

***Hidden in Plain Sight: Pyroglutamic Acidosis as A Cause of Unexplained Hagma*****John Gaul¹, Martin Thomas¹, Anup Bansal^{1*} and Kush Deshpande²**¹Department of Intensive Care Services, Westmead Hospital, Westmead, NSW2145, Australia²Department of Intensive Care Services, St George Hospital, Kogarah, NSW2217, Australia

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Abstract

Pyroglutamic acidosis is an infrequent cause of high anion gap metabolic acidosis (HAGMA). Also known as 5-oxoprolinemia, it is often under-recognised in critically ill patients however remains an important differential to consider. It results from the disruption of the glutathione cycle due to factors such as sepsis, medication use, and malnutrition. We present a case of acquired pyroglutamic acidosis in a 43-year-old female with chronic comorbidities and sepsis. The case illustrates multiple factors associated with 5-oxoproline accumulation and provides insight into the principles of management and safe reintroduction of contributing agents.

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Submitted: 23.07.2026**Accepted:** 23.08.2026**Published:** 23.09.2026**Introduction**

Pyroglutamic acid (also known as 5-oxoproline, 5-OP) is a metabolite in the glutathione cycle, present in nearly all human cells [1]. Disruption of this cycle through critical illness, medication interactions, or nutritional deficiencies can result in the accumulation of 5-OP, leading to high anion gap metabolic acidosis (HAGMA) [2,3]. Though infrequent, timely recognition and management are essential due to its reversible nature. This case report explores a clinical presentation of pyroglutamic acidosis in the setting of sepsis, chronic medication use, and malnutrition, and reviews the underlying biochemical mechanisms and approach to management.

Case Report

A 43-year-old female was brought to the Emergency department (ED) by ambulance from home with clinical features of septic shock. She had a 3-month history of progressive decline in her functional status with reduced oral intake. She was complaining of increasing lower limb pain due to worsening bilateral lower limb ulceration, nausea, vomiting and increasing pain prior to presentation to hospital. Her medical history included chronic lower limb ulcers, traumatic brain injury, epilepsy, and hypertension. Her regular medications included paracetamol, carbamazepine, and antihypertensives. She had difficulty in mobilising due

to chronic lower limb ulcers and was bedbound and reliant on full time carers for activities of daily living.

On presentation, she was febrile, tachycardic and hypotensive, with extensive sloughy, bilateral leg ulcers. Laboratory investigations revealed elevated inflammatory markers [white cell count (WCC) $16.7 \times 10^9/L$, c-reactive protein (CRP) 296 mg/L], severe hypoalbuminemia (14 g/L), hyponatremia (129 mmol/L), and pre-renal acute kidney injury (urea 14.3 mmol/L, Creatinine 137 $\mu\text{mol/L}$, eGFR 47 mL/min/1.73m²) and normal liver functions tests. She was resuscitated in ED with intravenous crystalloid fluids and started on flucloxacillin for presumed cellulitis as a source of septic shock. She was transferred to the Intensive Care Unit (ICU) for ongoing management of septic shock and renal failure. Due to persistent requirement of high dose of noradrenaline, antibiotics were escalated to meropenem to broaden the gram negative and gram-positive microorganism cover and flucloxacillin was ceased after two doses.

An arterial blood gas (ABG) revealed a compensated HAGMA: pH 7.38, HCO_3^- 12 mmol/L, base excess -11.3, anion gap 37 mmol/L, with normal lactate and ketones. Despite clinical improvement, serial ABGs showed persistent unexplained HAGMA. Her AKI resolved with fluid therapy and no other causes of HAGMA were found. Given her clinical context and risk factors, chronic use of paracetamol and underlying malnutrition, a presumptive diagnosis of pyroglutamic acidosis was made. A urine metabolic screen was sent, though results were pending at the time. Management included discontinuation of paracetamol, administration of isotonic sodium bicarbonate infusion (150 mmol), 5 units (100ml) of 20% intravenous albumin to assist with intravascular volume expansion. Meropenem was continued, noradrenaline was titrated to maintain MAP > 65 mmHg and was commenced on multivitamin supplementation (high dose thiamine -900mg/day). she was also encouraged to increase her oral nutritional intake. Within 48 hours, the patient showed marked clinical and biochemical improvement. Vasopressors were able to be ceased, oral intake was established, and markers of systemic inflammation improved (WCC 6.2, CRP 100). Repeat ABG showed resolution of HAGMA (pH 7.43, HCO_3^- 27 mmol/L, base excess 2.5, anion gap 16). Figure 1 shows the trends of these biochemical parameters.

