

Original Article

# Chemotherapy-induced constipation among children: An observational study

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## ABSTRACT

**Objectives:** Chemotherapy-induced constipation [CIC] is a common and underreported morbidity among children. There is a lack of consensus about its reporting and management.

**Material and Methods:** A prospective observational study was conducted on children receiving chemotherapy for various malignancies. Exclusion was made for preexisting gastrointestinal disorders, children in intensive care, or in an altered sensorium. Constipation assessment and Bristol stool form scales were used to assess the incidence of CIC.

**Result:** A total of 90 children were observed and CIC was reported by 41 (45.5%) cases as self-declared as well as on the constipation assessment scale. On the Bristol stool form scale, 47 (52.3%) cases had some grade of CIC. CIC was associated with vincristine, cytarabine, and L-asparaginase chemotherapy schedules. Oral laxatives were the most common remedy used and only 11 cases required rectal enema. Despite interval admission noted among 12 cases and chemotherapy schedule modification among 22 cases, the impact of CIC on the quality of life was expressed by 26.6% of caregivers only.

**Conclusion:** CIC is a common morbidity and it needs more active surveillance.

**Keywords:** Chemotherapy-induced constipation, Constipation, Bristol stool form, Bowel, Children

## INTRODUCTION

Childhood cancers constitute about 2% of all malignancies, but the majority of cases are getting cured due to a better understanding of disease biology, improved supportive care, and our ability to deliver intense chemotherapy.<sup>[1]</sup> While cure is a norm for many pediatric cancers, focus has been broadened to put emphasis on reducing treatment morbidities and late effects. Chemotherapy constitutes the backbone of childhood malignancy treatment plan in a majority of cases. The common side effect of chemotherapy and supportive medicine like antiemetics and antifungals is constipation. Altered bowel habit making defecation hard or less frequent is more common and the least addressed issue in childhood malignancy. Lack of guidelines to adhere makes the treatment of chemotherapy-associated constipation variable and sometime nonbeneficial.

Constipation is a subjective feeling, and no consensus has been reached for universal definition. It has been defined

as a slow movement of feces through the large intestine, resulting in infrequent bowel movement and passage of dry, hard stool.<sup>[2]</sup> The most used criteria to define chemotherapy-induced constipation (CIC) is ROME III, which includes bowel movement, incontinence, retention, and large and painful defecation as defining parameters.<sup>[3]</sup> CIC has been graded by the National Cancer Institute as well into grades I to V; these parameters are often used to define the severity or morbidity of CIC.<sup>[4]</sup> Treatment of CIC is variable and often includes laxative, enema, and gut motility enhancers. Lack of consensus guidelines is making the practice uneven. Moreover, being multifactorial, including dietary and physical habits, one regimen might not be enough for all children with CIC.<sup>[5]</sup>

We present the data of a tertiary cancer center from North India about the incidence of CIC in children on chemotherapy and various measures used in such cases.

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## MATERIAL AND METHODS

This observational prospective study was an institutional research and ethics committee-approved (SRHU/HIMS/ETHICS/2024/68) thesis for postgraduation degree (MD) in pediatrics. Study included children with cancer on chemotherapy, and exclusion was made for any gastrointestinal surgery cases, very sick children who were in intensive care unit, and children with neurological bowel problems. The objective of the study, which enlisted 90 cases for the study period of one year, was to estimate incidence and morbidities of CIC and to note ongoing pharmacological interventions done for CIC and their impact. Considering confidence level as (Z) 95%, margin of error (d) as 10%, and the incidence of CIC (P) as 30%, the n (= sample size) comes out to be 81.

After proper consent, CIC events were noted in semi-structured proforma which used constipation assessment scale (CAS) and Bristol stool form scale.<sup>[6,7]</sup> The impact of CIC was assessed by the quality of life (QoL) questionnaire (on scales 1–4 where 1 is no problem while 4 is very problematic). Impact in the form of interval admission, unplanned hospital visit, investigation, and delay in planned chemotherapy were noted as well. Various treatment modalities directed toward CIC were noted and analyzed for efficacy. Data regarding dietary habit and food intake were noted as well. Children and parents were asked about bowel movements during chemotherapy to assess constipation. Information about their perception of constipation as a morbidity was also collected.

