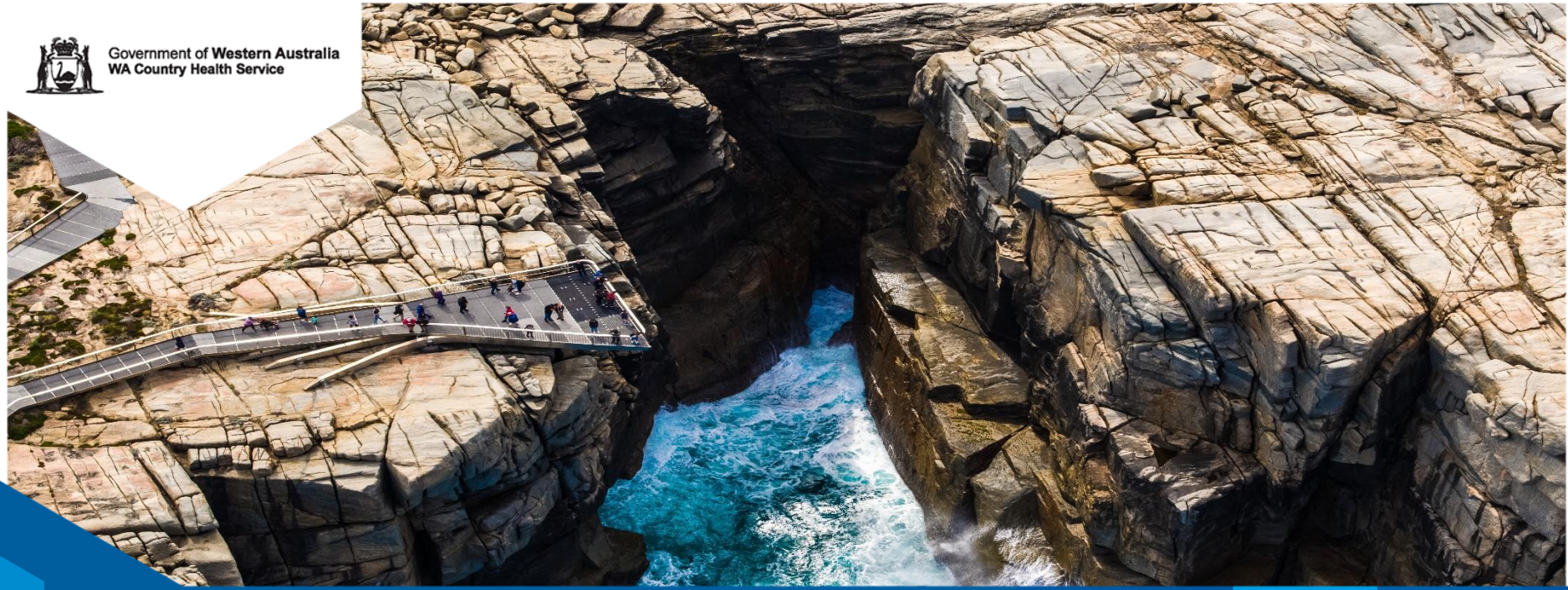
Government of Western Australia
WA Country Health Service



WARPW 2025 PERTH

Managing the Unfamiliar: A Complex Rash in Rural Practice

Date: 18.10.2025

Presenter: Dr Eduard NOVAK

Region: Geraldton Hospital

Government of Western Australia
WA Country Health Service

Acknowledgement of Country

The WA Country Health Service acknowledges the traditional custodians throughout Western Australia and their continuing connection to the land, waters and community. We pay our respects to all members of the Aboriginal communities and their cultures; and to Elders both past and present and emerging.

PRIMUM NON NOCERE

"FIRST, DO NOT HARM"

ARS LONGA, VITA BREVIS

"ART LONG, LIFE SHORT"

WHY RURAL IS SPECIAL?

