

Case report Recurrent dialysis-dependent acute kidney injury caused by distinct tubulointerstitial mechanisms with complete recovery

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Case Report

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Abstract

Background.

Acute kidney injury (AKI) requiring renal replacement therapy (RRT) is a critical, life-threatening emergency encountered in the emergency department (ED). While recurrent AKI is a documented clinical phenomenon, cases featuring two distinct, temporally separated, dialysis-dependent episodes caused by completely different pathophysiological mechanisms—each culminating in full functional recovery—are exceptionally rare.

Case presentation.

A 35-year-old male initially presented to the ED with anuria and severe AKI (peak creatinine 665 $\mu\text{mol/L}$) following parenteral gentamicin therapy for a dog bite wound. Diagnosed with toxic acute tubular necrosis (ATN), the patient required four hemodialysis sessions but achieved complete renal recovery (creatinine 80 $\mu\text{mol/L}$) within six weeks. Twelve years later, the same patient (now 47 years old) presented to the ED with fever, thrombocytopenia, and oliguric AKI (peak creatinine 1020 $\mu\text{mol/L}$) following potential rodent exposure. Serological testing and PCR confirmed an acute Dobrava-Belgrade hantavirus infection. This immune-mediated tubulointerstitial AKI, consistent with acute interstitial nephritis (AIN), necessitated five hemodialysis sessions alongside supportive care. At the 3-month follow-up, the patient again demonstrated complete renal recovery (creatinine 90 $\mu\text{mol/L}$).

Conclusions.

This case highlights two severe, temporally isolated episodes of dialysis-dependent AKI driven by distinct tubulointerstitial injury pathways (toxic ATN and immune-mediated AIN). Emergency physicians should recognize that even recurrent, catastrophic renal insults requiring emergency RRT can carry an excellent prognosis for complete reversibility, allowing patients to completely avoid chronic kidney disease.

Background

Acute kidney injury (AKI) is a serious complication in hospitalised patients, linked to higher rates of illness, death, and an increased likelihood of developing chronic kidney disease (CKD) [1–4]. The global incidence of AKI is on the rise, driven by ageing populations and the growing use of complex medical procedures [2, 3]. Although most AKI cases are due to sepsis or hypovolemia [5, 6], it is important to identify less common intrinsic causes. Intrinsic AKI is mainly categorised into glomerular, vascular, and tubulointerstitial disorders [7]. Among these, acute tubular necrosis (ATN) and acute interstitial nephritis (AIN) are the most common. ATN is often caused by ischemia or nephrotoxic substances, such as aminoglycosides, which are still a key treatment for severe Gram-negative infections despite their narrow

therapeutic range [8–10]. On the other hand, AIN usually arises from drug-induced hypersensitivity, autoimmune reactions, or infections [11]. Differentiating between these two conditions can be difficult, as both typically present with oliguria and rapidly increasing creatinine levels. Among infectious causes, hantaviruses, which are zoonotic RNA viruses spread through rodent excreta, are known to cause AKI, especially in Eurasia, where they appear as hemorrhagic fever with renal syndrome (HFRS) [12–14].

Hantavirus-associated AKI is characterised by endothelial cell dysfunction and immune-mediated interstitial inflammation, and not by tubular cell necrosis. It may require temporary RRT [15, 16]. In severe Dobrava virus infection, necrotic cell death may be present, but it is interstitial in nature. Recurrence of dialysis-dependent AKI in the same patient is unusual and may be due to a predisposition to tubulointerstitial disease [17, 18]. While recurrent AKI has been described in the literature, reports of dialysis-dependent episodes with completely different pathophysiological mechanisms in the same patient are extremely scarce.

We report a rare case of a patient with two distinct episodes of severe AKI requiring RRT, with a twelve-year interval between them. Despite having similar clinical manifestations, both episodes were caused by different pathophysiological mechanisms: gentamicin-induced ATN and hantavirus-associated tubulointerstitial AKI consistent with AIN, resulting in full recovery.