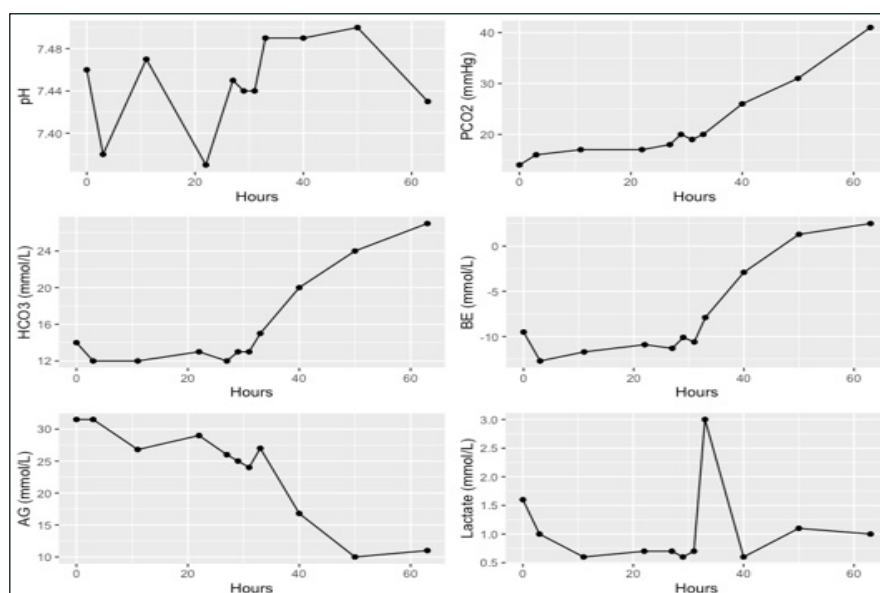


Figure 1: Trends of Biochemical Parameters

PCO₂: Partial Pressure of Carbon Dioxide, **HCO₃⁻:** Bicarbonate Concentration, **BE:** Base Excess, **AG:** Anion Gap

Paracetamol was reintroduced and she received a total dose of 5 g over the following week without recurrence of acidosis. Flucloxacillin was restarted two days after the resolution of HAGMA (2 g QID IV for 10 days, followed by oral therapy). Daily biochemical monitoring showed no further metabolic derangements. Urine metabolic screen returned two weeks later which showed marked elevation of urinary 5-oxoproline, confirming

the diagnosis of pyroglutamic acidosis.

Discussion

Pyroglutamic acid is a part of the glutathione cycle. Glutathione is an organic compound found in all cells in high concentrations – roughly 5mmol/L [1-3], and is vital to a range of functions including regulation of cellular proliferation, mitochondrial function, regeneration of vitamins C and E and neutralisation of free radicals [1]. The glutathione cycle plays a central role in detoxification, mitochondrial function and redox balance [4]. The enzymes involved in the γ -glutamyl cycle and the factors which block the various steps are shown in Figure 2 [5,6].

