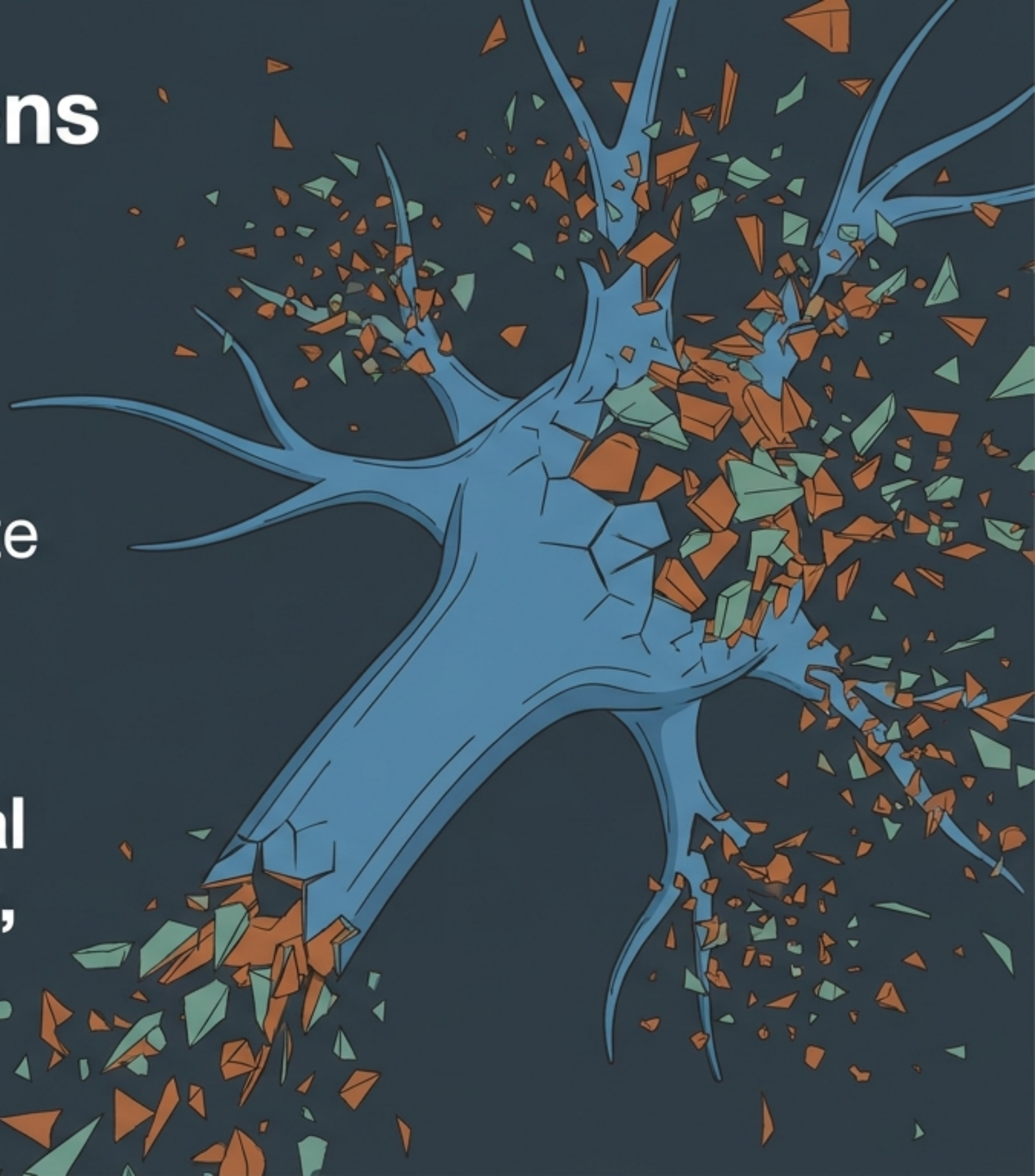
Systemic Disease Poisons the Nervous System: A Clinical Guide for Australian Practice

Screening, diagnosis, and acute rescue protocols for **metabolic neurotoxicity.**

Designed for **Australian General Practice, Emergency Medicine, and Internal Medicine.**



The Australian Neurologic Burden

1.7M+

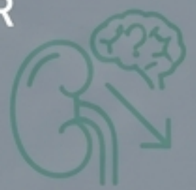
Australians with Diabetes

30–50% develop peripheral neuropathy by the time of Type 2 diagnosis.