Case Presentation

First Episode (2011): Toxic acute tubular necrosis

In June 2011, a previously healthy 35-year-old male presented after sustaining severe forearm lacerations from a dog bite. He underwent surgical debridement and was treated with parenteral gentamicin (80 mg three times daily) to cover possible infection with Gram-negative flora. At admission, the patient's weight was 85 kg. While staying in the traumatology ward, no monitoring of gentamicin concentrations was performed. On the fifth day of therapy, oliguria developed with progressive elevation of serum creatinine from 110 $\mu\text{mol/L}$ to 330 $\mu\text{mol/L}$. Referred to the nephrology ward, the patient was stable hemodynamically, had no signs of volume overload. Investigations revealed the peak level of serum creatinine equal to 665 $\mu\text{mol/L}$ and anuria (less than 100 mL/day). Urinary sediment analysis revealed granular casts and mild proteinuria without hematuria. No immune or viral markers (C3, C4, ANA, ANCA, anti-GBM, HBV, HCV, HIV, EBV, CMV) were positive. Based on the time of use of aminoglycosides and the data of urinalysis, acute tubular necrosis induced by gentamicin was diagnosed. Gentamicin therapy was discontinued and conservative measures were taken; however, oliguria persisted and progressive azotemia occurred, therefore intermittent hemodialysis was performed. Renal biopsy was delayed owing to early clinical improvement. Following four dialysis sessions, he started passing urine, and his kidney function slowly improved. Six weeks after his discharge, his serum creatinine was found to be normal (80 $\mu\text{mol/L}$), with no urinary problems (Fig. 1).

Second Episode (2023): Viral acute interstitial nephritis

Twelve years later, in January 2023, the now 47-year-old patient presented with a 3-day history of fever (38.7°C), nausea, muscle pain, and oliguria (< 200 mL/day). He mentioned recent exposure to rodent excreta in a rural area but denied taking new medications or nephrotoxins. Physical examination was unremarkable except for hypertension (160/95 mmHg) and fever. Laboratory tests showed severe AKI (creatinine 1020 µmol/L), mild thrombocytopenia (126.2 G/L), anemia (hemoglobin 12.7 g/dL), and proteinuria (1 g/day) with granular casts and hematuria. Imaging ruled out obstruction. Despite initial fluid resuscitation, renal function did not improve, necessitating five sessions of intermittent high-flux hemodialysis. Given the "clinical triad" of fever, thrombocytopenia, and AKI following rodent exposure, hantavirus infection was suspected. Serology (IgM/IgG) and PCR confirmed an acute infection with the Dobrava-Belgrade virus (DOBV) [15, 16, 19]. Tests for Leptospira and other viral/immunological screenings were negative. Polyuric recovery began on the fifth day, allowing for the cessation of dialysis. Serum creatinine rapidly decreased to 110 µmol/L at discharge. A 3-month follow-up confirmed normalization of the renal function (creatinine 90 µmol/L) with resolved proteinuria and hypertension (Fig. 2). The chronological sequence of clinical events and laboratory progression for both episodes is summarized in Table 1. The key laboratory findings from both episodes are summarized in Table 2.

Table 1
Clinical timeline of the two AKI episodes

Time Point	First Episode (June 2011)	Second Episode (January 2023)
Day 0	Admission: forearm dog bite, surgical debridement.	Symptom onset: fever (38.7°C), nausea, myalgia.
Days 1–4	Parenteral Gentamicin (80 mg TID) administered.	Progressive oliguria (< 200 mL/day) at home.
Day 5	AKI diagnosis (Cr: 330 µmol/L), anuria (< 100 mL/day).	Admission: severe AKI (Cr: 1020 µmol/L).
Days 6–10	Nephrology transfer, Intermittent HD (4 sessions).	Intermittent HD (5 sessions), Hantavirus serology sent.
Day 11	Onset of diuresis, renal function improving.	Onset of polyuric phase, cessation of dialysis.
Day 21	Discharge (Cr: 110 µmol/L).	Discharge (Cr: 110 µmol/L).
Follow-up	6 weeks later: Complete recovery (Cr: 80 µmol/L).	3 months later: Complete recovery (Cr: 90 µmol/L).
AKI: acute kidney injury; Cr: serum creatinine; HD: hemodialysis; TID: ter in die (three times a day).		

