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# Piperacillin–Tazobactam–Associated Refractory High–Anion Gap Metabolic Acidosis in Septic Shock: A Case Report

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## ABSTRACT

High-anion gap metabolic acidosis (HAGMA) in critically ill patients is most commonly attributed to lactic acidosis, renal failure, or toxin accumulation. Drug-induced HAGMA is uncommon and particularly difficult to establish in patients requiring renal replacement therapy.

We report the case of an 86-year-old man with septic shock and severe acute kidney injury (AKI) who developed profound HAGMA requiring daily intermittent hemodialysis and continuous bicarbonate infusion. Despite normalization of lactate levels and improvement in renal function—evidenced by a decrease in serum creatinine from 8.9 to 1.8 mg/dL—persistent elevation of the anion gap and hypokalemia remained unresolved. Discontinuation of empirically initiated piperacillin–tazobactam (P/T) on day 4 resulted in resolution of the HAGMA within 48 hours, enabling cessation of dialysis.

Though the improvement in the conditions of sepsis and renal function can be responsible for resolving the problem, the time factor associated with the discontinuation of piperacillin/tazobactam is suggestive of drug-related cause for the occurrence of the event. Nonetheless, the concomitant improvement in the condition of both renal dysfunction and sepsis is considered as a very important confounder in evaluating the causality for the drug.

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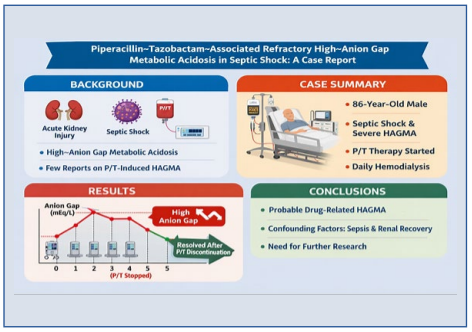


## INTRODUCTION

High-anion gap metabolic acidosis (HAGMA) is a prevalent, potentially fatal, acid-base disorder among patients in the critical care setting. The primary causes of HAGMA include lactic acidosis, ketoacidosis, renal failure, and toxic ingestion [1, 2]. In septic shock, tissue hypoperfusion and impaired renal clearance often coexist, resulting in complex and multifactorial acid–base disorders.



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Persistent elevation of the anion gap despite normalization of lactate levels and appropriate renal replacement therapy should prompt evaluation for alternative causes, including medications [1, 3]. Given piperacillin–tazobactam's predominantly renal route of elimination, drug accumulation may occur in severe renal dysfunction despite dose adjustment. Although drug-induced metabolic acidosis is well described, reports implicating piperacillin–tazobactam (P/T) are rare and typically involve electrolyte disturbances such as hypokalemia rather than HAGMA [4].

We describe a case of persistent HAGMA temporally associated with P/T therapy in a patient with septic shock and dialysis-dependent AKI, highlighting diagnostic challenges and emphasizing cautious interpretation of causality.

## CASE PRESENTATION

An 86-year-old male was admitted with profuse diarrhea and episodic vomiting over the last 4 days. The B.P. was 94/60 mmHg with MAP ≈71 mmHg, and the patient required vasopressors. The patient also had acute respiratory failure, and intubation and mechanical ventilation were performed.

Initial evaluation demonstrated severe HAGMA, which was associated with a high blood lactate concentration of 16.4 mmol/L, a low blood pH level of 6.93, and very low blood bicarbonate concentration of 3 mmol/L. In addition, the blood ketones in the patient's body were low, with no elevation in β-hydroxybutyrate increase. Furthermore, the blood albumin was at 4.5 g/dL. The toxicology screen was negative for salicylates, acetaminophen, and toxic alcohols, and the patient had not been on acetaminophen during his ICU stay; therefore, pyroglutamic acidosis secondary to acetaminophen toxicity was ruled out.

His medical history included type 2 diabetes mellitus, hypertension, and prior traumatic leg amputation. Baseline serum creatinine three months prior was 1.1 mg/dL. Home medications had been discontinued 24 hours before admission.