1 in 10

Adults with Chronic Kidney Disease (CKD)

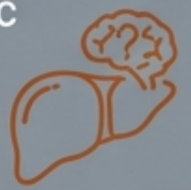
Uraemic encephalopathy threatens patients with rapidly declining eGFR (<15 mL/min).



7,000+

Annual Liver Disease Deaths

30–45% of patients with decompensated cirrhosis will experience hepatic encephalopathy.



Pathophysiology: The Mechanisms of Injury

The Sugar Burn

Systemic: Hyperglycaemia

Toxin: Sorbitol (Polyol pathway) + Advanced Glycation End-products (AGEs)

Impact: Endothelial dysfunction -> Vasa Nervorum Ischaemia -> Axonal demyelination

The Ammonia Swell

Systemic: Portosystemic Shunting (bypassing the urea cycle)

Toxin: Ammonia (NH3) + Manganese

Impact: Astrocytes convert NH3 to glutamine -> Astrocyte Swelling -> Cerebral Oedema

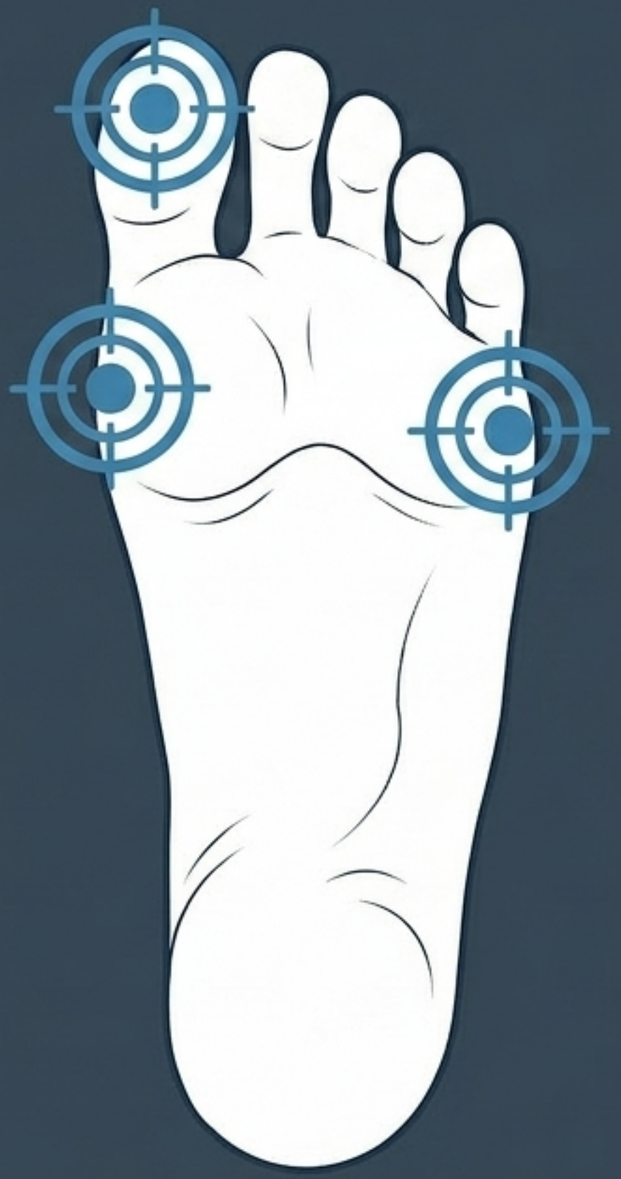
The Toxin Buildup

Systemic: Glomerular Filtration Failure

Toxin: Middle Molecules, Indoxyl Sulphate, Urea

Impact: Blood-Brain Barrier disruption + Neurotransmitter synthesis failure

The Annual Primary Care Screening Mandate



Plantar Screening Sites

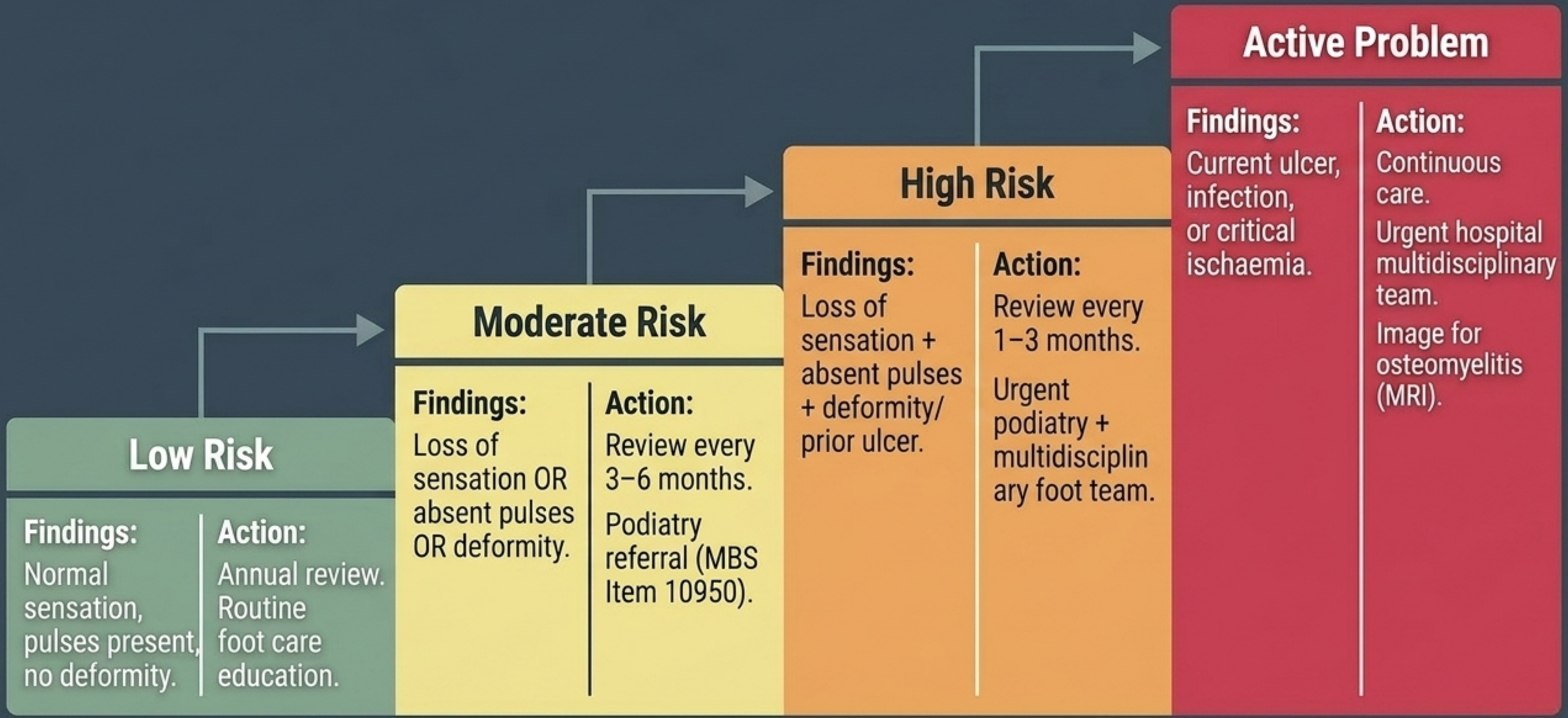
The Primary Care Toolkit:

- ☑ **10g Semmes-Weinstein Monofilament:** Test the 3 mapped plantar sites. Inability to detect = abnormal.
- ☑ **128 Hz Tuning Fork:** Assess vibration sense at the dorsum of the great toe.
- ☑ **Reflex Hammer:** Compare ankle reflex to knee reflex (absent/diminished is significant).