Table 2
Comparison of laboratory findings during the two AKI episodes

Parameter	First Episode (2011)	Second Episode (2023)	Reference Range	Units
Serum Creatinine (baseline)	110	100	60–110	μmol/L
Serum Creatinine (peak)	665	1020	60–110	μmol/L
Serum Creatinine (recovery)	80	90	60–110	μmol/L
Urine Output	< 100	< 200	> 500	mL/day
Proteinuria	Mild	~ 1	< 0.15	g/day
Hematuria	Absent	Present	Negative	–
Granular Casts	Present	Present	None	–
Hemoglobin	13.5	12.7	13.5–17.5	g/dL
Platelet Count	165.2	126.2	150–400	G/L
Complement (C3, C4)	Normal	Normal	Normal	–
Autoimmune markers (ANA, ANCA, anti-GBM)	Negative	Negative	Negative	–
Viral serology (HBV, HCV, HIV, EBV, CMV)	Negative	Negative	Negative	–
Hantavirus serology/PCR	Not applicable	Positive (DOBV)	Negative	–
C3: complement 3; C4: complement 4; ANA: antinuclear antibody; ANCA: antineutrophil cytoplasmic antibody; HBV: hepatitis virus B; HCV: hepatitis C; HIV: human immunodeficiency virus; EBV: Epstein-Barr Virus; CMV: cytomegalovirus; PCR: polymerase chain reaction, DOBV: Dobrava-Belgrade virus.				

Differential diagnostic considerations

For the first episode, alternative etiologies of AKI included acute interstitial nephritis, sepsis-related AKI, and rhabdomyolysis. The patient did not exhibit signs of sepsis with a stable hemodynamic profile or systemic infection. Creatinine kinase values were not suggestive of rhabdomyolysis. Furthermore, urine analysis revealed typical muddy-brown granular casts without eosinophilia or skin lesions that would be associated with AIN. The recent use of gentamicin made the diagnosis of toxic ATN highly probable.

As for the second episode, differential diagnoses could include leptospirosis, thrombotic microangiopathy, rapidly progressive glomerulonephritis, or infection-related nephropathy. However, all autoimmune serologies have been negative; there was no sign of obstruction by means of imaging or schistocytes or hemolytic anemia. Moreover, the diagnosis of acute Dobrava-Belgrade hantavirus infection was confirmed with PCR and serology, and tests for *Leptospira* and viral infections have shown

negative results. A renal biopsy was not performed because of rapid recovery, but fever, thrombocytopenia, history of rodent contact, and reversible oligo-anuric AKI strongly supported the diagnosis of hantavirus-associated interstitial nephritis.

Discussion

To our knowledge, recurrent dialysis-dependent AKI caused by two distinct tubulointerstitial mechanisms with complete renal recovery has not previously been reported.

While gentamicin-induced ATN and hantavirus-associated AIN are well-recognized causes of AKI, their sequential occurrence in the same patient has not previously been reported. Despite two dialysis-dependent AKI episodes, neither event resulted in CKD. The present case demonstrates that even severe recurrent tubulointerstitial injury may remain fully reversible with preserved renal functional recovery.

The similarities and differences between the two episodes, including the distinct pathophysiological mechanisms, clinical features, and renal outcomes, are summarized in Fig. 3 (Central illustration).

The first episode was caused by gentamicin-induced ATN, a well-known form of nephrotoxicity. Aminoglycoside antibiotics are concentrated in the renal cortex by the megalin/cubilin receptor complex, leading to oxidative stress and mitochondrial injury [8, 10]. Once inside the cell, they accumulate in lysosomes, causing rupture and the release of enzymes into the cytoplasm, which triggers apoptosis. The diagnosis was supported by the clinical timeframe and the presence of granular casts. Although high cumulative doses often require RRT, the prognosis for recovery is generally favorable once the drug is discontinued [9, 11].