Lower health literacy *→ patients often misunderstand conditions and long-term medicines*

Poor access to specialists

Long distances for follow-up & fragmented monitoring *→ lacking regular safety checks*

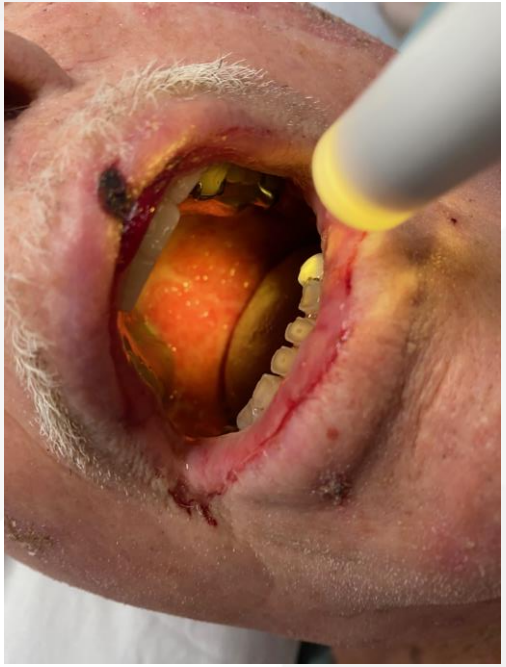
Limited resources for investigations *→ reliance on clinical judgement when tests are unavailable*

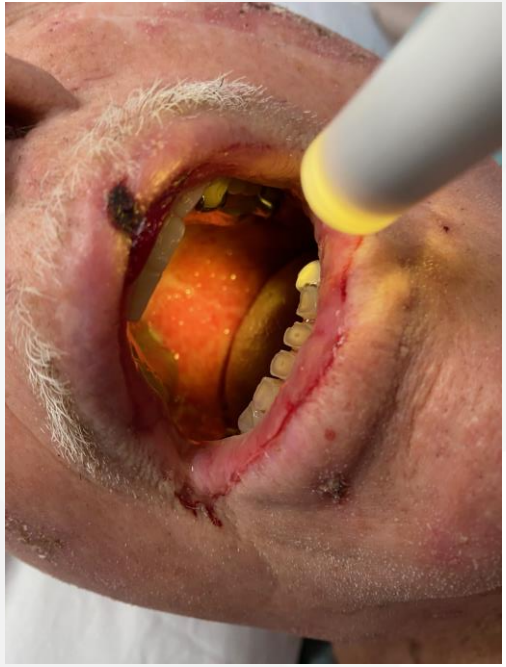
Fragmented medication monitoring *→ chronic therapies may lack regular safety checks*

Comorbidities & polypharmacy *→ responsibility for first stabilisation with broad differential*

Rural physicians must balance *broad differentials*
with limited support, making early recognition and decisive action critical

82M PRESENTED WITH PAINFUL ORAL ULCERS

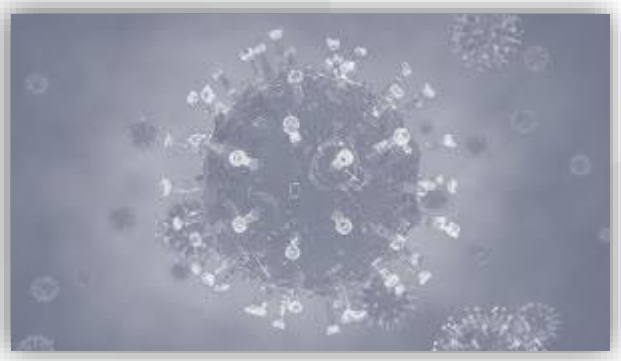




- extensive mucosal ulceration
- erosions on the inner lips and gingiva
- inflamed friable mucosa
- angular cheilitis/crusting at lip margins

** At the initial presentation, lesions may have appeared less extensive than shown here*

SWAB CONFIRMED HSV-1



Discharged home on antivirals

Broad differential for “simple” herpes

- ***Infective**: **HSV**, bacterial superinfection, candidiasis*
- ***Inflammatory/immune**: Aphthous ulcers, Behçet’s, vasculitis*
- ***Drug-related/toxic**: chemotherapy, NSAIDs, antibiotics*
- ***Haematological**: Neutropenia, anaemia, leukaemia*
- ***Other**: Trauma, nutritional deficiencies (B12, folate, iron)*

SECOND PRESENTATION – 2 DAYS LATER

The **mouth ulcers** are not improving:

