RESEARCH PAPER

Acute Methotrexate Toxicity Secondary to Inadvertent Daily Dosing in Psoriasis Vulgaris: A Case Series with Review of Literature

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ABSTRACT

Background: Methotrexate (MTX), an established anchor therapy for psoriasis vulgaris, carries a narrow therapeutic index when dosing frequency is misjudged. Acute toxicity arising from inadvertent daily administration of a prescribed weekly regimen is under-recognised in dermatology and general medicine practice.

Objectives: To describe the clinical presentation, laboratory findings, management strategies, and outcomes of three consecutive patients who developed acute MTX toxicity through accidental daily overdosing, and to consolidate evidence-based management guidance.

Methods: Retrospective case series from a tertiary care teaching hospital (January 2025–March 2026). All adult patients with confirmed acute MTX toxicity secondary to dosing frequency errors were included.

Results: Three patients (ages 53–70 years) with psoriasis vulgaris presented after taking MTX daily for 3–7 days, accruing cumulative doses of 60–90 mg. Universal findings included mucocutaneous ulceration and haematological compromise (haemoglobin 8–9 g/dL; platelets 90,000–95,000/cmm). All three received IV leucovorin rescue and recovered fully within 7–14 days without sequelae.

Conclusion: Inadvertent daily MTX dosing constitutes a preventable medical emergency. Oral mucosal ulceration is the cardinal early warning sign preceding haematological nadir. Prompt leucovorin rescue yields excellent outcomes; however, patient and prescriber education regarding the weekly dosing schedule remains the most critical preventive strategy.

Keywords: *Methotrexate toxicity; dosing error; psoriasis; leucovorin rescue; pancytopenia; mucositis; medication safety*

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INTRODUCTION

Methotrexate (MTX) is a folate antimetabolite that has been the cornerstone pharmacological agent for moderate-to-severe psoriasis vulgaris for more than five decades. At the approved low-dose weekly regimen (7.5–25 mg/week), it inhibits dihydrofolate reductase (DHFR), thereby suppressing keratinocyte hyperproliferation and the underlying T-cell–driven inflammation. [1][2] Despite its well-characterised efficacy, the narrow therapeutic index of MTX-and its unique weekly dosing schedule, which stands in sharp contrast to the daily rhythms of most oral medications-renders it uniquely susceptible to administration errors.

The global literature has consistently documented inadvertent daily dosing as the single most common trigger of acute MTX toxicity, accounting for up to 67% of cases in some series. [3][4] This pattern of error arises because patients, and occasionally caregivers or pharmacists unfamiliar with the drug's distinctive schedule, default to the intuitive but catastrophic assumption that the prescribed tablet quantity should be taken daily. The consequences are severe: unlike a true single-dose acute overdose-where gastrointestinal saturation limits systemic absorption-repeated daily ingestion circumvents mucosal saturation and allows full intracellular accumulation of MTX polyglutamates, mimicking the kinetics of high-dose oncology protocols. [5]

The Institute for Safe Medication Practices (ISMP) has classified oral methotrexate as a high-alert medication, and international patient safety databases in the United States and Australia have identified frequency errors as a leading cause of preventable MTX fatalities. [6] Despite this recognition, published case series from resource-constrained tertiary care settings in South Asia-where written prescription literacy may be limited and community pharmacist oversight is variable-remain sparse.

We present a case series of three consecutive patients managed at a tertiary teaching hospital in Tamil Nadu,

India, all of whom developed acute MTX toxicity following inadvertent daily ingestion of their weekly psoriasis prescription. The series illustrates the stereotyped clinical phenotype, delineates the management pathway that led to universal recovery, and advocates for scalable, system-level preventive interventions.

2. CASE REPORTS

2.1 Case 1 – Inadvertent Escalation Driven by Disease Frustration

A 60-year-old woman with a 12-year history of plaque psoriasis presented to the emergency department with a 4-day history of severe burning pain at the site of her psoriatic plaques, progressive skin tenderness, and inability to bear clothing contact. She had been initiated on oral MTX 7.5 mg once weekly by a private dermatologist eight weeks prior. Out of frustration with perceived inadequate disease control, she increased her dose frequency to once daily for four consecutive days, accruing a cumulative dose of 75 mg.

On examination, her psoriatic plaques showed florid erythema, superficial ulceration, and active oozing. The oral mucosa was intact. **Key investigations:** haemoglobin 8.1 g/dL, total platelet count 90,000/cmm, total leucocyte count 3,200/cmm, serum creatinine 0.9 mg/dL, liver function tests within normal limits. Chest X-ray: clear. Blood culture: no growth.