The chest examination showed evidence of pneumonia, and the patient was admitted to the intensive care unit. The patient received IV fluid resuscitation (4L/48 hours), bicarbonate infusion, and intermittent hemodialysis with 5 hours duration and blood flow rate of 350 mL/min and adequacy was assessed by Kt/V > 1.3 per session. The patient was given enteral nutrition support on day 2. Empiric P/T was initiated (2.25 g IV q 12 h, adjusted for renal impairment).

Serum lactate decreased from 16.4 to 1.0 mmol/L, and urine output improved. Despite dialysis, the patient continued to have a high anion gap (31–38 mmol/L), persistent metabolic acidosis, and ongoing hypokalemia.

## KEY MESSAGES

***What is already known on this topic?***

High-anion gap metabolic acidosis (HAGMA) in critically ill patients is most commonly attributed to lactic acidosis, renal failure, or toxin exposure. Medication-related causes are less frequently recognized and can be particularly difficult to identify in patients requiring renal replacement therapy.

***What this study adds?***

This report describes the first detailed case of refractory HAGMA requiring dialysis that was temporally associated with piperacillin–tazobactam after alternative causes were extensively evaluated and excluded. The report provides a comprehensive clinical timeline, including laboratory trends, dialysis sessions, vasopressor requirements, and urine output, and discusses important confounding factors such as concurrent recovery from sepsis and renal dysfunction to ensure a cautious interpretation of causality.

***How this study might affect research, practice or policy?***

Clinicians should consider medication-related causes when investigating unexplained HAGMA in critically ill patients, particularly those with renal impairment. This case also highlights a potential pharmacovigilance signal regarding piperacillin–tazobactam and underscores the need for further research into its possible metabolic consequences.

## CLINICAL TIMELINE

The patient was admitted to the ICU on day zero with acidosis due to elevated lactate levels as well as with acute kidney injury (elevated serum creatinine, 8.9 mg/dL). The patient received vasopressors, mechanical ventilation, bicarbonate infusion, and intermittent hemodialysis. On day 1, treatment was initiated with piperacillin-tazobactam (2.25 g every 12 hours) for suspected pneumonia.

During days 2–3, the lactic acid level returned to normal (from 16.4 to 1.2 mmol/L), but the HAGMA was not resolved (anion gap 27–38 mmol/L) and hemodialysis continued. Piperacillin-tazobactam was stopped on day 4 and replaced with ceftriaxone.

After two more days (days 5–6), the anion gap, serum bicarbonate, and potassium levels quickly stabilized (12 mmol/L, 24 mmol/L, respectively), allowing cessation of hemodialysis. Despite improvement in lactate and urine output, persistent HAGMA and hypokalemia had continued until P/T discontinuation (Table 1).

**TABLE 1 - Time course of laboratory, electrolytes, arterial blood gas parameters, dialysis, vasopressor, and urine output parameters during hospitalization. Serum anion gap (mEq/L) values are corrected for albumin.**

| Day | Creatinine (mg/dL) | pH | $HCO_3^-$ (mmol/L) | Base Excess (mEq/L) | Potassium (mmol/L) | Chloride (mEq/L) | Sodium (mEq/L) | Lactate (mmol/L) | Anion Gap (mmol/L) | Δ Anion Gap (mEq/L)* |
|---|---|---|---|---|---|---|---|---|---|---|
| *Normal* | 0.9–1.2 | 7.35–7.45 | 22–26 | −2 to +2 | 3.5–5.2 | 96–106 | 135–145 | 0.5–2.2 | 4–12 | 0 |
| *Initial* | 8.9 | 6.93 | 3 | -26.3 | 6.0 | 98 | 140 | 16.4 | 39 | +27 |
| *Day 1 post-HD* | 5.9 | 6.99 | 9 | -24.9 | 4.1 | 98 | 145 | 4.0 | 38 | +26 |
| *Day 2 post-HD* | 5.1 | 7.12 | 11 | -13 | 3.2 | 110 | 148 | 2.1 | 27 | +15 |
| *Day 3 post-HD* | 5.5 | 7.19 | 7 | -18 | 3.1 | 100 | 145 | 1.2 | 38 | +26 |
| *Day 4 post-HD†* | 4.2 | 7.22 | 14 | -9 | 3.1 | 100 | 145 | 1.0 | 31 | +19 |
| *Day 5* | 1.8 | 7.52 | 24 | 0 | 2.8 | 109 | 145 | 0.8 | 12 | 0 |
| *Day 6* | 1.5 | 7.56 | 26 | +4 | 4.0 | 104 | 140 | 0.9 | 10 | -2 |

* Δ Anion Gap = measured anion gap − upper limit of normal (12 mEq/L).