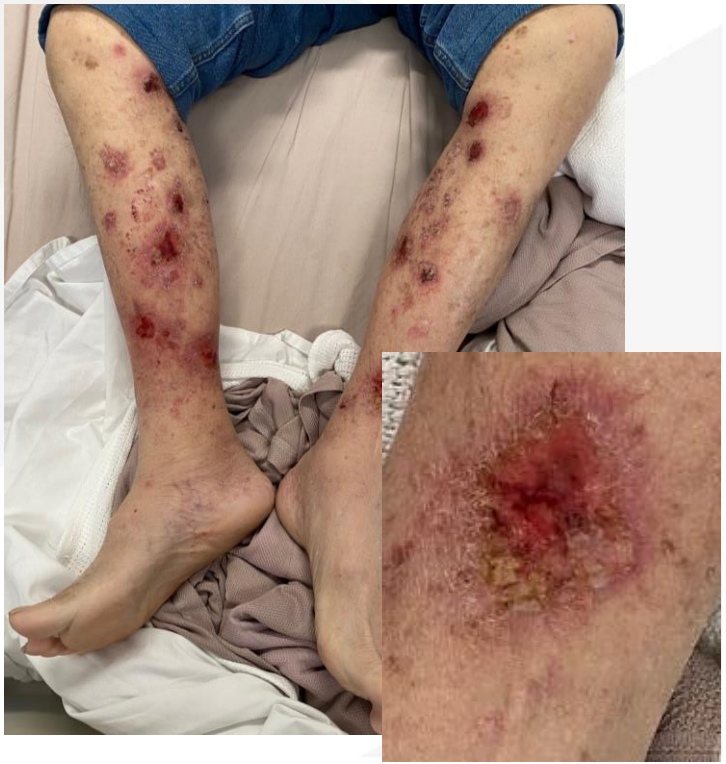
- unable eat and drink due to pain

He revealed that he has had **rash on lower legs** “for years” and it is also worse:

- multiple ulcerated plaques

- haemorrhagic crusts

- surrounding erythema



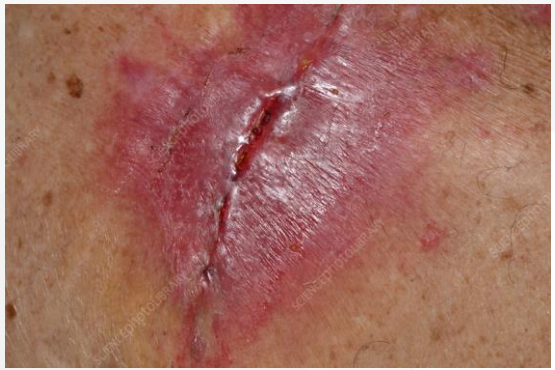
ANY OTHER RASH, SIR?

ANY OTHER RASH, SIR?

Yes, doctor!

*- a recently **excised lesion on the back**, with stitches removed 2 days earlier*

- post-op scar mildly erythematous and swollen, not impressive — possibly mild cellulitis



ANY OTHER RASH, SIR?

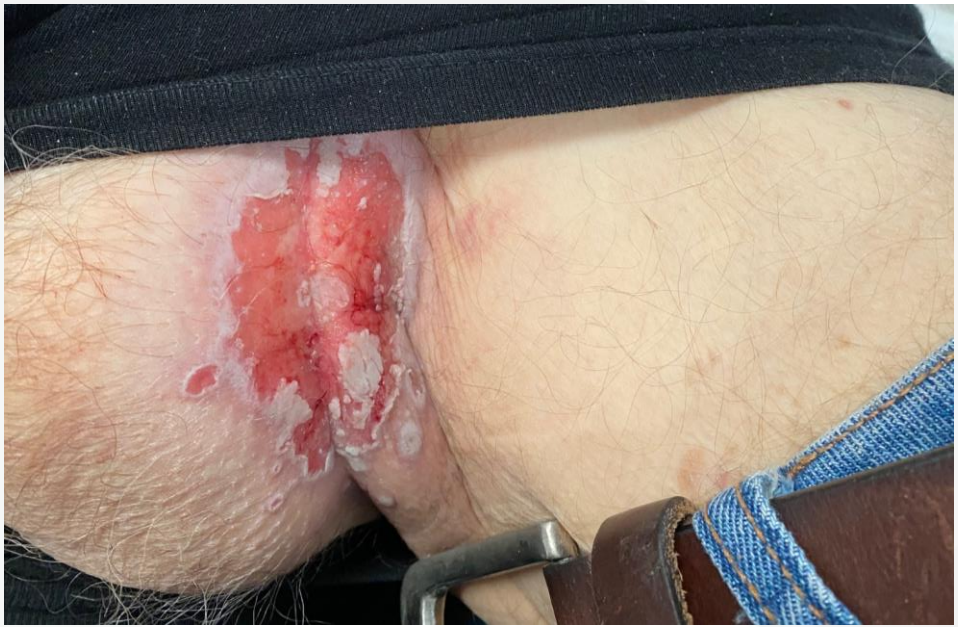
ANY OTHER RASH, SIR?

