Original Article

# Acute methotrexate toxicity: experience in a tertiary care hospital of Bangladesh

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## ABSTRACT

***Background:*** *Methotrexate (MTX) is one of the commonly prescribed disease-modifying anti-rheumatic drugs (DMARDs) used in various rheumatic diseases. It can potentially cause life-threatening neutropenic sepsis and acute renal and hepatotoxicity when taken erroneously at high doses. Here, we present the clinical profile and risk factors of patients who presented with clinical features of acute MTX toxicity.*

***Methods:*** *This hospital based observational study was carried out in the Department of Internal Medicine, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) General Hospital, Dhaka, Bangladesh from July 2022 to May 2024. The clinical profile, risk factors and outcome of patients taking MTX erroneously at high doses were analyzed.*

***Results:*** *Total 12 cases including 8 females were taking erroneously higher dose of MTX. The mean age was 55 (range 40 - 67) years. Mean dose of MTX was 70 (range 60 - 200) mg on the week of toxicity. The reason for overdose in our cohort was daily intake instead of weekly. The major adverse event was thrombocytopenia and stomatitis (91.7%) with 58.3% having oral bleeding. Gastrointestinal adverse events like vomiting and diarrhoea were seen in 41.7% and 25% of the patients respectively. Our cohort had two patients who succumbed to the complications due to neutropenic sepsis. The dose of MTX did not correlate with the severity of the disease or duration of hospital stay; however, the latter was significantly influenced by lower absolute neutrophil count (ANC) 250 $10^9$/L.*

***Conclusion:*** *In our study two patient died, five patient needed ICU care and two patient developed severe neutropenic sepsis. So, sensitization of physicians is of paramount importance to clinch the signs of MTX toxicity at the earliest to avoid morbidity and mortality.*


***Key words:*** *methotrexate toxicity, overdosing, pancytopenia, skin and mucosal ulceration, neutropenic sepsis.*

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## INTRODUCTION

Methotrexate (MTX) is the most frequently prescribed disease-modifying anti-rheumatic drug (DMARD) in the field of rheumatology. Rheumatoid arthritis (RA) is the primary condition treated with MTX and the drug's endorsement is as a first-line therapy.[1] MTX has become the treatment of choice for a variety of disorders, including psoriasis, systemic sclerosis with predominant skin and joint involvement, newly diagnosed non-organ or non-life-threatening anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, musculo-skeletal manifestations of Sjögren's syndrome and systemic lupus erythematosus etc.[1–3] It is typically administered as a single weekly dose to manage these conditions. However, medication errors involving the incorrect administration of daily doses can result in severe complications, including

life-threatening cytopenia, renal and hepatic dysfunction and mucositis.[4]

While the adverse effects of MTX have been extensively documented in the literature, reports on acute MTX toxicity are largely scarce, with some insights derived from an Indian series by Ajmani et al., which described pancytopenia associated with MTX, including 13 cases involving dosing errors.[5] Low-dose MTX (<25 mg/week) is generally well tolerated, with a low incidence of adverse effects such as stomatitis and bone marrow suppression leading to cytopenias (anemia, neutropenia, thrombocytopenia), reported in only about 3% of cases. A recent meta-analysis involving nearly 4,000 patients revealed that neutropenia occurred in approximately 1.77% of cases, while anemia was observed in 2.5%.[6] However, most of the existing data on the adverse effects of MTX come from cohorts receiving stable doses, where these side effects were primarily attributed to chronic bone marrow suppression rather than acute toxicity. In this study we want see the clinical and biochemical profile of acute erroneous dose of MTX toxicity.

## METHODS

All patients presenting to the Internal Medicine Department with a history of erroneous consumption of higher doses of MTX (>25 mg/week), from July 2022 to May 2024 were included in this hospital-based observational study. Erroneously means daily intake instead of weekly and high doses means daily intake of 15 to 25 mg instead of weekly intake. Patients taking MTX weekly presented with sepsis due to other causes were excluded. In this study total 12 patients were included who took MTX for various rheumatological diseases.

