JoTH Journal of Tropical Health

Case Report

Successful Management of Acyclovir-Induced Nephrotoxicity in a Patient with Varicella Zoster Virus Encephalitis in a Resource-Limited Setting- A Case Report

Supun Wedasingha[1,2*], Rathnasiri Rajapaksha[1], Thilina Rathnasekara[1,2], Hemal Senanayake[2], Chamara Sarathchandra[2]

[1]Postgraduate Institute of Medicine, University of Colombo, Sri Lanka.
[2]Department of Medicine, Faculty of Medicine & Allied Sciences, Rajarata University of Sri Lanka, Sri Lanka.
[3]Department of Pharmacology, Faculty of Medicine & Allied Sciences, Rajarata University of Sri Lanka, Sri Lanka.

Abstract

This case report describes a 42-year-old male patient who developed acyclovir-induced nephrotoxicity while being treated for varicella zoster virus encephalitis. The case report underscores the challenges faced in a low-income setting where continuing acyclovir at a reduced dose was necessary due to the lack of alternative antiviral treatments. The patient's condition was successfully managed through careful dose adjustment and intensive monitoring, resulting in a gradual recovery of renal function.

Funding: None
Competing interests: None
Received: 18 April 2025 **Accepted:** 25 May 2025 **Published:** 30 June 2025

***Corresponding author:** swnadeeja@gmail.com https://orcid.org/0000-0002-3703-9764

Cite this article as: Wedasingha S et al. Successful management of Acyclovir-Induced nephrotoxicity in a patient with Varicella Zoster virus Encephalitis in a resource-limited setting- A case report. Journal of Tropical Health 2025;1 (2): 98-103. DOI: http://doi.org/10.4038/joth.v1i2.8

Introduction

Acyclovir is an antiviral medication commonly used for the treatment of herpes simplex and varicella-zoster viral infections [1]. It is generally well-tolerated but is associated with the risk of nephrotoxicity, specifically crystal nephropathy, particularly in high doses or in patients with pre-existing renal impairment [2]. Crystal nephropathy is a form of acute kidney injury (AKI) that occurs when acyclovir precipitates in the renal tubules, leading to obstruction and subsequent tubular damage. Acyclovir, in general, has low solubility in tubular urine, particularly in the distal tubular lumen. A reduced urine volume due to renal failure and/or dehydration, excessive drug dosage, and too rapid infusion are among the factors which can increase the precipitation of crystals. The drug is primarily excreted unchanged by the kidneys, and high urinary concentrations can lead to crystal formation. These crystals can, in turn, cause tubular obstruction, inflammasome-mediated inflammation, and direct tubular toxicity, resulting in a rapid decline in renal function [3]. Acyclovir-induced nephrotoxicity is usually dose-dependent [4].

Patients with acyclovir-induced nephrotoxicity typically present with an acute onset of oliguria, increased serum creatinine (SCr), and elevated blood urea nitrogen (BUN) levels within about 24-72 hours of initiating treatment [5]. Diagnosis is mainly clinical, supported by a history of recent acyclovir administration and the exclusion of other causes of AKI [6]. The management of acyclovir-induced nephrotoxicity primarily involves discontinuation or dose adjustment of the drug, substitution with alternative antiviral agents [7], and initiation of

aggressive intravenous hydration to flush out the crystals and restore renal function. Recent guidelines recommend practices such as volume repletion before acyclovir and slow diluted drug infusion instead of rapid bolus infusion [8].

However, managing acyclovir-induced nephrotoxicity, particularly in a resource-poor setting, is undoubtedly challenging. Here, we describe the successful management of acyclovir-induced nephrotoxicity in a patient with varicella zoster encephalitis in a resource-limited setting.

Case presentation

A 42-year-old male patient with hypertension and dyslipidaemia presented to the medical ward with an acute onset of confusion. He had been diagnosed with herpes zoster nine days earlier, as he had a blistering, painful skin rash in the upper trunk and had been previously started on oral acyclovir. However, at the time of admission, he did not have a fever, headache, or any weakness/ numbness. He did not complain of any respiratory or urinary symptoms. Even though he was diagnosed with hypertension and dyslipidaemia, he was not on treatment for either. There was no history suggestive of substance abuse and alcohol withdrawal. No history of psychiatric conditions was noted. Other than acyclovir, the patient has not been given any other medications recently, including paracetamol. Upon examination, he was afebrile and not dehydrated. His GCS was 14/15, and he was disoriented in time and space. His pulse rate was 104 beats per minute, and his blood pressure was 160/100 mm Hg. On the back of the chest, there was a tender, blistering skin rash in the distribution of a dermatome, which was suggestive of herpes zoster. Neurological examination was unremarkable, apart from confusion, with no focal neurological deficits or signs of meningeal irritation. There was no papilledema on the fundoscopic examination.