Yes, doctor!

*- in the **inguinal fold***

- large, erythematous, well-demarcated ulcer

*- with **superficial erosions**, fibrinous exudate and irregular whitish patches*



A COMPLEX RASH

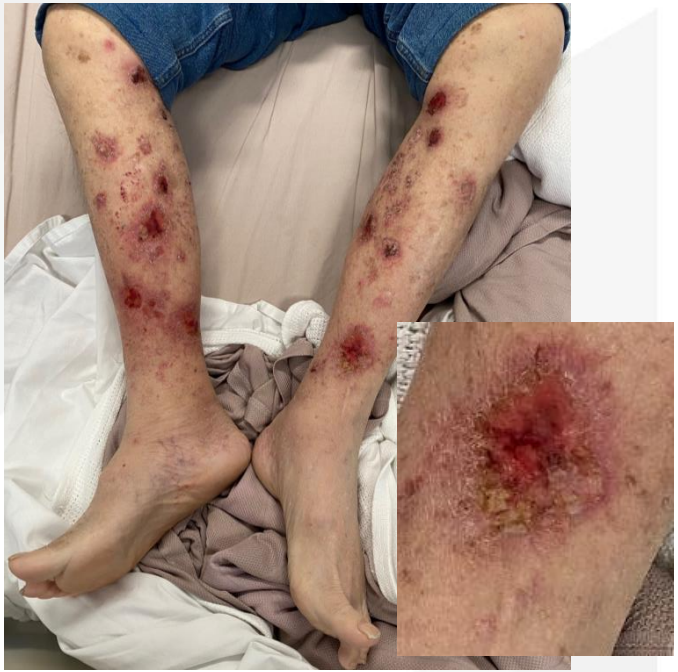
- *Oral mucositis* -> ? HSV
- *Chronic lower-leg ulcers* - ? Disseminated superficial actinic porokeratosis*
- *Post-op wound on the back* -> ? Cellulitis
- *Groin lesion* -> ? Fungal

***Multiple concurrent lesions** across different sites made it difficult to determine whether this was infection, vasculitis, drug reaction, or malignancy-related*

** DSAP is an AD inherited keratinisation disorder that causes discrete dry patches on the arms and legs, its frequency in affected families increases steadily with age*

DISSEMINATED POROKERATOSIS

Plaque of squamous cell carcinoma on left shin, on a background of longstanding DSAP



https://www.dermcoll.edu.au/atoz/porokeratosis/

PATIENT HISTORY – KEY POINTS

- **82-year-old man with multiple comorbidities**
  - *Rheumatoid arthritis (on long-term methotrexate 20mg ?weekly with folic acid)*
  - *COPD, AVR, HTN, OSA*
  - *Past asbestos exposure → pleural thickening & round atelectasis*
- **Chronic issues**
  - *Longstanding rash on lower legs (assumed DSAP, never biopsied)*
  - *History of recurrent skin lesions removed by GP*
  - *Anaemia and neutropenia noted 1 year prior, not investigated further*
- **Recent deterioration**
  - *Progressive oral ulcers → 2/7 treated with antivirals, confirmed HSV-1*
  - *Worsening skin lesions on legs, groin lesion, post-op back wound*
  - *Functional decline, weight loss (~10 kg), poor oral intake*

EXAM & INVESTIGATIONS – KEY POINTS

Examination

- *Oral*: multiple painful ulcers, gingivitis, difficulty eating
- *Skin*: longstanding ulcerated/scabbed lesions on legs, new groin rash, mild post-op back wound erythema
- No conjunctivitis or urethritis
- Mild *weight loss*, fatigue, dehydrated appearance

