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A Review on NSAID-Induced Acute Kidney Injury: Insights into Current Evidence, Risk Factors and Prevention Strategies

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A B S T R A C T

Aim and Objectives: This review examines the relationship between nonsteroidal anti-inflammatory drug (NSAID) exposure and acute kidney injury (AKI), focusing on renal mechanisms, clinical evidence, risk factors, diagnosis, and prevention. Methods: A focused narrative review was prepared using ten selected publications: mechanistic and clinical reviews, a KDIGO guideline, a systematic review with meta-analysis, and observational studies. The selected evidence addressed renal physiology, AKI risk, interacting medicines, and prevention. This was not a systematic database search. Results: NSAID-mediated cyclooxygenase inhibition reduces renal prostaglandin synthesis and may impair afferent arteriolar dilation. A meta-analysis reported increased odds of AKI in the general population (OR 1.73) and in people with chronic kidney disease (CKD; OR 1.63) (Zhang et al., 2017). Among older adults, 30-day AKI occurred in 0.82% of new NSAID users and 0.59% of non-users (OR 1.41) (Nash et al., 2019). The NSAID–diuretic–ACEI/ARB combination is an important avoidable risk (Dreischulte et al., 2015; Lapi et al., 2013). Conclusion: Risk reduction requires identifying vulnerable patients, reviewing concurrent medicines, avoiding unnecessary exposure, using the lowest effective dose for the shortest practical duration, and monitoring renal function and potassium when indicated.

Keywords: Nonsteroidal anti-inflammatory drugs; Acute kidney injury; Nephrotoxicity; Renal prostaglandins; Cyclooxygenase; Risk factors; Prevention

1. INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to relieve pain, fever, and inflammation. Their availability without prescription makes them easy to obtain, but unsupervised or repeated use may cause avoidable adverse effects. The kidney is particularly vulnerable when renal perfusion is already reduced or compensatory mechanisms are needed to maintain filtration (Drożdżal et al., 2021; Whelton, 1999; Wongrakpanich et al., 2018).

The risk depends on baseline renal reserve, hydration, acute illness, dose, duration, and concurrent medicines. Thus, the same regimen may be tolerated by one person but cause a clinically important decline in kidney function in another, particularly in older adults and people with chronic diseases or polypharmacy (Drożdżal et al., 2021; Klomjit & Ungprasert, 2022; Wongrakpanich et al., 2018).

Renal prostaglandins help preserve perfusion during dehydration, heart failure, and other states of reduced effective circulating volume. Inhibiting their synthesis can therefore have a greater effect when renal circulation is already compromised (Klomjit & Ungprasert, 2022; Whelton, 1999).

1.1 NSAIDs and renal physiology

NSAIDs inhibit cyclooxygenase enzymes (COX-1 and COX-2), reducing prostaglandin synthesis from arachidonic acid. Renal PGE_2 and prostacyclin (PGI_2) support renal blood flow and influence sodium and water handling. Their role becomes especially important during volume depletion, acute illness, or heart failure (Drożdżal et al., 2021; Klomjit & Ungprasert, 2022; Whelton, 1999).

1.2 Acute kidney injury

AKI is an abrupt reduction in kidney function identified by changes in serum creatinine and/or urine output. KDIGO provides standardized criteria for recognizing and staging AKI (Khwaja, 2012). Creatinine may rise after renal function has already begun to deteriorate; comparison with baseline results, urine-output assessment, and fluid-status review can aid recognition.

1.3 Scope and review approach

This focused narrative review synthesizes ten selected publications. The evidence set includes mechanistic and clinical reviews, a KDIGO clinical practice guideline, a systematic review with meta-analysis, and observational studies. Publications were considered for their relevance to renal mechanisms, AKI definitions, population-level risk, medicine interactions, and prevention. No claim of exhaustive literature coverage is made.

2. RESULTS AND DISCUSSION

2.1 Mechanisms of NSAID-associated renal injury

The best-established short-term mechanism is haemodynamic. When renal perfusion is reduced, prostaglandins help maintain afferent arteriolar dilation. NSAID-mediated COX inhibition lowers PGE_2 and PGI_2, reducing this compensatory response. Afferent arteriolar tone may increase, renal blood flow falls, and glomerular filtration rate (GFR) may decline, producing haemodynamically mediated AKI in susceptible patients (Drożdżal et al., 2021; Klomjit & Ungprasert, 2022; Whelton, 1999).

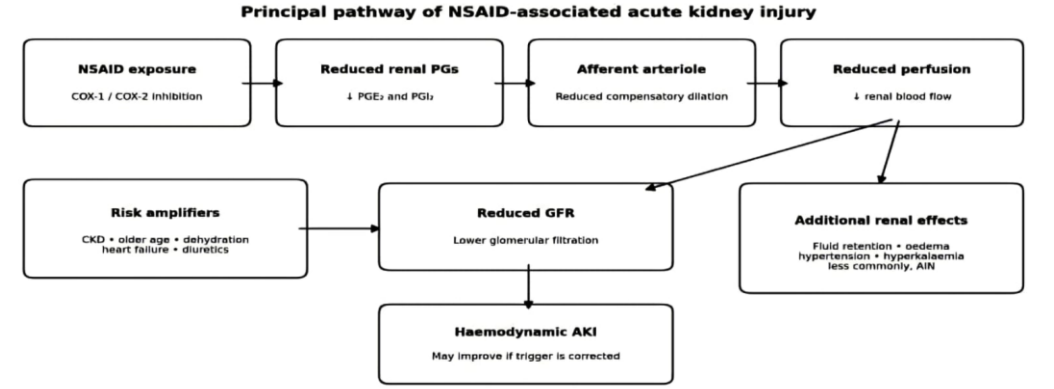


Figure 1. Principal pathway of NSAID-associated AKI. Author-prepared diagram based on Drożdżal et al. (2021), Klomjit and Ungprasert (2022), and Whelton (1999).