Clinical Action Requirement

Annual screening is **mandatory**. Document assessment in GP Management Plans (MBS Item 721) and Team Care Arrangements (MBS 723). Consider baseline Nerve Conduction Studies (MBS 11600-series).

Diabetic Foot Risk Stratification & Action Protocol

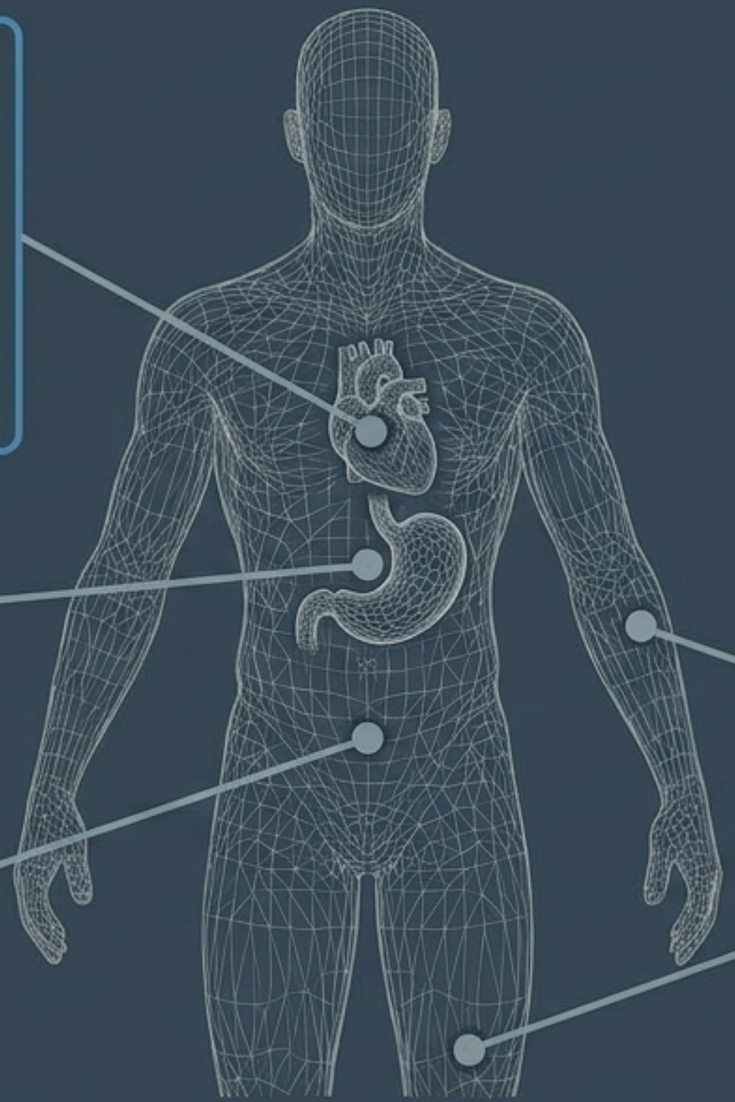


The Hidden Threat of Autonomic Neuropathy

Cardiovascular Autonomic Neuropathy (CAN)
Orthostatic hypotension (Drop >= 20/10 mmHg).
Resting tachycardia.
Fix: Midodrine 2.5–10 mg PO TDS (specialist) or Fludrocortisone.
⚠ **WARNING:** Severe CAN carries a 50% 5-year mortality rate.

Gastroparesis
Erratic glucose, early satiety.
Fix: Domperidone 10 mg PO TDS (PBS) or short-term Metoclopramide.

Genitourinary
Erectile dysfunction or neurogenic bladder.
Fix: Sildenafil 50–100 mg PO PRN (PBS Authority) or self-catheterisation.