Non-contrast computed tomography of the brain did not show any abnormalities. On admission, the full blood count showed a white cell count of 14.61×10^9/L, with neutrophils at 1.66×10^9/L and lymphocytes at 1.7×10^9/L. His C-reactive protein level was 66.7 mg/L, serum creatinine was 71.1 µmol/L, and blood urea nitrogen was 3 mmol/L. His serum potassium level was 4 mmol/L, sodium level was 134 mmol/L, and corrected calcium level was 2.35 mg/dL (Table 1). Lumbar puncture was abandoned, as there was evidence of local sepsis. Acyclovir-induced neurotoxicity was initially considered as a differential diagnosis but ruled out due to the absence of typical features such as hallucinations, myoclonus, or seizures and because the altered mental status predated Intravenous acyclovir initiation and improved despite continued treatment. Given the clinical context and the lower likelihood of alternative diagnoses, a working diagnosis of varicella zoster virus encephalitis was made based on clinical grounds, including the characteristic rash and acute-onset neurological symptoms. The patient was started on intravenous acyclovir at a dose of 10 mg/kg every eight hours. In anticipation of nephrotoxicity, acyclovir was administered as an infusion over one hour, preceded by and followed by hydration with intravenous normal saline.

Within 48 hours of commencing acyclovir treatment, the patient experienced a significant reduction in urine output. Despite this, he remained hemodynamically stable, with no signs of dehydration and no features suggestive of a urinary tract infection. Additionally, the patient was not on any other nephrotoxic medications. His SCr level had risen to 274 µmol/L, and blood urea (BU) was elevated at 8.3 mmol/L. These findings led to a diagnosis of acyclovir-induced crystal nephropathy.

Urinalysis performed after the rise in serum creatinine was negative for red blood cells, white blood cells, granular casts, and eosinophils. No crystals were detected; however, polarising light microscopy was unavailable to adequately assess their presence. A renal ultrasound scan after serum creatinine elevation showed bilateral globular echogenic enlarged kidneys (right kidney 12.1mm and left kidney 13.1 mm) compatible with a diagnosis of bilateral acute kidney injury. There was no evidence of obstruction. Fractional excretion of sodium was 2%, thus indicating tubular damage. The patient was started on vigorous intravenous fluids with hourly urine output monitoring. The patient was switched to a renal-adjusted dose of acyclovir, which was 10mg/kg/24 h (500 mg daily). Each day, a bedside ultrasound scan was performed twice to assess the collapsibility of the inferior vena cava and guide the fluid management.

The patient's serum creatinine peaked on Day 3 of hospitalisation but began to decline with continued rigorous fluid management and reduced-dose acyclovir. By Day 6, his renal function had improved significantly, with serum creatinine returning towards baseline levels. The patient remained hemodynamically stable throughout the illness, and no further complications of acute kidney injury were observed. See Figure 1 for the timeline of events.

Table 1: Summary of investigations

	Normal range	D1	D2	D3	D4	D5	D6	D8	D10	D12
Haemoglobin (g/dL)	11.0-17.0	10.3			9		9.7			
White blood cells (1000/µL)	4.0-10.0	14610			11320		9540			
Platelets (1000/µL)	150-400	634000			472000		498000			
CRP (mg/L)	0.0-5.0	66.7	59.3				42			
Procalcitonin (ng/mL)							0.806			
Serum creatinine (µmol/L)	60-120	71.1	275	463	542	607	530	189	128	97
Blood urea (mmol/L)	2.5-6.4	3	8.3	12.2	13.6	16.1		8.2	4.08	3.3
Sodium (mmol/L)	135-148	132						141	140	
Potassium (mmol/L)	3.6-5.0	4						3.4	3.4	
Corrected calcium (mmol/L)	2.1-2.6	2.35		2.29	1.97	2.03				
Phosphorus (mmol/L)	0.7- 1.45			1.44	1.48					
AST (U/L)	10-35	60			20					
ALT (U/L)	10-40	118			27					
Creatinine kinase (U/L)	≤ 195				57					
Albumin (g/L)	10-35	37.97		28.22	29.36	30.67				
Fractional excretion of sodium				2%						
Blood culture					Negative					
Urine culture					Negative					
Urine albumin (g/L)		Nil								
Urine pH				6.9						
Urine pus cells /HPF		6								
Urine red blood cells /HPF		1-2								
Urine casts /HPF		Nil								
Urine crystals /HPF		Nil								