She was admitted, MTX discontinued, and IV folinic acid (leucovorin) commenced at 20 mg 6-hourly on day 1, followed by 10 mg 6-hourly until blood counts normalised. Folic acid 5 mg daily and supportive wound care were added. She recovered fully within seven days without sequelae and was discharged with structured counselling regarding weekly dosing and disease management expectations.

2.2 Case 2 – Dosing Schedule Misunderstanding

A 70-year-old man with chronic plaque psoriasis of 8 years' duration was started on oral MTX 7.5 mg weekly. He presented after three days of inadvertent daily dosing (total cumulative dose 90 mg), reporting sudden-onset ulceration and spontaneous bleeding from his psoriatic lesions and painful oral ulcerations that impaired swallowing.

He admitted he had not understood his prescription and assumed the tablet was to be taken daily. **Examination:** multiple punched-out oral ulcers on the buccal mucosa and tongue, bleeding psoriatic plaques bilaterally. **Investigations:** haemoglobin 8.0 g/dL, platelets 92,000/cmm, leucocytes 2,800/cmm, SGOT 220 U/L, SGPT 270 U/L (reflecting significant hepatotoxicity), serum creatinine 1.0 mg/dL. Blood culture sterile.

MTX was immediately withheld. IV leucovorin was commenced (20 mg 6-hourly × 1 day, then 10 mg 6-hourly). Given transaminase elevation exceeding 5× the upper limit of normal, hepatoprotective measures-including N-acetylcysteine and strict alcohol abstinence-were initiated. Blood counts and liver enzymes normalised by day 10. He was discharged with written illustrated dosing instructions and pharmacist verification at the community level arranged.

2.3 Case 3 – Polypharmacy and Extended Daily Dosing

A 53-year-old man with psoriasis vulgaris and hypertension (on amlodipine 5 mg daily and hydrochlorothiazide 12.5 mg daily) presented with the most severe clinical picture in this series. He had taken MTX 7.5 mg daily for seven days (cumulative dose 52.5 mg) before presenting with extensive ulceration and haemorrhage from psoriatic plaques, painful oral and genital mucosal ulceration, fever (38.4 °C), and productive cough.

He reported self-escalating the frequency because his disease had flared after missing his previous weekly dose the preceding fortnight. **Investigations:** haemoglobin 9.0 g/dL, platelets 95,000/cmm, neutrophils 1,100/cmm, SGOT 85 U/L, serum creatinine 1.3 mg/dL, CRP elevated (78 mg/L). High-resolution CT chest: bilateral lower zone ground-glass opacities consistent with MTX-induced pneumonitis vs community-acquired pneumonia (later confirmed microbiologically as Klebsiella pneumoniae). Sputum culture: Klebsiella pneumoniae sensitive to piperacillin-tazobactam.

In addition to IV leucovorin rescue, he received IV piperacillin-tazobactam (4.5 g 8-hourly), antifungal prophylaxis (fluconazole 150 mg daily), IV granulocyte colony-stimulating factor (filgrastim 300 mcg subcutaneously daily), and aggressive IV hydration. Blood counts recovered by day 12, and he was discharged on day 14.

2.4 Comparative Summary of All Three Cases

Table 1. Comparative clinical and laboratory profiles of all three patients.

Feature	Case 1 (60F)	Case 2 (70M)	Case 3 (53M)
Trigger / Reason	Disease frustration; self-escalation	Misunderstood dosing schedule	Missed weekly dose; fear of flare
Duration of Daily Dosing	4 days	3 days	7 days
Cumulative Dose	75 mg	90 mg	52.5 mg
Mucocutaneous Features	Skin ulceration & oozing; oral mucosa intact	Oral ulcers + skin haemorrhage	Oral + genital ulceration; extensive skin ulceration
Haemoglobin (g/dL)	8.1	8.0	9.0
Platelets (/cmm)	90,000	92,000	95,000

Hepatotoxicity	Absent	SGOT 220; SGPT 270 U/L	Mild elevation SGOT 85 U/L
Treatment	IV Leucovorin + supportive care	IV Leucovorin + hepatoprotection	IV Leucovorin + G-CSF + antibiotics + antifungals
Recovery Duration	7 days	10 days	14 days
Outcome	Full recovery; no sequelae	Full recovery; no sequelae	Full recovery; no sequelae

Table 3. Known Risk Factors for Acute Methotrexate Toxicity

Risk Factor	Mechanism / Comment
Frequency error (daily instead of weekly)	Most common cause (40–67%); bypasses GI saturation kinetics
Renal impairment (CKD)	Reduced MTX clearance (80–90% renal excretion); prolongs exposure
Advanced age (> 65 years)	Physiological decline in GFR; reduced folate stores; polypharmacy
NSAIDs / PPIs / Trimethoprim	Compete for renal tubular secretion, elevating serum MTX levels
Hypoalbuminaemia	Increases free (unbound) drug fraction
Dehydration	Reduces renal clearance; promotes renal tubular precipitation
Folate deficiency	Reduces physiological buffering against DHFR inhibition
Diabetes mellitus	Increased risk of NAFLD and hepatotoxicity; impaired immune response
Concurrent infections	Inflammatory cytokines impair MTX clearance; synergistic immunosuppression