Sudomotor
Anhidrosis of feet, gustatory sweating.
Fix: Glycopyrrolate cream, emollients.

Painful Neuropathy: First-Line Pharmacotherapy

Amitriptyline (Endep)

- **Dose:** 10–25 mg nocte (titrate to 75–150 mg).
- **Renal:** Caution in CKD (lowest dose).
- **Hepatic:** Reduce or avoid.
- **PBS:** General Benefit.

Duloxetine (Cymbalta)

- **Dose:** 30 mg OD (titrate to 60 mg OD).
- **Renal:** Avoid if eGFR < 30.
- **Hepatic:** Contraindicated.
- **PBS:** General Benefit.

Pregabalin (Lyrica)

- **Dose:** 75 mg BD (titrate to 150–300 mg BD).
- **Renal:** Strict titration (eGFR <15: 25mg OD).
- **Hepatic:** No adjustment required.
- **PBS:** Authority Required.

Gabapentin (Neurontin)

- **Dose:** 300 mg OD, titrate up to 600 mg TDS.
- **Renal:** Strict renal titration.
- **Hepatic:** No adjustment required.
- **PBS:** Authority Required.

Focal Diabetic Mononeuropathies

CN III Palsy

Context: Ischaemic injury to vasa nervorum.

RED FLAG: Pupil-sparing is classic, BUT up to 33% involve the pupil. If the pupil is involved, order an URGENT MRI/MRA to exclude a posterior communicating artery (PCOM) aneurysm.

CN VII (Bell's Palsy)

Action: Prednisolone 50 mg PO daily for 10 days if presented within 72 hours.

Management: Eye lubricant drops and tape at night.

Carpal Tunnel Syndrome (Median Nerve)

Action: Nocturnal splinting.

Management: Corticosteroid injection (MBS rebated) or surgical release if refractory.

Clinical Pearl: Most diabetic mononeuropathies recover spontaneously over 3–6 months with optimized HbA1c.

Grading Hepatic Encephalopathy: The West Haven Criteria

Covert / Mild
(Grades I–II)

Symptoms: Trivial lack of awareness, lethargy, altered sleep, obvious personality change. Asterixis present in Grade II.

Setting: Outpatient / Ward.

Action: Diagnose via psychometric testing.

Overt / Marked Confusion
(Grade III)

Symptoms: Somnolence to semi-stupor, marked confusion, bizarre behaviour, prominent asterixis.

Setting: Inpatient Ward / Hepatology.

Action: Require daily ammonia monitoring.

Coma
(Grade IV)

Symptoms: Comatose, decerebrate posturing, unresponsive to pain. High cerebral oedema risk.

Setting: ICU. Intubation required.

Action: Immediate transplant assessment (Alert: MELD score ≥ 15 warrants transplant referral).

Hunting the Precipitants

90% of HE has an identifiable trigger

Trigger: Infection (SBP, UTI, Pneumonia)

- **Action:** Diagnostic ascitic tap (PMN > 250 = SBP), blood cultures.

Trigger: GI Bleeding (Variceal/Ulcer)

- **Action:** Urgent endoscopy, Ceftriaxone 1g IV for SBP prophylaxis.

Trigger: Constipation

- **Action:** Titrate Lactulose to 2-3 soft stools/day.

Trigger: Electrolyte Shift (Low K+, Low Na+)

- **Action:** Cautious correction, halt aggressive diuresis.

Trigger: Medications (Opioids, Benzos)

- **Action:** Cease sedatives. Flumazenil 200 µg IV (use with extreme caution).

Trigger: Renal Impairment

- **Action:** Volume assessment, rule out hepatorenal syndrome.

The Hepatic Encephalopathy Treatment Cascade

Step 1: Eliminate the Trigger

Identify and treat the underlying precipitant immediately (infection, bleed, drugs).

Step 2: Ammonia Clearance

Administer Lactulose 20–30 mL PO/NG every 2–4 hours.
Target: 2 to 3 soft stools per day.
(Use 200mL in 800mL water PR enema if patient is nil by mouth).