The second episode was attributed to hantavirus-associated tubulointerstitial AKI consistent with acute interstitial nephritis, confirmed by serology and PCR. Hantaviruses infect endothelial cells, increasing vascular permeability and leading to “capillary leak syndrome,” which causes significant interstitial edema and inflammation in the kidneys [13, 14]. In Hungary, while Puumala virus typically causes mild HFRS, Dobrava-Belgrade virus (DOBV) infection is frequently associated with severe AKI requiring RRT [15, 16, 19]. This is particularly prevalent in the Transdanubian region [20]. A critical question is whether the initial ATN episode predisposed the patient to a more severe second insult. Current evidence suggests that even with normalized creatinine levels, “molecular scarring”—including epigenetic changes and low-grade inflammation—may persist. This “maladaptive repair” can diminish the kidneys’ capacity to respond to subsequent stressors [4, 17, 18].

The contrasting mechanisms of injury in this patient—direct tubular epithelial toxicity in gentamicin-associated ATN and immune-mediated endothelial/interstitial injury in hantavirus-associated AKI—suggest that recovery from severe AKI may depend more on preserved tubular regenerative capacity and timely supportive management than on the initiating insult itself. Despite two episodes severe enough to require temporary renal replacement therapy, complete recovery occurred in both cases, emphasizing the remarkable regenerative capacity of the renal tubulointerstitium [21, 22].

Experimental and clinical studies indicate that maladaptive repair processes may persist after apparent recovery from AKI, including tubular dedifferentiation, mitochondrial dysfunction, epigenetic alterations, and chronic low-grade inflammation. These mechanisms are thought to contribute to progression from AKI to CKD. Nevertheless, our patient maintained preserved renal functional reserve and recovered completely from a second severe AKI episode twelve years after the initial insult.

The absence of kidney biopsy and long-term biomarker assessment limits definitive mechanistic characterization of the second episode.

Conclusion

In conclusion, this case demonstrates that life-threatening AKI requiring RRT can arise from diverse pathophysiological mechanisms, such as toxic ATN and immune-mediated AIN, within the same individual. The twelve-year interval between two severe episodes followed by complete recovery suggests significant renal resilience and emphasizes the vital role of timely supportive care. Emergency physicians should recognize that even recurrent, catastrophic renal insults requiring emergency RRT can carry an excellent prognosis for complete reversibility, allowing patients to completely avoid chronic kidney disease.

This case also demonstrates that recurrent dialysis-dependent AKI may be fully reversible with appropriate supportive management.

Abbreviations

- **AIN**

Acute interstitial nephritis

- **AKI**

Acute kidney injury

- **ANA**

Antinuclear antibody

- **ANCA**

Antineutrophil cytoplasmic antibody

- **anti**

GBM—Anti-glomerular basement membrane antibody

- **ATN**

Acute tubular necrosis

- **CKD**

Chronic kidney disease

- **CMV**

Cytomegalovirus

- **Cr**

Serum creatinine

- **DOBV**

Dobrava–Belgrade virus

- **EBV**

Epstein–Barr virus

- **HBV**

Hepatitis B virus

- **HCV**

Hepatitis C virus

- **HD**

Hemodialysis

- **HFRS**

Hemorrhagic fever with renal syndrome

- **HIV**

Human immunodeficiency virus

- **PCR**

Polymerase chain reaction

- **RRT**

Renal replacement therapy

- **TID**

Ter in die (three times daily)

Declarations

Ethics approval and consent to participate

Ethical approval was not required for this case report in accordance with local legislation and institutional requirements.

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

BS and TJK conceived the study and supervised the clinical management of the patient. BS, AB, and VB collected and interpreted the clinical data. BC contributed to nephrological management, literature review, and manuscript preparation. BS drafted the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version of the manuscript.