3. DISCUSSIONS

3.1 Pathophysiology of Daily-Dosing Toxicity

MTX is a competitive inhibitor of DHFR, the enzyme responsible for converting dihydrofolate to tetrahydrofolate-an essential cofactor for de novo purine and thymidylate synthesis and hence DNA replication. [1][2] At therapeutic weekly doses, tissue polyglutamate accumulation reaches a steady state compatible with haematopoiesis and mucosal renewal. The critical kinetic feature that distinguishes daily overdosing from acute single-dose ingestion is gastrointestinal absorption saturation: the mucosal folate transporter becomes saturated at single doses exceeding approximately 25 mg/day, severely limiting systemic bioavailability after a large single ingestion. [5] With repeated daily low-to-moderate doses, each dose is fully absorbed and completely taken up by cells before the preceding polyglutamate burden can be cleared, given an intracellular half-life of MTX active metabolites of 1–4 weeks. [5] Cumulative intracellular exposure therefore escalates rapidly, disproportionately affecting the most mitotically active compartments: bone marrow precursors, gastrointestinal mucosa, and hepatocytes.

3.2 Clinical Phenotype and Early Warning Signs

The published literature, corroborated by our series, establishes mucocutaneous ulceration as the harbinger of haematological toxicity. [7][8] Oral ulcers, stomatitis, and painful dysphagia typically emerge 3–7 days after toxicity is established, consistently preceding the haematological nadir by 3–5 additional days. Pancytopenia is the dominant laboratory finding (reported in 78–93% of cases), with thrombocytopenia and neutropenia conferring the highest risk of immediate life-threatening complications. [9] In our series, all three patients had platelet counts between 90,000–95,000/cmm at presentation; Case 3's evolving neutropenia and fever provided the first signal of impending sepsis.

A clinically significant-and underscore observation-is that the haematological nadir may not coincide with symptom onset. Psoriatic lesions superimposed on diffuse erythroderma can mask early mucosal changes, particularly when providers focus on skin disease. Clinicians must specifically inquire about oral pain and dysphagia in any psoriasis patient on MTX who presents with disease exacerbation, as these symptoms may herald toxicity rather than therapeutic failure.

3.3 Risk Stratification

While all three patients recovered fully, several risk factors are documented to substantially worsen outcomes in acute MTX toxicity: advanced age; renal impairment (the primary route of MTX excretion is unchanged renal elimination-80–90% of the drug is cleared renally); [10] polypharmacy with drugs that compete for tubular secretion (NSAIDs, proton-pump inhibitors, trimethoprim, penicillins); hypoalbuminaemia (reducing protein binding and elevating free drug fraction); dehydration; and baseline folate deficiency. Case 3's concurrent antihypertensive therapy (thiazide diuretic inducing mild volume depletion) and elevated serum creatinine reflect a borderline higher-risk profile.

Population-level data from Australia and the United States identify frequency errors as the source of 40–67% of acute MTX toxicity admissions, [3][4] reinforcing that the clinical phenotype observed in our series represents the predominant real-world presentation, not an outlier.

3.4 Management Principles

The therapeutic hierarchy in acute MTX toxicity rests on four simultaneous pillars: (i) immediate MTX discontinuation; (ii) leucovorin rescue; (iii) supportive haematological and anti-infective care; and (iv) close biochemical monitoring.

Leucovorin (folinic acid) bypasses DHFR inhibition by directly providing reduced folate, thereby restoring

nucleotide synthesis in normal tissues without rescuing malignant cells. [11] Per StatPearls (2023) and the NCBI recommendations, leucovorin should be initiated at 10 mg/m² IV every 6 hours for inadvertent overdose and continued until serum MTX levels fall below 10^{-8} mol/L, with serial 24-hourly MTX level monitoring where available. [11] In our resource-constrained setting, serum MTX levels were unavailable; we therefore administered leucovorin until haematological normalisation-a pragmatic approach supported by published case series from similar settings. [12]

For severe neutropenia (ANC < 1,000/mm³) or consistent downward trend in total leucocyte count, G-CSF should be added; the combination of G-CSF with leucovorin has been shown to accelerate leukopoietic reconstitution and may be life-saving. [2][13] Case 3's concurrent lower respiratory tract infection exemplifies the four-fold increased risk of septicaemia when neutropenia and mucositis coexist, as documented by Pearce and colleagues. [9] Broad-spectrum antibiotic and empiric antifungal cover should therefore be initiated promptly whenever fever accompanies cytopenia.