The clinical profile, risk factors and outcome of patients with MTX toxicity were analysed. We defined acute toxicity in patients who had consumed daily doses of the prescribed MTX instead of weekly dose that resulted in one or more of the adverse events. The data regarding cumulative dose of MTX, severity of neutropenia, renal and hepatic dysfunction and presence of pre-existing poor prognostic factors like chronic kidney disease (CKD) were analysed. Haematological adverse events were further divided into anaemia, leukopenia, neutropenia and thrombocytopenia.

All our patients were treated symptomatically and neutropenia, leucopenia and thrombocytopenia were treated with maintenance of hydration and nutrition, broad-spectrum antibiotics, add-on anti-fungal according to need and granulocyte colony stimulating factor (G-CSF), as required. In patients who developed acute renal failure, additional step of alkalinisation of urine was done. Along with this, supportive measures, barrier nursing and strict hygiene for the maintenance of stomatitis and ulcers were followed.

Statistical analysis was conducted with IBM SPSS version 22. The comparison between groups were performed using the Student's t-test. The Karl Pearson correlation coefficient was calculated to explore the relationship between the lowest absolute neutrophil count (ANC), the total MTX dosage and the length of hospital stay. The odds ratio was used to assess the effect of covariates on mortality. Clinical and laboratory parameters were examined as possible prognostic indicators for survival or mortality. In this study, severe neutropenia was used as an important indicator of duration of hospital stay and mortality. A p-value of less than 0.05 was considered statistically significant.

## RESULTS

Total patients were 12 including 8 females. Mean age was 55.9 (range 40 - 67) years. All the patients received daily doses of MTX instead of prescribed weekly dose. There was no prescription error or intentional overdose. Mean dose of MTX was 70 (range 60 - 200) mg in the week of toxicity. Stomatitis (91.7%) (Figure 1) was the most common symptom and 58.3% had oral mucosal bleeding. Vomiting (41.7%) and diarrhoea (25%) were also common (Table I). Skin involvement was common (Figure 2). Nine (75%) patients had neutropaenia, lowest ANC was 250/cmm, three patients had severe neutropaenia (ANC < 500/cmm) and two patients died due to sepsis (due to *Staphylococcus aureus* and the *Escherichia coli* septicaemia) having the ANC count of <350/cmm. Ten (83.3%) patients had raised hepatic enzymes and 10 (83.3%) had acute kidney injury (33% had CKD) (Table I).

**Figure 1.** Oral mucosal inflammation with ulceration and bleeding

**Table I.** Demographic, clinical and laboratory features of patients having acute methotrexate toxicity (N = 12)

| Feature | Frequency (Percentage) | Mean ± SD (Range) |
|---|---|---|
| Male/Female | 4 (33.3) / 8 (66.7) | - |
| Age (years) | - | 55.9 ± 7.2 (40 – 67) |
| Cumulative dose of MTX (mg/week) | - | 88.33 ± 39.96 (60 – 200) |
| Clinical features | | |
| Stomatitis | 11 (91.7) | - |
| Cutaneous toxicity | 8 (66.7) | - |
| Gum bleeding | 7 (58.3) | - |
| Fever | 8 (66.7) | - |
| Vomiting | 5 (41.7) | - |
| Diarrhoea | 3 (25) | - |
| Laboratory parameters | | |
| Haemoglobin | - | 8.53 ± 1.07 (6.8 – 10) |
| Anaemia | 10 (83.3) | - |
| White cell count | - | 822.2±466.4 (250 – 1800) |
| Neutropenia | 9 (75) | - |
| Platelet count | - | 68636 ± 30503.3 (20000 – 110000) |
| Thrombocytopaenia | 11 (91.7) | - |
| Pancytopaenia | 7 (58.3) | - |
| Serum creatinine (mg/dl) | - | 3.24±1.27 (1.8 – 5.4) |
| Acute kidney injury | 10 (83.3) | |
| ALT(U/L) | - | 165.55±90.98 (80 – 350) |
| Raised ALT | 10 (83.3) | - |
| AST(U/L) | - | 191.11±98 (100 – 400) |
| Raised AST | 10 (83.3) | - |
| Risk factors for adverse effects of MTX | | |
| Concomitant NSAID intake | 5 (41.7) | - |
| CKD | 4 (33.3) | - |
| Outcome | | |
| Death | 2 (16.7) | - |