### Statistical analysis

The presentation of categorical variables utilized numbers and percentages, while quantitative data were represented by means with standard deviation and medians with interquartile range. The association between qualitative variables was analyzed using the Chi-square test, with Fisher's exact test employed if any cell had an expected value of less than 5. Data entry was conducted in Microsoft Excel and final analysis was performed using Statistical Package for Social Sciences (SPSS) software, version 25.0, by IBM in Chicago, USA. Statistical significance was determined by a p-value less than 0.05.

## RESULTS

A total of 90 cases were enrolled in the study. The median age was eight years where boys outnumbered girls (64:26). The distribution of baseline characteristics is depicted in Table 1.

Antiemetics used during chemotherapy cycles were analyzed where ondansetron was the most used antiemetic. While the regimens used in various conditions were different, standard protocols were used. Gross protocol violations were not present. Individual drug use was also analyzed,

**Table 1:** Baseline characteristics and disease distribution

Parameters		
Male/female	64/26	2.46 (ratio)
Median Age	8 years	2–18 years (range)
Diagnosis	Frequency	Percentage (%)
Acute lymphoblastic leukemia	61	67.7
Acute myeloid leukemia	10	11.1
Bone cancers (osteosarcoma and Ewings sarcoma)	8	8.8
Others	11	12.2
Total	90	100%

**Table 2:** Constipation assessment scale and Bristol stool form scale

Constipation assessment scale	Frequency	Percentage
No problem	49	54.44
Some problem	38	42.22
Severe problem	3	3.33
Total	90	100
Bristol stool form scale		
Normal	43	47.78
Mild	26	28.89
With mild diarrhea	1	1.11
Severe	19	21.11
With severe diarrhea	1	1.11
Total	90	100

and methotrexate, vincristine, and adriamycin were the commonly used drugs in patients. Dose modifications were noted in 10% cases only.

Constipation was self-reported by 41 cases (45.5%) while on chemotherapy. On CAS, 49 cases reported no problem while three cases reported severe problem due to constipation [Table 2]. The Bristol stool scale indicated that in 47.78% (43) cases, bowel movements were normal while severe problem was noted among 21.11% (19) cases.

For 73.33% (66) cases, the impact of constipation on QOL was reported as “not at all,” 17.78% (16) cases indicated “a little,” and 8.89% (8) cases reported “quite a bit.” Five cases required imaging study (all X-ray of abdomen) for constipation.

Interval admissions were observed in 13.3% (12) cases, while 24.4% (22) cases required chemotherapy schedule modification in the form of delay. Among 20 cases, constipation was diagnosed as the main reason for bloating and abdominal pain after clinical evaluation.

In 55.56% (n = 50) cases, no treatment was administered. For 22.22% (20) cases, oral lactulose was prescribed while liquid paraffin was given to 20% (18) cases. Rectal enemas were

**Table 3:** Association of impact on quality of life with the constipation assessment scale

CAS → Impact on quality of life	No problem (n = 49)	Some problem (n = 38)	Severe problem (n = 3)	Total	P value
Not at all	48 (97.96%)	18 (47.37%)	0 (0%)	66 (73.33%)	< 0001
A little	1 (2.04%)	15 (39.47%)	0 (0%)	16 (17.78%)	
Quite a bit	0 (0%)	5 (13.16%)	3 (100%)	8 (8.89%)	
Total	49 (100%)	38 (100%)	3 (100%)	90 (100%)	

\*Fisher's exact test. CAS: Constipation assessment scale

employed in 11.11% (10) cases of the treatments. All cases showed improvement in constipation with these measures. Rectal enema was given after a trial of oral laxatives in all ten cases. Individual chemotherapy agents showing strong correlation with constipation were vincristine, cytarabine, and L-asparaginase in this group of children.

Although constipation was reported by 41 children, labeling it as a significant problem was less than expected. The association of constipation and its impact on QoL showed that despite having constipation, 18 cases showed no impact on the QoL. On assessing QoL vis-à-vis CAS, again the fact of no impact among 73.3% cases were noted [Table 3].