For serum MTX levels exceeding 1 µmol/L at 48 hours (predominantly in high-dose or severe renal failure contexts), glucarpidase-an enzyme that hydrolyses MTX to inactive metabolites-should be considered. Urinary alkalinisation (targeting urine pH > 7.0) and aggressive hydration (3 L/m²/day) facilitate renal MTX clearance and reduce nephrotoxicity. [6]

Table 2. Stepwise Management Protocol for Acute MTX Toxicity (Frequency Error)

Step	Intervention	Details / Targets
1	MTX Cessation	Immediate discontinuation of all MTX doses
2	Leucovorin Rescue	IV 20 mg q6h Day 1 → 10 mg q6h until haematological normalisation (or MTX level < 10^{-8} mol/L)
3	Hydration + Alkalinisation	IV fluids 3 L/m²/day; IV sodium bicarbonate to target urine pH > 7.0
4	G-CSF (if neutropenia)	Filgrastim 300 mcg SC daily if ANC < 1,000/mm³ or declining trend
5	Antibiotics / Antifungals	Broad-spectrum IV antibiotics + antifungal prophylaxis if febrile neutropenia
6	Transfusion Support	Packed RBCs (Hb target ≥ 7.5 g/dL); Platelets if < 20,000/cmm or bleeding
7	Glucarpidase	Consider if MTX level > 1 µmol/L at 48h (predominantly high-dose / renal failure contexts)
8	Monitoring	CBC, LFTs, serum creatinine q12–24h; serial MTX levels (if available) until < threshold

3.5 Prevention – The Paramount Imperative

The most striking feature of this case series is that all three episodes of toxicity were entirely preventable. Evidence-based prevention operates across three domains:

Patient Education: Verbal instructions alone are insufficient. Written, illustrated weekly dosing cards in the patient's vernacular language, calendar-based blister pack dispensing (dispensing only seven tablets labelled with specific days of the week), and reinforcement of the 'once per week only' rule at every prescription renewal have been shown to reduce dosing frequency errors significantly. [14]

Prescriber and Pharmacist Vigilance: The AAD/National Psoriasis Foundation guidelines stipulate that MTX prescriptions in dermatology should explicitly state 'once weekly' on every written prescription, and that community pharmacists should independently verify frequency before dispensing. [15] MTX has been classified as a high-alert medication by ISMP precisely because frequency errors are frequent and potentially fatal. [3]

Folic Acid Co-prescription: Supplemental folic acid 1–5 mg daily (given on non-MTX days) reduces mucosal and haematological toxicity without compromising therapeutic efficacy, and should be co-prescribed universally. [15]

Monitoring: Baseline and quarterly CBC, liver function tests, and serum creatinine are recommended, with additional monitoring after each dose escalation. Higher-risk patients (elderly, CKD, polypharmacy) warrant monthly surveillance during the first six months. [10][15]

4. CONCLUSION

This case series contributes to the growing body of evidence establishing inadvertent daily dosing as the dominant, preventable mechanism of acute MTX toxicity in dermatological practice. The stereotyped clinical phenotype-mucocutaneous ulceration as the harbinger, followed by haematological compromise-provides clinicians with an actionable diagnostic framework. Prompt leucovorin rescue, even in settings without serum MTX level monitoring, yields excellent outcomes. Universal recovery in our three patients-spanning a spectrum of severity, age, and comorbid burden-corroborates the >80% recovery rates documented in the contemporary literature when management is initiated without delay.

The imperative for patient education cannot be overstated. In resource-limited environments where prescription literacy is variable, prescribers must assume responsibility for ensuring patients understand that MTX is a once-weekly drug, no less explicitly than they would counsel patients about insulin or anticoagulant safety. Illustrated weekly dosing cards, calendar blister packs, pharmacist verification, and mandatory folic acid co-prescription are practical, low-cost interventions capable of preventing episodes such as those presented here. Sensitisation of general practitioners, emergency physicians, and community pharmacists to the early mucocutaneous

warning signs of MTX toxicity will further compress the recognition-to-treatment interval and reduce morbidity in future cases.

Author Contributions, Ethics and Declaration

Author Contributions: Dr. Vijay A: conception, Dr. Elambarithi M: clinical management , : Dr. Yeddula Pranay Raja , Dr. Vijay A: data collection , Dr.Preethi ,Dr. Vimalaadhityan S ,Dr Vijay A: manuscript drafting, **Dr. Nirmala Devi Chandrasekaran** :conception, Literature review, final approval and supervision

Ethics Statement: This retrospective case series was conducted in accordance with the Declaration of Helsinki. Informed written consent was obtained from all three patients for publication of their anonymised clinical information.

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Data Availability: De-identified patient data supporting the findings are available from the corresponding author upon reasonable request.

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