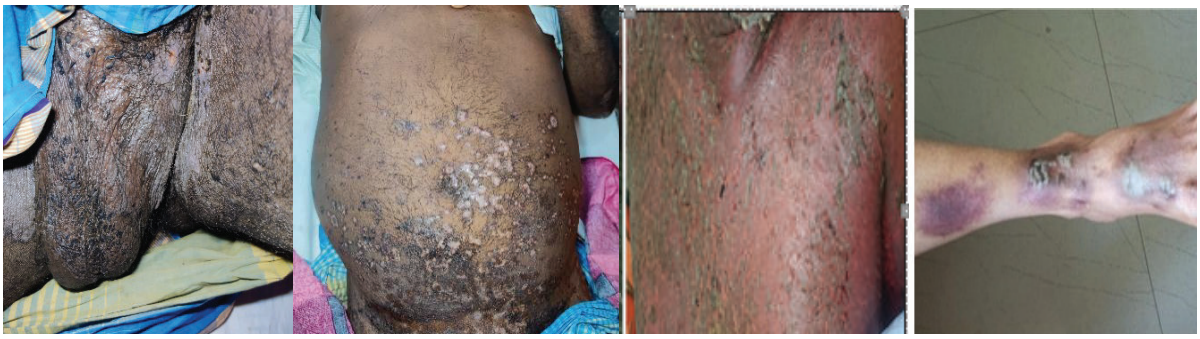


**Figure 2.** Vescicular-papular rash over lower abdomen and genital region, erythema and erosion on psoriatic plaque

The dose of MTX did not correlate with the severity of the disease or duration of hospital stay; however, the latter was significantly influenced by lower ANC. However, a dose-dependent relationship could not be established, likely due to the small sample size. Although the total MTX dose did not correlate with ANC or hospital stay duration, a significant correlation (r= -0.012) was found between the severity of neutropenia (as measured by ANC) and longer hospital stays (p= 0.009) (Figure 3, 4 and 5 respectively). A non-significant trend towards mortality was observed with the total MTX dose, with an odds ratio (OR) of 0.6 (95% CI: -7.12–4.14, p = 0.68). The OR for other established risk factors of mortality, such as renal impairment (OR=2.33;95%CI:0.05-6.79, p=0.61) was also not significant.