Step 3: Gut Flora Modulation

Add Rifaximin 550 mg BD (PBS Authority Required).
Proven to reduce HE recurrence by 50%.

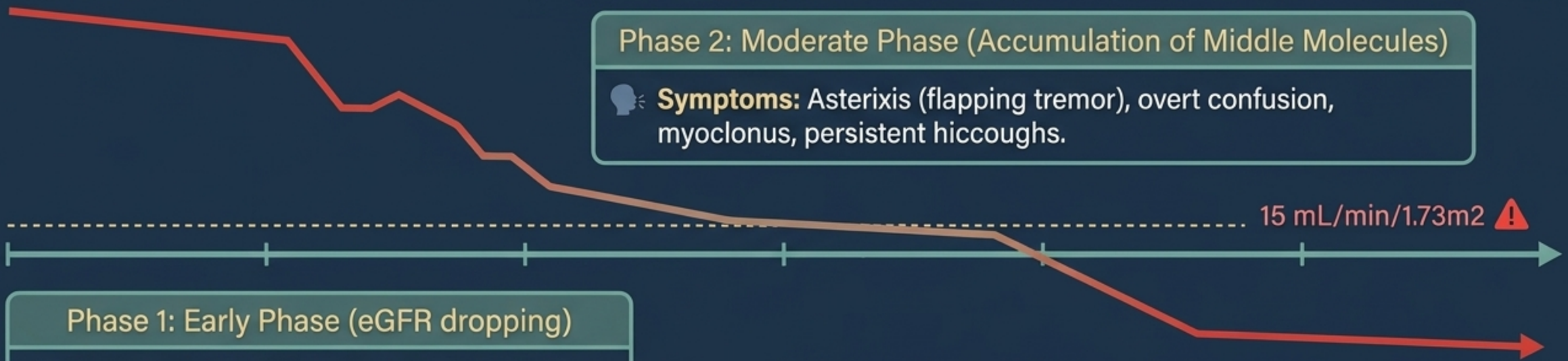
CLINICAL MYTHBUSTER

DO NOT RESTRICT DIETARY PROTEIN.

Ensure 1.2–1.5 g/kg/day to prevent severe catabolism.

Vegetable and dairy proteins are preferred over animal protein.

Uraemic Encephalopathy: When the Filter Fails



Phase 1: Early Phase (eGFR dropping)

Symptoms: Fatigue, difficulty concentrating, irritability, nausea, anorexia.

Phase 2: Moderate Phase (Accumulation of Middle Molecules)

Symptoms: Asterixis (flapping tremor), overt confusion, myoclonus, persistent hiccoughs.

Phase 3: Severe Phase (Critical Toxicity, eGFR < 15)

Symptoms: Generalised tonic-clonic seizures, stupor, decerebrate posturing, coma.

Crucial Diagnostic Alert: Uraemic encephalopathy is a clinical diagnosis. Always perform a non-contrast CT Brain to exclude subdural haematoma, stroke, or mass lesion before attributing coma to uraemia.

Acute Uraemic Rescue & Management Protocol

Definitive Therapy

- Initiate or escalate Renal Replacement Therapy (RRT).
- Intermittent Haemodialysis (standard).
- Continuous Renal Replacement Therapy (CRRT) in hemodynamically unstable ICU patients.

Seizure Control

- **First line:** Levetiracetam 1,000–1,500 mg IV (preferred, minimal hepatic metabolism, adjust for renal clearance).
- **Avoid:** Benzodiazepines (prolonged clearance) and Phenytoin (altered protein binding in uraemia).

Hyperkalaemia Control

- Calcium Gluconate 10% (10-20 mL IV over 10 mins) for cardioprotection.
- Insulin 10 units + 50mL 50% Dextrose IV to shift potassium intracellularly.

Nutritional Rescue

- Administer Thiamine 300 mg IV immediately if there is any suspicion of nutritional deficiency or alcohol use to prevent Wernicke encephalopathy.