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Figures

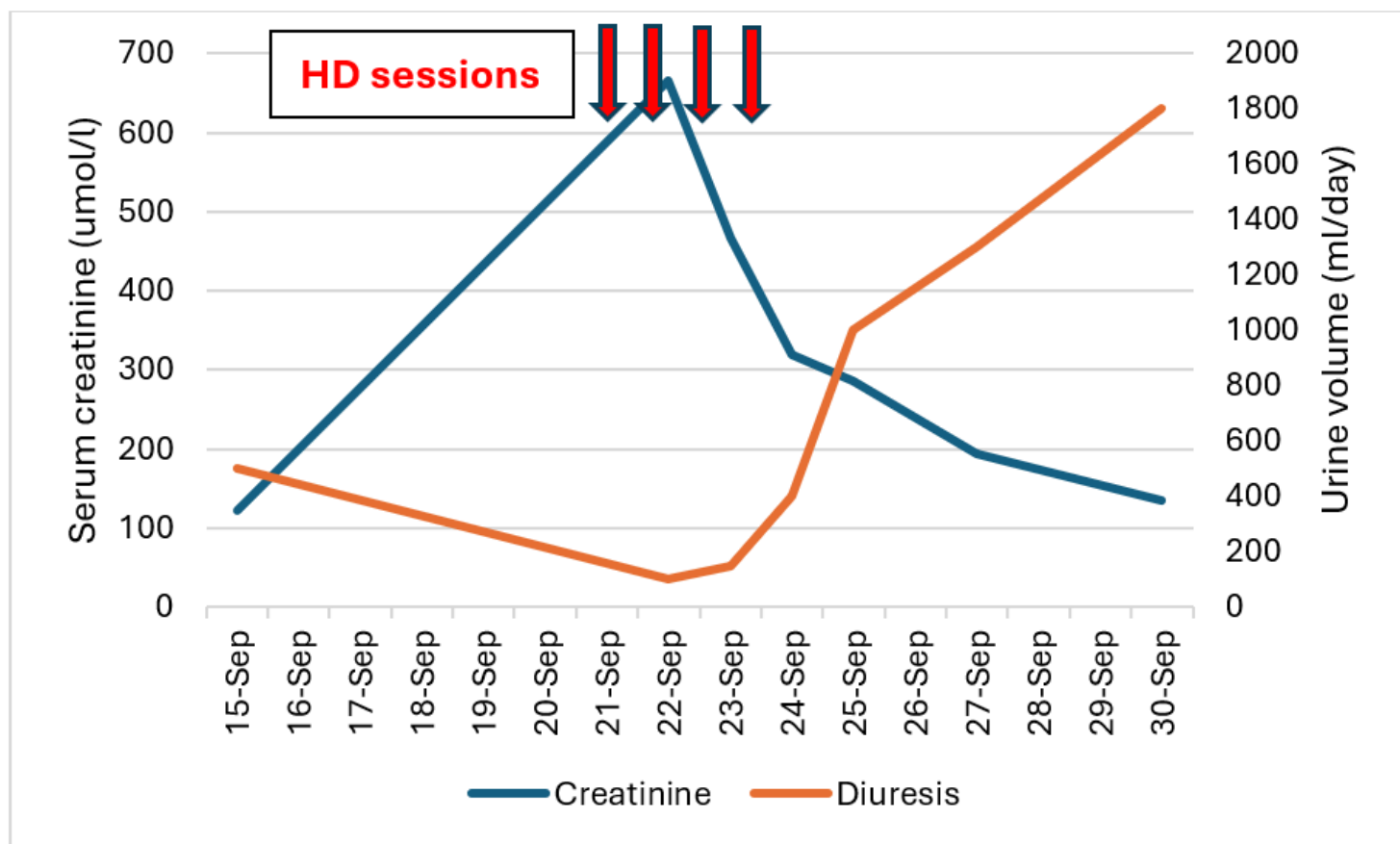


Figure 1

Clinical course of the first AKI episode (2011). Serial measurements of serum creatinine ($\mu\text{mol/L}$) and daily urine output (mL) demonstrating recovery from gentamicin-induced ATN.