## DISCUSSION

The gastrointestinal (GI) side effects induced by chemotherapy pose significant challenges in cancer management, often underestimated in clinical settings. CIC and diarrhea present persistent obstacles in achieving effective and tolerable cancer treatment, frequently leading to dose adjustments, treatment delays, and even discontinuation.<sup>[8]</sup>

CIC is a well-documented complication among adult oncology patients, affecting 50–87% of those with advanced cancer and ranking as the third most common symptom in individuals undergoing cytotoxic chemotherapy.<sup>[8,9]</sup> Similarly, constipation emerges as the primary gastrointestinal concern for children on chemotherapy in hospital settings and affects more than 505 children.<sup>[10]</sup> As constipation depends on multiple factors attributing independently or in synergy, there is variation in incidence with similar chemotherapeutic agents as well.<sup>[11]</sup> Dietary habits, physical activity level, roughage intake, and personal tolerance are affecting bowel health. Sociodemographic factors should be analyzed to delineate correctable causes. The basis of CIC is vague and newer hypothesis points toward deranged enteric nervous system as the main cause of CIC.<sup>[12,13]</sup> This might open the therapeutic advancement in the form of neuroprotection to decrease CIC.

Both pharmacological and non-pharmacological methods are being utilized to alleviate constipation symptoms. However, non-pharmacological approaches, like increased

physical activity and oral hydration as well as addressing medical factors contributing to constipation, may be hard for children with cancer to follow due to treatment-related side effects such as nausea, mucositis, anorexia, fatigue, or others. Consequently, oral medications are often the primary, and sometimes the sole, option for healthcare providers to consider in this scenario. Moreover, certain supportive care measures, such as total parenteral nutrition (TPN), have shown an increased likelihood of causing constipation. Despite ongoing progress in pediatric oncology, our understanding of CIC as well as its treatment has increased; but there's still a lack of clear consensus guidance for oncology teams regarding constipation management.<sup>[14]</sup>

This study noted CIC across variable chemotherapeutic agents, while association was stronger with vincristine, cytarabine and L-asparaginase. Vincristine, a vinca alkaloid, is a known neurotropic agent and its association with CIC has been well documented. Agents causing CIC is not limited to chemotherapeutics but encompass 5HT3 blockers as well.<sup>[15]</sup> Index study noted ondansetron as the most frequent antiemetic used while one for or other 5HT3 blockers were used in every case. Additional fluconazole also increases the risk of constipation.<sup>[16]</sup>

The perception of constipation was variable, and some cases of moderate constipation on Bristol stool assay were comfortable on self-declaration. Similarly, the effect on QoL is not correlating<sup>[10]</sup>; it could be explained by the unknown acceptance of constipation as a normal thing. The perception of CIC as a significant morbidity is not accurate even among pediatric oncologists.<sup>[17]</sup>

The therapy directed for CIC has no consensus. If the multifactorial pathogenesis is being considered, then the consensus seems hard to achieve. This study noted the frequent use of oral laxative in the form of lactulose and paraffin, and only nonresponders were given rectal enemas; however, almost all cases showed relief in symptoms with these measures. Studies have used senna and methylnaltrexone as well for opioid-induced constipation in cancer cases and noted good efficacy.<sup>[18,19]</sup> Among pediatric cases, lactulose was noted to be at par with polyethylene glycol, as were other

agents for constipation also effective, leaving room for choice in a practicing clinician to select one over the other.<sup>[20–23]</sup>

Literature has revealed cases of severe CIC leading to surgical intervention as well.<sup>[24]</sup> Based on a smaller sample size, it is difficult to negate the role of surgical intervention in refractory cases. Non-pharmacological intervention like posturing, colonic massage, and positioning in defecation has been noted to be effective in relieving constipation.<sup>[25,26]</sup> This study has not recorded such interventions.

CIC causes significant morbidity despite its lower impact on perceived QoL in this study. Interval admissions and delay in scheduled chemotherapy were noted among 13.3% and 24.4% cases, respectively, where the impact of such interruptions is not known.

### LIMITATIONS OF STUDY

This study is an observational one; thus, inference about superiority of one treatment modality over the other for CIC is not feasible. Smaller sample size also makes results indicative of trends only. The tools used in this study—CAS and Bristol stool form—although validated, have shown variable sensitivity and specificity in practical use. This study also lacks in collecting data about non-pharmacological and dietary modification done by caregivers for CIC cases, which may have affected the outcome of CIC.

### CONCLUSION

CIC is a common morbidity with multifactorial reasonings. There is a lack of consensus on management and individual-level preferences of treatment of CIC being used. There is a need of awareness and data collection for this morbidity.

### Author contributions

All authors contributed in study designing, data collection, analysis and manuscript writing. Final manuscript is approved by all authors.

### Ethical approval

The research/study approved by the Institutional Review Board at SRHU/HIMS, number SRHU/HIMS/ETHICS/2024/68, dated 27th March 2024.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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### Conflicts of interest

There are no conflicts of interest.

### Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of AI-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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