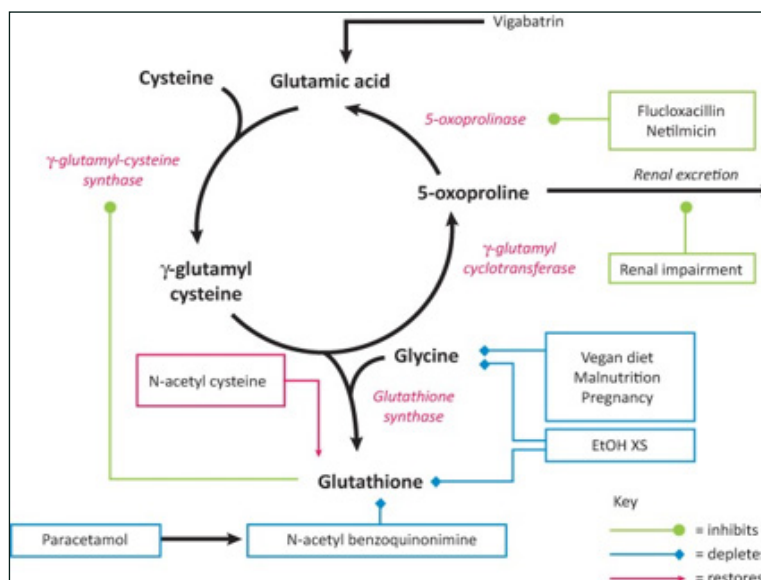


Figure 2: The γ -Glutamyl Cycle

EtOH XS: Excess Alcohol

Acquired Pyroglutamic acidosis is a rare but reversible cause of high anion gap metabolic acidosis (HAGMA) [7-11]. When glutathione is depleted as seen in patients with chronic paracetamol use, carbamazepine use (CYP enzyme upregulation), malnutrition (cysteine deficiency), sepsis (increased reactive oxygen radicals), the glutathione cycle is disrupted leading to excessive 5-oxoprolinone (5-OP) production [12,13]. The impaired metabolism of 5-OP due to flucloxacillin (which inhibits 5-oxoprolinase) and reduced renal clearance during acute kidney injury (AKI) further exacerbates its accumulation [14].

Our patient had multiple predisposing factors: chronic paracetamol use (>10 days) carbamazepine use, sepsis from lower limb cellulitis, AKI and hypoalbuminemia [15,16]. Long-term use of paracetamol caused glutathione depletion [17,18]. The lower limb cellulitis led to sepsis due to increased production of reactive oxygen species (ROS), which glutathione typically detoxifies in redox reactions to maintain oxidative balance. Our patient was also malnourished due to poor oral intake in the weeks leading up to admission exacerbated by vomiting whilst acutely unwell. This malnutrition led to decreased cysteine levels, which are required for glutathione production [19]. Thus, multiple factors causing increased glutathione utilization and decreased production due to substrate deficiency meant that glutathione could not be adequately replenished following utilization. This depletion disrupted the normal cycle and instead resulted in pyroglutamic acid accumulation.

Pyroglutamic acid also accumulates when it cannot be metabolized or cleared by the body [11]. Flucloxacillin a common antibiotic prescribed for skin and soft tissue infections, inhibits 5-oxoprolinase, which results in pyroglutamic acid accumulation [13,15]. In our case, the patient received two doses of flucloxacillin within 8 hours of presentation, making it difficult to establish a strong association. Previous case reports and literature have demonstrated stronger associations with prolonged exposure to β -lactams (>10 days) rather than just a few doses

[16,20]. However, given the broad range of factors that impact the glutathione cycle, it is reasonable to consider stopping B-lactam antibiotics and changing to another class when managing a HAGMA suspected to be caused by 5-oxoproline accumulation.

Another important consideration is the excretion of 5-OP by the kidneys [10,12]. When the kidney function is acutely impaired, there is a higher risk of pyroglutamic acidosis. Our patient presented with multifactorial acute renal failure that improved with fluid resuscitation and treatment of sepsis. The resolution of renal failure also improved the clearance of 5-OP and minimized the accumulation of pyroglutamic acid. Thus, addressing renal failure is equally important as managing other predisposing factors.

Prompt withdrawal of contributing agents, correction of sepsis and AKI, and supportive treatment with bicarbonate and nutritional optimization led to resolution of the acidosis within 60 hours. This management approach aligns with the approach taken in other documented situations of pyroglutamic acidosis. However, in our case HAGMA resolved within 3 days compared to the median time of 4 to 7 days reported in previous case reports, case series and reviews [19,20].

The existing literature surrounding the topic of pyroglutamic acid accumulation emphasises the importance of early diagnosis and prompt cessation of contributing agents. There is limited literature regarding the timing of reintroduction of these medications and recurrence of pyroglutamic acidosis-induced HAGMA. In our case, we determined that the main contributing factor in addition to the paracetamol use, was depletion of glutathione stores due to severe malnutrition. The active involvement of a dietitian and patient engagement helped us establish 60-70% of dietary needs on day 1 itself. We were fully aware of the patient's social circumstances and dependence for activities of daily living (ADLs), so efforts were made to arrange full-time care to ensure the patient continued to maintain satisfactory dietary intake. As a result, reintroduction of paracetamol and flucloxacillin after resolution of the underlying contributing conditions, without recurrence of HAGMA was successful. This suggests that in appropriately managed patients, early

cautious reintroduction of these medications may be feasible.

Conclusion

Pyroglutamic acidosis should be considered in patients with unexplained HAGMA, particularly in the presence of sepsis, polypharmacy, and malnutrition. Early recognition, withdrawal of precipitating factors, and supportive care are key to its management. This case also highlights the potential for safe re-introduction of contributing agents after recovery, a consideration not often addressed in current literature.

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