CRP, C-reactive protein; HPF, High Power Field

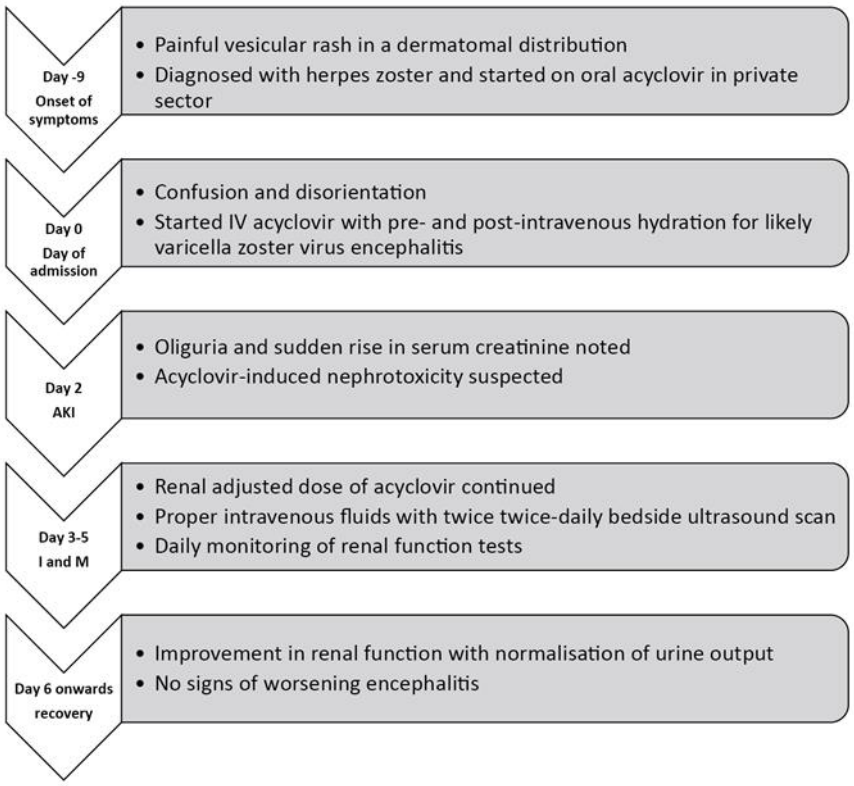

Figure 1: Timeline of events**.** I and M, Intervention and monitoring, IV: Intravenous, AKI, Acute Kidney Injury

Discussion

Varicella zoster virus can cause a wide array of central nervous system manifestations if the infection invades the spinal cord or cerebral arteries, including cerebellar ataxia, arteritis, myelitis, meningitis, and encephalitis. Central nervous system infection can occur with both primary and secondary reactivation of the virus. Varicella zoster virus encephalitis typically presents with headache, fever, vomiting, altered level of consciousness, or seizures [9]. Acyclovir is the cornerstone in the management of varicella viral infections. Despite having good tolerability in general, acyclovir is rarely associated with nephrotoxicity as well as neurotoxicity [2]. Although acyclovir-induced neurotoxicity was initially considered as a differential diagnosis, it was deemed unlikely in this case as the patient did not have classic features such as hallucinations, tremors, myoclonus, or seizures, which are typically associated with acyclovir-related neurotoxicity [10]. Moreover, the timing of his altered sensorium before initiation of intravenous acyclovir, along with a compatible clinical history and dermatome-distributed rash, supported a diagnosis of varicella zoster encephalitis rather than acyclovir-induced neurotoxicity. His neurological status also gradually improved despite the continued administration of acyclovir, making acyclovir-induced neurotoxicity less likely. This case presents a scenario where acyclovir-induced nephrotoxicity was observed in a patient treated for varicella zoster virus encephalitis, highlighting the challenges of diagnosing and managing such cases in a resource-limited setting. Here, the patient developed acyclovir-induced nephrotoxicity despite receiving it as an infusion over one hour with pre- and post-hydration with intravenous normal saline.