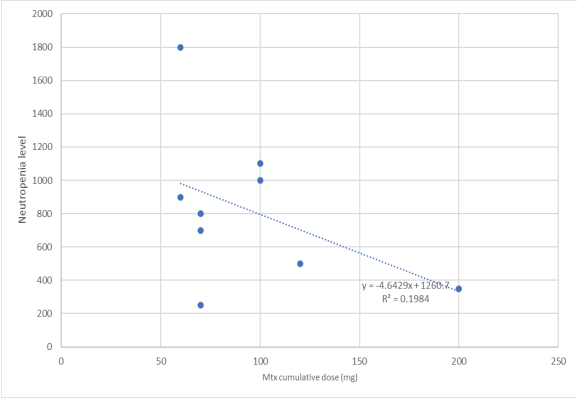



**Figure 3.** Correlation graph between MTX dose and absolute neutrophil count (ANC)

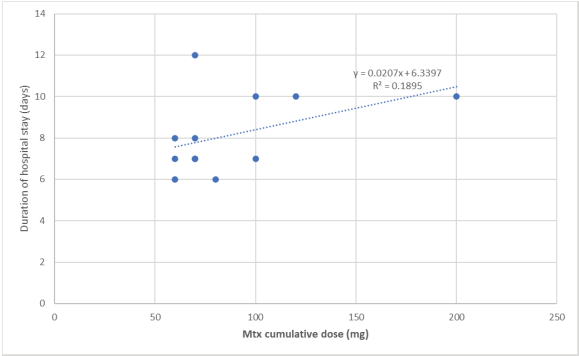



**Figure 4.** Correlation graph between MTX dose and duration of hospital stays

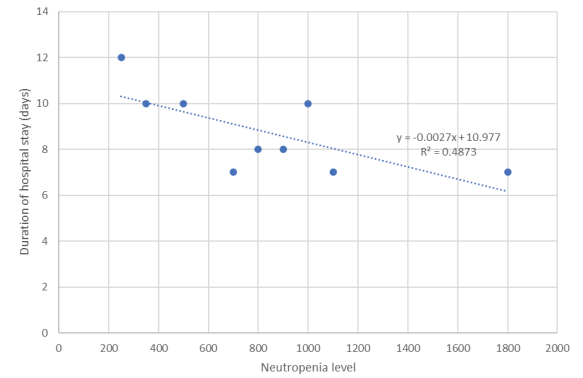
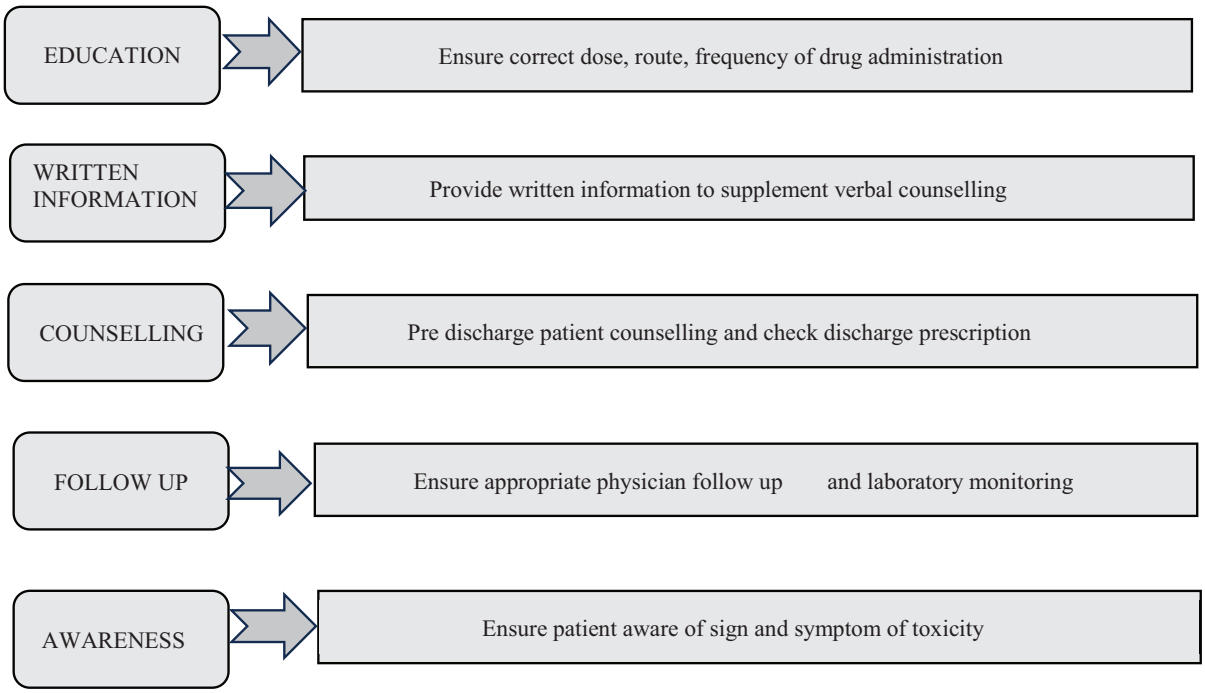



**Figure 5.** Correlation graph between absolute neutrophil count (ANC) and duration of hospital stays

## DISCUSSION

This study explores the clinical characteristics of acute MTX toxicity caused by erroneous overdoses, where patients ingested the drug daily instead of weekly. Consistent with previous literature, unintentional




overdoses remain the leading cause of toxicity, often stemming from miscommunication or misunderstanding of prescription instructions.[7] However, intentional overdoses have been reported in some cases, accounting for up to 20% of MTX poisoning incidents in a United States poison control center analysis.[8]