† Piperacillin–tazobactam discontinued and replaced with ceftriaxone on day 4.

On hospital day 4, P/T was discontinued and replaced with ceftriaxone. Within 48 hours, arterial pH normalized (7.52), serum bicarbonate increased to 24 mmol/L, the anion gap normalized to 12 mmol/L, potassium levels corrected, and dialysis was discontinued **(Figure 1)**. The patient was extubated on day 6 and transferred from the ICU on day 7.

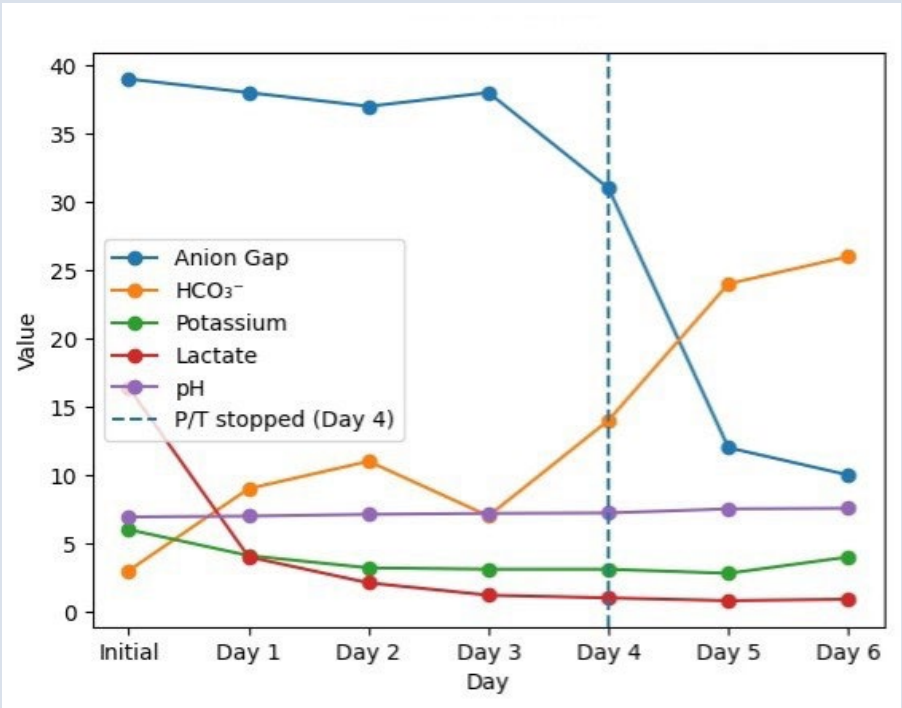


**FIGURE 1 - Trend of serum Anion Gap (mEq/L) corrected for albumin, Bicarbonate ($HCO_3^-$) (mmol/L), Potassium (mmol/L) and Lactate (mmol/L) levels over hospitalization.**

The dashed blue line indicates discontinuation of P/T on Day 4. Dialysis sessions are marked with vertical gray bars (Days 0–4). Vasopressor support was required until Day 3, after which it was discontinued. Urine output is shown as a secondary trend line, demonstrating progressive recovery from <100 mL/24h on admission to >1.5 L/24h by Day 6. The normalization of acid–base parameters coincided temporally with cessation of P/T therapy, recovery of renal function, and discontinuation of dialysis.

## DISCUSSION

Evidence linking P/T to high-anion gap metabolic acidosis (HAGMA) remains extremely limited, with most reports describing electrolyte disturbances—particularly hypokalemia—rather than clinically significant acid–base abnormalities [4]. This case extends the literature by describing persistent, dialysis-requiring HAGMA temporally associated with P/T therapy in a critically ill patient.

Persistent HAGMA in the ICU is diagnostically challenging, especially when lactate levels normalize and renal replacement therapy is ongoing [1, 2]. In this patient, the initial severe acidemia was attributable to lactic acidosis in septic shock compounded by acute kidney injury (AKI) [2, 5]. However, continued elevation of the anion gap despite lactate normalization and adequate dialysis suggests ongoing generation or accumulation of unmeasured anions.