Laboratory Findings

- *Pancytopenia*: Hb ~80, Plt ↓ to 50, Neutrophils ↓ <1
- *Renal impairment*: Cr ↑ 148, eGFR ↓ 37, alb 34
- *Inflammation*: CRP 142, ESR >90
- *Electrolytes*: Hyperkalaemia (K 5.7), metabolic acidosis (bicarb 16)

Other investigations:

- *CXR*: Bibasal atelectasis and coarsened bronchovascular markings
- *Skin biopsy* (leg): Lichenoid inflammatory process with keratinocyte atypia
- *Bone marrow*: Granulocytic maturation arrest at promyelocyte stage; erythroid atypia

MEDICAL SCHOOL REMINDERS

- **Undress the patient** → skin clues may change the whole diagnosis
- **Explore patient & family beliefs** → long-standing "diagnoses" may be assumptions, not confirmed (e.g., DSAP in this case)
- **Take a thorough medication history** → clarify what is actually taken, who manages it, and how reliably
- **Actively search for collateral history** → from family, GP, pharmacy, past records
- **Re-examine often** → rashes, ulcers, and labs evolve rapidly
- **Don't anchor on first diagnosis** → HSV confirmed, but broader picture revealed toxicity
- **Think systems, not symptoms** → mouth ulcers + pancytopenia + renal dysfunction = multisystem red flags

METHOTREXATE TOXICITY 1

Mucocutaneous manifestations

- Painful oral ulcers, **mucositis**, gingivitis
- Cutaneous eruptions: erosive, vasculitic-like, or lichenoid reactions; **may mimic Stevens–Johnson Syndrome or drug hypersensitivity syndromes**

Hematologic abnormalities

- **Pancytopenia** due to bone marrow suppression (neutropenia, anemia, thrombocytopenia)
- Characteristic maturation **arrest at promyelocyte stage** on bone marrow examination

Gastrointestinal involvement

- Nausea, vomiting, diarrhea
- ***Stomatitis often heralds systemic toxicity***

MTX SKIN REACTIONS: LITERATURE REVIEW

- The review included 31 descriptive studies, covering **38 patients** (12-78yo) taking methotrexate for conditions like rheumatoid arthritis, ankylosing spondylitis, psoriasis
- Idiosyncratic nature of some reactions (i.e., not strictly dose-dependent) means they can **occur even with "standard" low doses**, which can lead to misattribution to other aetiologies
- **Overlap with other skin disorders** (psoriasis flares, drug rashes, idiopathic vasculitis) complicates clinical attribution, other diagnoses (TEN / SJS, vasculitis) considered first
- In many cases, cutaneous reactions occurred alongside **mucosal involvement** (oral ulcers, stomatitis), **hepatotoxicity**, and **cytopenias**
- Lack of **prompt biopsy** or immunofluorescence in some cases delayed confirmation
- In most reports, **immediate MTX withdrawal** plus supportive therapy (topical steroids, anti-inflammatory agents, folinic/folate rescue) led to improvement.

Zuber M, Harikrishna, Vidhyashree, et al. Methotrexate related cutaneous adverse drug reactions: a systematic literature review. *J Basic Clin Physiol Pharmacol*. 2021;33(5):549-565. Published 2021 Oct 27. doi:10.1515/jbcpp-2021-0165

LOW-DOSE MTX-INDUCED CYTOPENIA

- Meta-analysis (30 RCTs, 3,858 RA patients, MTX + folic acid): cytopenias are **uncommon with monitoring and folate** (<5%)
- A **triggering factor** is found in almost two thirds of cases (dehydration, infection, renal decline)
- Frequently due to MTX **medication errors**
- **Older patients and oral dosing** are at higher risk of MTX medication errors

- Vanni KMM, Lyu H, Solomon DH. Cytopenias among patients with rheumatic diseases using methotrexate: a meta-analysis of randomized controlled clinical trials. Rheumatology (Oxford). 2020;59(4):709-717. doi:10.1093/rheumatology/kez343
- Lalevée S, Lebrun-Vignes B, Simon C, Laugier D, Fardet L; French Network of Regional Centres of Pharmacovigilance. Cytopenia induced by low-dose methotrexate: An analysis of 433 cases from the French pharmacovigilance database. Eur J Intern Med. 2019;67:97-101. doi:10.1016/j.ejim.2019.07.016

