URT focus of infection would be at risk for treatment failure after initial CFT-AMK empiric therapy and need antibiotic upgrade. Hence, caution should be applied for using this combination on OPD basis for patients having a non-URT focus, especially in high-risk FN episodes.

Blood cultures were positive in ~16.5% episodes where data were available. However, in view of the significant number of missing results, the incidence of positive cultures may be much lower. Gram-negative organisms predominated in our study. Antibiotic sensitivity data available in a limited number of patients shows high incidence of resistant gram-negative organisms. The use of CFT-AMK combination as empiric therapy for a patient having infection with a resistant organism could potentially cause risk to life. However, only in 17/877 (~2%) of the episodes (3.6% of high-risk episodes), we have to change antibiotics because of clinical deterioration. Overall mortality was also low (less than 1%) and compares favorably with other studies in developing as well as developed countries.[23–31] With suitable patient selection (excluding those with clinical evidence of serious infection), use of initial OPD approach with CFT-AMK combination for empiric management of FN in children does not seem to have compromised clinical outcomes.

Being a retrospective study, our study would obviously have a few limitations. However, the management of FN in our institute has remained consistent throughout the study period. All patients have been treated under supervision of a single pediatric oncologist, thereby lending consistency to the study methods. Reason for admission in each case has not

been documented. It is possible that many patients may have been admitted solely for convenience or insurance purposes, and the true need for admission may be lower than that seen in our study.

Conclusion

In conclusion, even in the era of increasing antibiotic resistance, OD CFT-AMK is a safe and effective empiric management strategy for carefully selected episodes of FN following chemotherapy in children. Most of the low-risk and a proportion of high-risk FN patients can be managed successfully on OPD basis. Suitable patient selection and strict clinical monitoring are essential for the success of this strategy. This strategy allows us to manage a majority of FN patients on OPD, which makes more indoor beds available for timely administration of chemotherapy, improves patient experience regarding cancer therapy, and helps in reducing cost of care, without compromising clinical outcomes.

Authors' Contribution

S.K. designed the study; helped in data collection and analysis, and manuscript preparation. A.M. designed the study; helped in data analysis and critical review of manuscript. A.D. and S.P. helped in data collection and critical review of manuscript. C.D. helped in data analysis and manuscript preparation and review.

Ethics

Institutional ethics committee approval: DMHRC Code—IHR_2021_Jan_SK_391; Dated: February 3, 2021. The study was approved by the institutional ethics committee.

Financial Support

None.

Conflict of Interest

None declared.

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