Several mechanisms may account for this observation. First, because both piperacillin and tazobactam are primarily renally eliminated, severe AKI may lead to accumulation of the parent compounds or their metabolites, which can behave as weak organic acids and contribute directly to the elevated anion gap. Intermittent hemodialysis may have been insufficient to prevent rebound accumulation between sessions. Second, P/T-associated hypokalemia—likely mediated by enhanced distal sodium delivery—may reflect altered tubular handling of electrolytes and acid–base balance, thereby contributing to acid–base disturbances in conjunction with other mechanisms. Third, although speculative, indirect effects on mitochondrial or hepatic metabolism may promote accumulation of unmeasured organic acids. Antibiotic-induced gut dysbiosis could theoretically favor production of D-lactate or other organic acids, though this was considered unlikely in the absence of neurological manifestations. Fourth, piperacillin contains approximately 64 mg of sodium per gram, which may contribute to electrolyte shifts and acid–base imbalance in critically ill patients through sodium load [6].

Finally, a mismatch between ongoing acid generation and intermittent dialysis clearance could sustain HAGMA despite apparently adequate dialysis delivery. The correlation between discontinuation of P/T and the rapid recovery of anion gap, bicarbonate, and potassium concentrations—leading to cessation of dialysis—adds credibility to the association, as evidenced by a Naranjo score of 6 indicating a probable adverse drug reaction. However, this score has limitations in critically ill patients with multiple concurrent processes, and causality should be interpreted cautiously [7]. Improvement of both sepsis and renal function remains a major confounding factor. Other potential sources of HAGMA were considered unlikely, including D-lactic acidosis [8], pyroglutamic acidosis [9, 10], and uremic acidosis despite dialysis therapy [1, 2].

This case underscores the need to consider drug-related factors in refractory HAGMA, particularly in patients with renal impairment, and highlights the importance of pharmacovigilance in critical care.

## LIMITATIONS

This case report has several limitations that warrant consideration. First, the causal relationship between P/T and refractory HAGMA cannot be definitively established, as resolution of acidosis coincided with improvement in septic shock, recovery of renal function, and discontinuation of vasopressors. These concurrent processes represent significant confounders. Second, while the Naranjo score suggested a probable adverse drug reaction, its application in critically ill patients with multiple overlapping pathophysiological processes is inherently limited and may overestimate causality. Third, although alternative causes of HAGMA such as D lactic acidosis, pyroglutamic acidosis, and uremic acidosis were considered unlikely, not all investigations (e.g., direct measurement of organic acid metabolites) were performed, and therefore these conditions cannot be definitively excluded. Finally, the proposed mechanisms remain speculative, as no biochemical assays were available to confirm accumulation of piperacillin, tazobactam, or their metabolites. These limitations highlight the need for cautious interpretation and underscore the importance of further research to clarify the metabolic consequences of P/T therapy.

## CONCLUSION

This case illustrates a probable association between P/T therapy and refractory high-anion gap metabolic acidosis in a critically ill patient with septic shock and acute kidney injury. While causality cannot be definitively proven, the temporal resolution of acidosis following discontinuation of P/T supports a drug related contribution. Clinicians should remain vigilant for medication related causes of unexplained metabolic acidosis, especially in patients with renal dysfunction. Further research is warranted to clarify the metabolic consequences of P/T administration and to guide safer prescribing practices in critical care.

### Keywords

**Case Report, High-Anion Gap Metabolic Acidosis, Piperacillin-Tazobactam, Acute Kidney Injury, Hemodialysis, Septic Shock, Drug-Induced Acidosis, Critical Care Nephrology**

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### Author contributions

AJZ conceptualized the case, managed patient care, collected and analyzed the data, and drafted and revised the manuscript. BLBC contributed to patient management, critically reviewed the manuscript, and assisted in developing the discussion. Both authors read and approved the final version of the manuscript.

### Declarations

#### Conflicts Of Interests

The Authors declare that there is no conflict of interest.

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#### Registration

No registration applicable.

#### Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

#### Ethical approval

Ethical approval for this study was not required.

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