METHOTREXATE TOXICITY 2

Hepatic effects

- Elevated transaminases
- With long-term use: risk of fibrosis and cirrhosis

Renal impairment

- **Impaired clearance** increases serum MTX levels → **higher toxicity risk**
- Common in elderly, dehydrated, or patients on nephrotoxic drugs

Pulmonary manifestations

- **MTX-induced pneumonitis**: acute or subacute, with cough, dyspnoea, fever, and diffuse infiltrates
- ? Interstitial lung disease / fibrosis: risk higher in older patients, prior lung disease, or asbestos exposure

LOW-DOSE MTX AND KIDNEYS

- Large, randomized, double-blind, placebo-controlled trial of LD-MTX for the prevention of atherosclerotic cardiovascular events
- N=4,786; LD-MTX 15–20 mg/week + folic acid vs placebo; median follow-up 23 months; excluded CrCl <40 ml/min
- Higher risk for adverse events such as **hepatotoxicity, pneumonitis, and skin cancer** compared with placebo
- Less eGFR decline with LD-MTX vs placebo
- In patients with normal RF or mild–moderate CKD, LD-MTX (with folate, appropriate monitoring) is **kidney-safe** when fluid status and drug interactions tightly managed

Sparks JA, Vanni KMM, Sparks MA, et al. Effect of Low-Dose Methotrexate on eGFR and Kidney Adverse Events: A Randomized Clinical Trial. J Am Soc Nephrol. 2021;32(12):3197-3207. doi:10.1681/ASN.2021050598

LUNG TOXICITY: LITERATURE REVIEW

- Methotrexate is associated with a **potentially fatal acute methotrexate pneumonitis**
- **Important to differentiate** acute MTX pneumonitis (real risk, potentially fatal) from chronic fibrotic lung disease (not MTX-driven)
- MTX has long been **suspected** to cause chronic pulmonary **fibrosis**
- Review: *11 supported MTX–fibrosis link (low quality, serious bias) and 11 refuted the link (higher quality: cohort studies, meta-analyses with >10,000 patients showed* ***no causal relationship***
- In RA–ILD, **MTX use was linked to improved survival**
- Withdrawal of MTX for fear of fibrosis is not evidence-based

Quah E, Amoasii C, Mudawi T, Dawson J. Systematic literature review investigating whether methotrexate causes chronic pulmonary fibrosis. Future Healthc J. 2019;6(Suppl 2):4. doi:10.7861/futurehosp.6-2s-s4

BACK TO PATIENT: TIMELINE OVERVIEW

>12 years: chronic leg rash, presumed DSAP, never biopsied

1 year before presentation: bloods already showed anemia and neutropenia

6–12 months before presentation: lung CT showed concerning changes (pleural plaques, atelectasis, inflammatory opacities)

2–3 months before presentation: worsening leg ulcers and weight loss

2 weeks before presentation: oral HSV lip sore; started antivirals

At admission: severe mucositis, generalized ulcerating rash, pancytopenia, AKI, poor healing wound, groin fungal infection

Hospital course: biopsy confirmed drug effect; MTX ceased; folate, G-CSF, transfusions given

MTX MONITORING: GUIDELINES COMPARISON

Source	Baseline Monitoring	Ongoing Monitoring	Side Effect Management	Notes / Rural Relevance
NSW CEC – High-Risk Medicines (Oral MTX)	Clear documentation of dosing (weekly, not daily), FBC, LFT, renal function	**FBC, LFT, U&Es every 1–2 weeks** after initiation, then monthly; educate patient on red flags	Early: nausea, oral ulcers, rash. Serious: marrow suppression, pneumonitis, liver failure → stop MTX immediately	Rural: highlights importance of **patient counselling**, as access to urgent review may be delayed
UK Guideline (RA)	FBC, LFTs, renal function before start; chest X-ray if lung disease suspected	FBC, LFTs, U&Es every 2 weeks for 6 weeks → monthly for 3 months → every 2–3 months if stable	Dose adjust or cease if WCC <3.5, neutrophils <1.6, platelets <140, rising ALT/AST >2x ULN	Strong emphasis on **shared care model** between GP & specialist, often difficult rurally
US (American Family Physician)	Baseline: CBC, LFTs, renal, hepatitis serology, TB screen, chest imaging if indicated	CBC, LFTs, U&Es every 2–4 weeks x3 months → every 8–12 weeks	Reinforce patient education; stop for cytopenia, mucositis, liver injury, pneumonitis	Rural: counselling patients to recognise **early warning signs** is crucial
EULAR / Rheumatology Recommendations	Baseline labs + infection screen	Regular FBC, LFTs, U&Es (no exact interval, but consistent with UK/US)	Emphasises structured monitoring and patient involvement	Highlights that **international consensus** expects MTX monitoring as **standard of care**