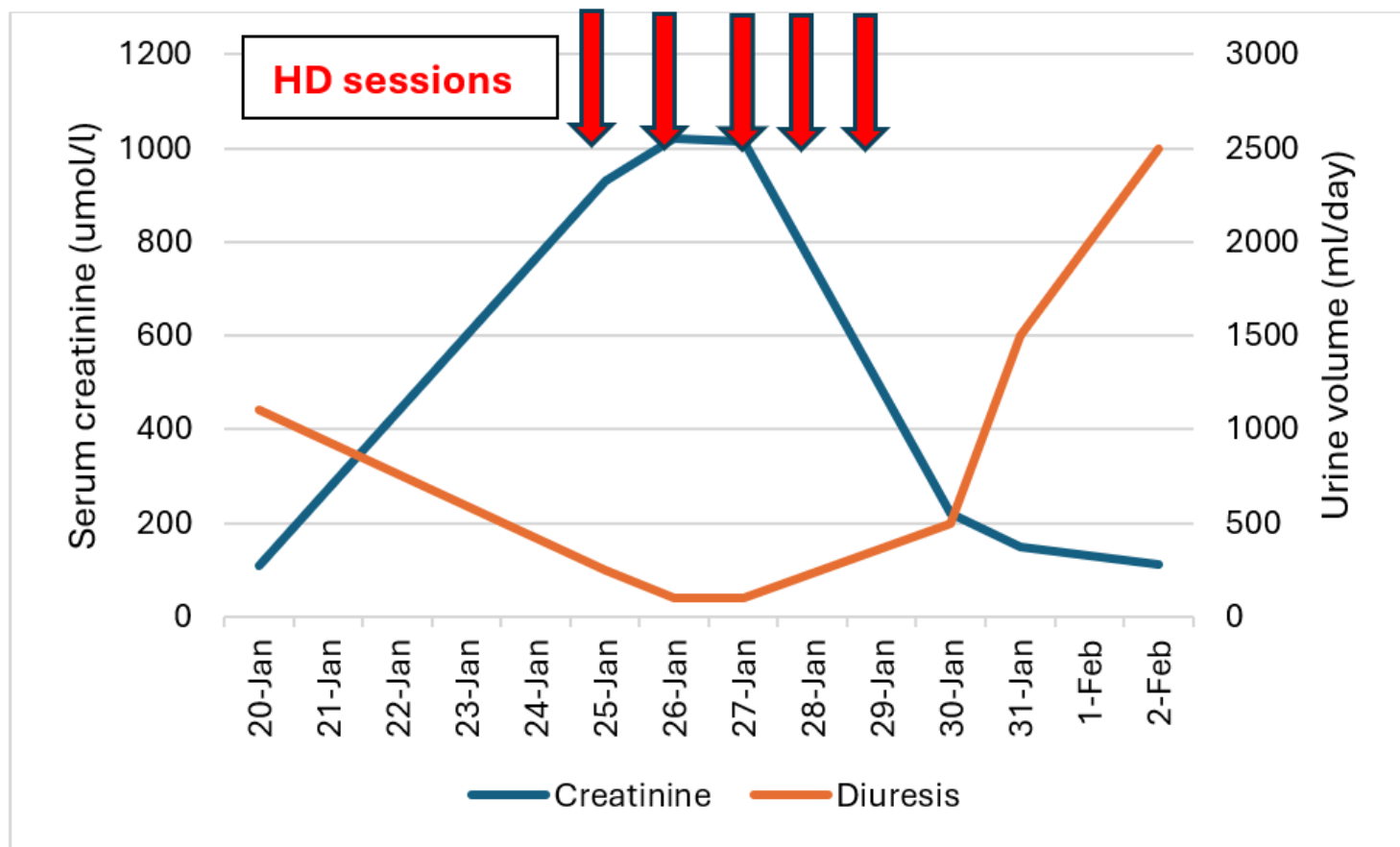


Figure 2

Clinical course of the second AKI episode (2023). Rapid recovery of renal function and resolution of thrombocytopenia following confirmed Dobrava-Belgrade hantavirus infection.