Encephalopathy Differentiation Matrix

	Hepatic Encephalopathy	Uraemic Encephalopathy
Primary Precipitants	Infections (SBP), GI Bleed, Constipation.	Dropping eGFR (<15), missed dialysis, nephrotoxins.
Characteristic Motor Signs	Asterixis, Rigidity.	Asterixis, Myoclonus, Hiccoughs.
Seizure Risk	Low.	High (Tonic-Clonic).
First-Line Pharmacotherapy	Lactulose + Rifaximin.	IV Levetiracetam + Calcium Gluconate (for K+).
Definitive Cure	Liver Transplant (MELD >= 15).	Renal Replacement Therapy / Dialysis.

Aboriginal and Torres Strait Islander Health Considerations

Diabetes Burden

Type 2 Diabetes occurs at 3–4x the national rate, often onsetting before age 40.

Amputation rates are 3–6x higher due to delayed remote podiatry access.

Renal & Hepatic Burden

CKD rates are 2–3x higher.

High prevalence of Hepatitis B necessitates early vaccination and direct-acting antiviral integration.

Culturally Safe Interventions

- Utilize MBS Item 715 (Health Checks) for funded, comprehensive neurological screening.
- Engage with ‘Ring the Alarm’ foot screening programs driven by Aboriginal Health Workers.
- Support community-controlled on-country care models (e.g., The Purple House for dialysis).
- Utilize telehealth and RFDS to bridge the specialist access gap.

Complex Care: Special Population Matrix

- Tighter glycaemic targets required (Fasting <= 5.0, 1-hr post-prandial <= 7.4).
- Avoid Duloxetine (Cat C) and Pregabalin (Cat B3). Amitriptyline is Cat B2 (use caution).
- Acute Fatty Liver/HELLP requires immediate obstetric delivery.

- DPN screening begins at age 10 (or 2 years post-T1DM diagnosis).
- Avoid Rifaximin in HE for children < 12 years.
- Lactulose dose: 1-3 mL/kg/day.

- Start Amitriptyline at 5-10 mg to avoid severe anticholinergic burden and falls.
- Conduct regular Home Medicines Reviews (MBS 900) to strip away compounding sedatives.
- Distinguish covert encephalopathy from dementia and delirium.

- Post-transplant patients on calcineurin inhibitors (tacrolimus/cyclosporine) can present with direct neurotoxicity—do not confuse this with worsening HE.
- Maintain a high index of suspicion for atypical infection-triggered encephalopathy.

Rapid Clinical Scenarios

Problem: Painful Diabetic Polyneuropathy

Rx: Amitriptyline 25–75 mg nocte **OR** Duloxetine 60 mg OD **OR** Pregabalin 150 mg BD.

Action: Review efficacy at 4–8 weeks.
⏱ Optimise HbA1c.

Problem: Overt Hepatic Encephalopathy

Rx: Lactulose 20–30 mL PO/NG 2-4 hourly + Rifaximin 550 mg BD.

Action: Identify precipitant (tap ascites).
📋 Cease all sedatives.

Problem: Uraemic Seizures

Rx: Levetiracetam 1,000–1,500 mg IV + Thiamine 300 mg IV.

Action: Urgent nephrology consult for haemodialysis. Correct hyperkalaemia.

Problem: SBP Prophylaxis (Post-Variceal Bleed)

Rx: Ceftriaxone 1 g IV OD.

Action: Administer for 7 days, then switch to
📋 Norfloxacin 400 mg PO OD for secondary prophylaxis.

Clinical Guidelines & Primary Evidence Base

Guidelines

RACGP Management of Type 2 Diabetes (2020)

AASLD Hepatic Encephalopathy Practice Guidelines

NHMRC Chronic Kidney Disease Guidelines

Epidemiology & Trials

AIHW Diabetes and CKD in Australia Reports (2023)

Rifaximin efficacy (Bass et al., NEJM)

Intensive glycaemic control (DCCT/Steno-2)

Source Reference

Synthesized from Med2Date Clinical Guidelines:

Neurologic Complications of Systemic Disease

(Last updated May 2026)