The kidneys primarily excrete Acyclovir through glomerular filtration and tubular secretion. The occurrence of acyclovir nephrotoxicity ranges from 12% to 48% [11]. Nephrotoxicity can occur following direct tubular toxicity as well as when acyclovir precipitates as crystals within the renal tubules, leading to obstructive nephropathy. This risk is much worse in cases of high-dose intravenous therapy, rapid infusion rates, dehydration, or pre-existing renal impairment [3]. The diagnosis of acyclovir-induced nephrotoxicity is mainly clinical, supported by laboratory findings and imaging studies. In this patient, the acute onset of oliguria, rising serum creatinine and blood urea, and ultrasound findings of bilaterally enlarged echogenic kidneys were all strongly indicative of acyclovir-induced crystal nephropathy. The absence of hematuria, pyuria, or casts is consistent with the non-inflammatory nature of crystal nephropathy. However, the lack of polarising light microscopy to detect crystals in the urine was a limitation, highlighting the diagnostic challenges faced in low-resource settings. The other differential diagnoses for acute kidney injury we considered in this patient included prerenal azotaemia, acute tubular necrosis, and obstructive uropathy. Prerenal causes were unlikely as the patient was quite adequately hydrated since the commencement of acyclovir. Imaging studies helped to rule out obstructive uropathy. However, the close temporal relationship between the commencement of acyclovir and the onset of renal impairment, along with the exclusion of other causes, supported the diagnosis of acyclovir-induced nephrotoxicity.

In resource-rich healthcare settings, alternative antiviral drugs, such as foscarnet or famciclovir [2], may be helpful in cases of acyclovir-induced nephrotoxicity. However, in low-income settings, these alternative agents are not freely available, necessitating continued use of acyclovir despite its nephrotoxic properties. Careful dose adjustment of acyclovir, cautious fluid resuscitation protocols, and close monitoring of urine output and renal function tests are crucial in mitigating the risk of crystal nephropathy and preserving renal function. In this case, the patient was initiated on a renal-adjusted dose of acyclovir (500 mg daily) in conjunction with an aggressive regimen of intravenous fluids to promote urinary excretion of the drug and prevent further crystal formation in the renal tubules. Daily monitoring of renal function, coupled with ultrasound-guided fluid management, was crucial in reversing the nephrotoxicity. The bedside ultrasound was beneficial for assessing the collapsibility of the inferior vena cava and then determining fluid therapy, ensuring adequate hydration without putting the patient at risk of fluid overload [12]. It was essential to continue acyclovir at a reduced dose, which would have otherwise risked the progression of the underlying varicella-zoster virus encephalitis, potentially leading to permanent neurological sequelae or death. On the other hand, continuing the same dose of acyclovir could have worsened the nephrotoxicity, potentially leading to irreversible nephrotoxicity.

When managing this patient, we encountered a few diagnostic challenges. The presence of zoster skin lesions on the patient's back precluded the performance of a lumbar puncture at the beginning of the diagnostic workup. A lumbar puncture would have been invaluable in analysing cerebrospinal fluid to confirm varicella zoster virus encephalitis. Nevertheless, the risk

of infection due to the lesions was deemed too great to go ahead with lumbar puncture. The lack of free accessibility to magnetic resonance imaging (MRI) posed another challenge. MRI is the gold standard for detecting the characteristic temporal lobe involvement observed in varicella zoster virus encephalitis. The limited availability of MRI complicated our ability to confirm the diagnosis and assess the extent of central nervous system involvement. Diagnosing acyclovir-induced nephrotoxicity is often supported by the detection of acyclovir crystals in urine, ideally visualised with phase-contrast microscopy, which was unfortunately not available in our setting. As the patient's renal function markedly improved with supportive management, the decision was made to forgo the renal biopsy. While a renal biopsy could have provided definitive evidence of crystal nephropathy and could delineate the extent of renal damage, the subsequent clinical improvement negated the necessity for such an invasive procedure.

Despite the diagnostic challenges, with supportive management, the patient's renal function gradually improved, with serum creatinine levels returning toward baseline within a few days. This favourable outcome highlights the potential for reversibility of acyclovir-induced nephrotoxicity with timely, supportive management. The lack of alternative antiviral options and limited diagnostic tools necessitated a more pragmatic approach to managing acyclovir-induced nephrotoxicity for the treating medical team.

In the literature, there are few case reports of acyclovir-induced nephrotoxicity, yet acyclovir therapy had to be continued due to the unavailability of alternative antiviral options [13]. Almost all these cases involved careful monitoring and supportive measures to manage renal function while continuing antiviral treatment. In some cases, even haemodialysis had to be initiated while continuing antiviral therapy [14,15].