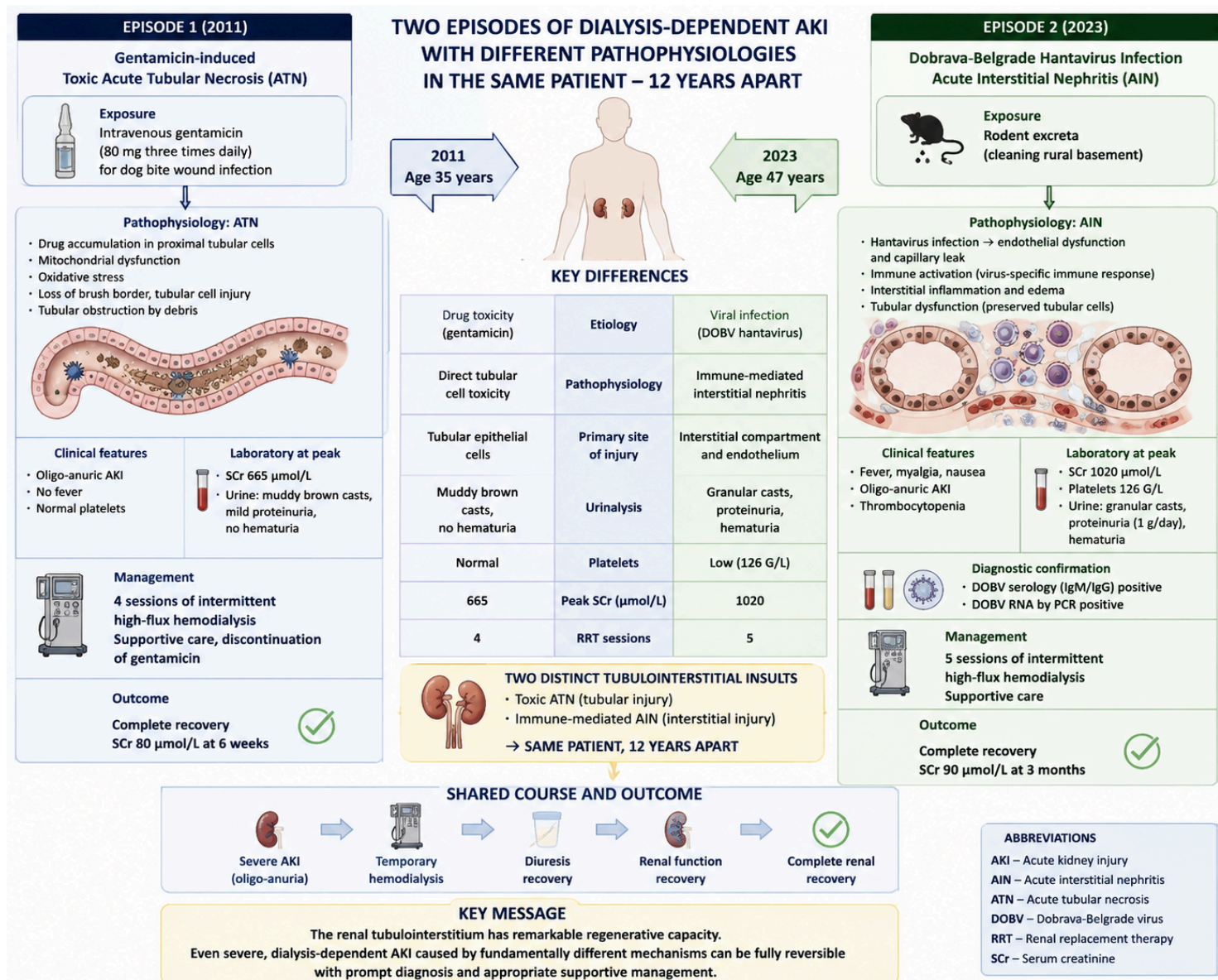


Figure 3

Central illustration: Two distinct pathophysiological mechanisms of recurrent dialysis-dependent acute kidney injury with complete renal recovery.

Comparative overview of two temporally separated episodes of dialysis-dependent acute kidney injury (AKI) in the same patient, caused by distinct tubulointerstitial pathophysiological mechanisms. The first episode (2011) was gentamicin-induced toxic acute tubular necrosis (ATN), characterized by direct tubular epithelial injury and complete renal recovery after temporary hemodialysis. The second episode (2023) was Dobrava-Belgrade hantavirus-associated acute interstitial nephritis (AIN), characterized by immune-mediated interstitial inflammation and endothelial dysfunction, also requiring temporary hemodialysis followed by full recovery. The figure summarizes the different etiologies, pathomechanisms, laboratory findings, management, and outcomes, highlighting the remarkable regenerative capacity of the renal tubulointerstitium despite recurrent severe AKI.

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