AREAS FOR IMPROVEMENT

Prescribing and Indication

- MTX commenced after a single rheumatology consultation for vague hip pain
- Patient reported no meaningful benefit, yet continued therapy for >5 years
- No evidence of ongoing specialist review, patient educations

Monitoring and Awareness

- Unclear ownership of monitoring: not tracked by specialists, and GPs may have assumed oversight was elsewhere
- Patient unaware of MTX side effects or monitoring requirements
- Wife was believed to “manage medications,” but she did not know the drug names or purpose

Rural Practice Context

- High GP turnover and reliance on locums → fragmented follow-up
- Distance from subspecialty services limits timely review and continuity of care
- In rural communities, health literacy is often lower, making self-advocacy difficult

TAKE-HOME MESSAGES

Think broadly in rural practice: Multisystem presentations may mask drug toxicity; always consider medication as a potential culprit

Methotrexate toxicity is rare but serious: Oral ulcers, rash, cytopenias, and renal impairment can herald life-threatening complications

Monitoring saves lives: Safe MTX use requires clear responsibility for prescribing, routine blood tests, and patient education

Rural complexity matters: Limited access to subspecialties, fragmented continuity of care, and health literacy gaps increase risk

Back to basics: Undress the patient, ask open questions, explore self-beliefs, and actively review medications at every visit

Shared vigilance: Clinicians, patients, carers, and systems must collaborate to detect toxicity early and prevent harm

AUSTRALIAN COMMISSION
ON SAFETY AND QUALITY IN HEALTH CARE

4 MEDICATION SAFETY

This standard aims to ensure that clinicians safely prescribe, dispense and administer appropriate medicines, and monitor medicine use. It also aims to ensure that consumers are informed about medicines, and understand their own medicine needs and risks.

The standard in the second edition is largely the same as the standard in the first edition, with one addition for health service organisations to assess patients' ongoing medication management and review their medication.

Why the standard is important

Medicines are the most common treatment used in health care. Although appropriate use of medicines can improve health, medicines can also be associated with harm.[1] Harm may occur because the wrong medicine is prescribed, supplied or used, or because the right medicine is dosed or used incorrectly.

It is estimated that 2–3% of hospital admissions are related to medicines.[2] This means that at least 230,000 people were admitted to hospital because of a medicine incident in 2011–12. Some groups have even higher rates of hospital admission related to medicines – for example, for those aged 65 years and over, up to 30% of admissions are related to medicines.[1]

The cost of such incidents to patients and the healthcare system is significant. A study published in 2009 estimated that medicine-related hospital admissions in Australia cost $660 million.[3] Estimates for 2011–12 place this figure closer to $1.2 billion.[1]

Up to 50% of medicine-related hospital admissions are potentially avoidable.[3] Making processes systematic and standardised can improve medication safety. This standard sets out these processes, and the elements that are needed in governance and communication strategies to ensure medication safety.

REFERENCES

- *Quah E, Amoasii C, Mudawi T, Dawson J. Systematic literature review investigating whether methotrexate causes chronic pulmonary fibrosis. Future Healthc J. 2019;6(Suppl 2):4*
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- *Lalevée S, Lebrun-Vignes B, Simon C, Laugier D, Fardet L; French Network of Regional Centres of Pharmacovigilance. Cytopenia induced by low-dose methotrexate: An analysis of 433 cases from the French pharmacovigilance database. Eur J Intern Med. 2019;67:97-101. doi:10.1016/j.ejim.2019.07.016*
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- *Smolen JS, Landewé RBM, Bergstra SA, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis. 2023;82(1):3-18*

THANK YOU FOR YOUR ATTENTION!
ANY QUESTIONS?

COMMUNITY | COMPASSION | QUALITY | INTEGRITY | EQUITY | CURIOSITY