Conclusion

Acyclovir-induced nephrotoxicity represents a considerable challenge in the management of viral infections, particularly in low-income settings where alternative treatments are scarce. This case illustrates the potential for successful management through renal adjusted doses, proper hydration, and careful monitoring, even without advanced diagnostic tools or alternative therapies. Prompt identification is key, as only timely intervention can prevent permanent renal damage. The lessons learned from this case underscore the need for adaptable, context-specific treatment strategies that balance the efficacy of treatment with the potential adverse effects in resource-constrained healthcare settings. In low-resource settings, a cautious continuation of acyclovir at a reduced dose, accompanied by a strict ultrasound-guided hydration protocol and close monitoring of renal function, can be recommended as a feasible approach to balance efficacy and the risk of nephrotoxicity.

Consent:

Informed written consent was obtained from the patient for publication of the clinical data in this case report.

References

1. King DH, Madera PDC. History, pharmacokinetics, and pharmacology of acyclovir. J Am Acad Dermatol. 1988;18:1769. doi:10.1016/s0190-9622(88)70022-5.
2. Orion E, Matz H, Wolf R. The life-threatening complications of dermatologic therapies. Clin Dermatol. 2005;23:182–92. doi:10.1016/j.clindermatol.2004.06.013.
3. Kwiatkowska E, Domański L, Dziedziejko V, Kajdy A, Stefańska K, Kwiatkowski S. The mechanism of drug nephrotoxicity and the methods for preventing kidney damage. Int J Mol Sci. 2021;22. doi:10.3390/ijms22116109.
4. Rao S, Abzug MJ, Carosone-Link P, Peterson T, Child J, Siparksy G, et al. Intravenous acyclovir and renal dysfunction in children: A matched case control study. J Pediatr. 2015;166:1462-8.e4. doi:10.1016/j.jpeds.2015.01.023.
5. Yildiz C, Ozsurekci Y, Gucer S, Cengiz AB, Topaloglu R. Acute kidney injury due to acyclovir. CEN Case Rep. 2013;2:38-40. doi:10.1007/s13730-012-0035-0.
6. Fleischer R, Johnson M. Acyclovir nephrotoxicity: A case report highlighting the importance of prevention, detection, and treatment of acyclovir-induced nephropathy. Case Rep Med. 2010;2010:6-8. doi:10.1155/2010/602783.
7. Htwe TH, Bergman S, Koirala J. Famciclovir substitution for patients with acyclovir-associated renal toxicity. J Infect. 2008;57:266-8. doi:10.1016/j.jinf.2008.06.008.

8. Richelsen RKB, Jensen SB, Nielsen H. Incidence and predictors of intravenous acyclovir-induced nephrotoxicity. Eur J Clin Microbiol Infect Dis. 2018;37:1965-71. doi:10.1007/s10096-018-3332-5.

9. Lizzi J, Hill T, Jakubowski J. Varicella Zoster Virus encephalitis. Clin Pract Cases Emerg Med. 2019;3:380-2. doi:10.5811/cpcem.2019.8.43010.

10. Watson WA, Rhodes NJ, Echenique IA, Angarone MP, Scheetz MH. Resolution of acyclovir-associated neurotoxicity with the aid of improved clearance estimates using a Bayesian approach: A case report and review of the literature. J Clin Pharm Ther. 2017;42:350-5. doi:10.1111/jcpt.12520.

11. Chávez-Iñiguez JS, Medina-Gonzalez R, Aguilar-Parra L, Torres-Vázquez EJ, Maggiani-Aguilera P, Cervantes-Pérez E, et al. Oral acyclovir induced hypokalemia and acute tubular necrosis: A case report. BMC Nephrol. 2018;19:1-5. doi:10.1186/s12882-018-1121-0.

12. Argaiz ER, Koratala A, Reisinger N. Comprehensive assessment of fluid status by point-of-care ultrasonography. Kidney360. 2021;2:1326-38. doi:10.34067/KID.0006482020.

13. Lim APW, Sung J, Ramburuth V, Oyibo SO. Acyclovir-induced nephrotoxicity and neurotoxicity: A report of two cases. Cureus. 2024;16:1–7. doi:10.7759/cureus.52367.

14. Roshanzamiri S, Mousavizadeh SA, Razazzadeh S, Ziaie S. Acyclovir-induced psychiatric and renal adverse effects in a diabetic patient: A case report. Clin Case Rep. 2024;12:3-6. doi:10.1002/ccr3.9310.

15. Abuhelwa Z, Beran A, Venkataramany BS, Hinch BT, Assaly R. Concurrent nephrotoxicity and neurotoxicity induced by oral valacyclovir in a patient with previously normal kidney function. Cureus. 2022;14:1-5. doi:10.7759/cureus.23693.