A retrospective study by Bebarta et al. involving 63 acute MTX toxicity cases revealed no mortality and none of the patients experienced severe complications such as bone marrow suppression.[9] This outcome contrasts sharply with our cohort, which had a mean cumulative dose of 88 mg compared to the much lower average dose of 24 mg in Bebarta's cohort. Similar findings were noted in a smaller American case series, where maximum MTX doses were approximately 13 mg and no major adverse effects were observed.[10] Conversely, a study from Iran reported 37% of acute MTX poisoning cases as intentional, further emphasizing the variability in overdose etiology.[7] The higher doses of MTX administered in our cohort, starting at 15 mg weekly, might explain the greater incidence of severe adverse events. In contrast, lower doses of 2.5–5 mg weekly are more commonly prescribed in American cohorts.[10] This disparity underscores the need for region-specific studies to understand toxicity patterns.

Hematological complications, particularly neutropenia, remain one of the most severe consequences of acute MTX toxicity. While chronic MTX use is associated with lower rates of cytopenia, acute overdose frequently results in neutropenia, with reported incidences as high as 80% in some studies.[11] Our findings align with this, as 75% of patients in the cohort experienced neutropenia, a figure consistent with data reported by Mruthyunjaya et al. Mortality in our study was linked to sepsis secondary to severe neutropenia.[12] Cutaneous adverse events were also observed, presenting as erythema, toxic eruptions and ulcerations. These symptoms likely result from hypersensitivity reactions or apoptosis induced by MTX's cytotoxic effects on keratinocytes.[12-14]

Pre-existing renal dysfunction was a significant risk factor in our study, with four patients exhibiting compromised renal function. Renal impairment amplifies MTX toxicity due to decreased drug clearance, even at low doses.[13] Among these patients, three developed severe neutropenia after cumulative MTX doses as low as 60 mg. The mechanism of acute MTX toxicity often involves impaired folate metabolism and intracellular accumulation of the drug, leading to renal and hepatic damage. This mechanism is more pronounced in high-dose MTX regimens used in chemotherapy but remains relevant in rheumatological cases.[14]

Predictors of poor outcomes, such as, pre-existing renal disease and concurrent use of other drugs with overlapping toxicity profiles, was noted in our cohort. Despite these findings, no statistically significant correlation was observed between these factors and mortality, likely due to the limited sample size. Mortality in our study (16.7%) was consistent with findings from other cohorts. A series of 106 patients in the United States reported a mortality rate of 25%, primarily due to sepsis resulting from unintentional overdoses.[14]

Although serum MTX levels have been proposed as a diagnostic tool, their clinical utility remains limited. The data on serum MTX levels is primarily extrapolated from high-dose regimens used in oncology, which may not directly apply to rheumatology cases.[15] Folic acid supplementation remains a cornerstone of MTX toxicity prevention. While the FOLVARI trial demonstrated no added benefit from higher folic acid doses, its consistent use at standard doses has been shown to mitigate bone marrow suppression in chronic MTX users.[16] However, its protective effects in acute toxicity scenarios require further investigation. All the patients in our cohort were on regular 5 mg folic acid/week.

Our study highlights the urgent need for improved patient education and healthcare provider communication to prevent dosing errors. Enhanced prescription protocols and better patient information materials, including pictorial instructions, could significantly reduce the risk of MTX toxicity. Future research with larger, multicenter cohorts is necessary to validate these findings and develop robust preventive strategies.

## Conclusion

From the present case series, our observation suggests that counselling about the course of disease, regarding dosing schedule of MTX and consequence of MTX overdosing should be mandatory for all patients in country like Bangladesh where drug regulation is not strict and patients often buy medications over the counter and resort to self medication. The cases are reported to make the physicians familiar with the different challenges of acute MTX toxicity due to overdosing in Bangladeshi patients where drug like MTX is easily available without prescription over the counter and also to create awareness regarding counseling the various aspects of disease and MTX.

**Authors' contribution:** MTI, MJI were involved in manuscript writing, data collection, data analysis and reviewing. SIR, RE were involved in data collection. HFH, AKMSA were involved in planning.

**Consent of patients:** Informed written consent was taken from patients / next of kin for publication of these case series and any accompanying images.

**Conflict of interest:** Nothing to declare.

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