NSAIDs can also promote sodium and water retention, oedema, and worsening blood-pressure control. Hyperkalaemia is more likely when renal function is impaired or NSAIDs are combined with potassium-raising medicines. Less commonly, NSAIDs are associated with acute interstitial nephritis (AIN), which may occur without the classic fever–rash–eosinophilia pattern and may include proteinuria (Drożdżal et al., 2021; Klomjit & Ungprasert, 2022; Sabatino et al., 2020). Risk varies with dose, duration, frequency, and dependence on prostaglandin-mediated compensation. Even short-term use may be problematic during dehydration or acute illness; repeated or prolonged exposure increases concern (Drożdżal et al., 2021; Klomjit & Ungprasert, 2022; Wongrakpanich et al., 2018). Haemodynamic dysfunction may improve after NSAID withdrawal and correction of volume depletion, although recovery depends on injury severity and baseline renal function (Drożdżal et al., 2021; Klomjit & Ungprasert, 2022; Whelton, 1999).

2.2 Clinical evidence linking NSAIDs with AKI

A systematic review and meta-analysis found increased odds of AKI during current NSAID exposure in the general population (OR 1.73; 95% CI 1.44–2.07) and in people with CKD (OR 1.63; 95% CI 1.22–2.19) (Zhang et al., 2017). In older adults, a population-based study reported 30-day AKI in 0.82% of new NSAID users versus 0.59% of non-users (OR 1.41; 95% CI 1.20–1.65); hyperkalaemia occurred in 0.40% versus 0.27% (OR 1.50; 95% CI 1.20–1.89) (Nash et al., 2019).

These estimates describe associations in study populations, not the probability that every individual NSAID user will develop AKI. Relative risk should be interpreted alongside absolute event rates, baseline kidney function, and clinical context. Differences in study design and patient characteristics may also contribute to variation between estimates (Klomjit & Ungprasert, 2022; Nash et al., 2019; Zhang et al., 2017).

Table 1. Selected clinical evidence relevant to NSAID-associated AKI

Study (Selected evidence)	Key finding	Clinical relevance
Zhang et al. (2017)	AKI odds: OR 1.73 in the general population and OR 1.63 in CKD.	Caution is warranted in patients with reduced renal reserve.
Nash et al. (2019)	30-day AKI: 0.82% vs. 0.59% (OR 1.41); hyperkalaemia: 0.40% vs. 0.27% (OR 1.50).	Older adults may need closer assessment and monitoring.

Study (Selected evidence)	Key finding	Clinical relevance
Lapi et al. (2013)	Triple therapy: AKI rate ratio 1.31; during the first 30 days, 1.82.	Review this combination, especially after initiation.
Dreischulte et al. (2015)	Combined NSAID use with diuretics and/or renin-angiotensin system inhibitors was associated with AKI.	Medication reconciliation can identify interacting regimens.

2.3 The NSAID–diuretic–ACEI/ARB interaction

Concurrent use of an NSAID, a diuretic, and an ACE inhibitor (ACEI) or angiotensin receptor blocker (ARB) is known as the "triple whammy." Diuretics may reduce circulating volume; ACEIs/ARBs reduce angiotensin-II-mediated efferent arteriolar constriction; and NSAIDs limit prostaglandin-mediated afferent arteriolar dilation. Together, these effects can impair the kidney's ability to maintain filtration (Dreischulte et al., 2015; Lapi et al., 2013).

Lapi et al. (2013) reported an increased AKI rate with triple therapy (rate ratio 1.31; 95% CI 1.12–1.53), with the greatest increase during the first 30 days (rate ratio 1.82; 95% CI 1.35–2.46). Medication review should include prescription and non-prescription products, including combination pain, cold, and fever preparations.

2.4 Risk factors and clinical manifestations

Important risk factors include older age, CKD or previous AKI, dehydration, vomiting or diarrhoea, acute infection, heart failure, liver disease, diabetes, and hypertension. Treatment-related risks include high doses, prolonged or repeated courses, duplicate NSAID use, and combinations with diuretics or renin–angiotensin system inhibitors (Drożdżal et al., 2021; Klomjit & Ungprasert, 2022; Lapi et al., 2013; Sabatino et al., 2020; Wongrakpanich et al., 2018).

Clinical presentation varies with the severity and type of injury. Haemodynamic AKI may be detected only by a rise in serum creatinine or a fall in urine output. Other possible findings include reduced urine output, oedema, fluid retention, increased blood pressure, and electrolyte disturbances, particularly hyperkalaemia. AIN may present with a less specific pattern and should be considered when kidney dysfunction persists or does not fit a simple haemodynamic explanation (Drożdżal et al., 2021; Klomjit & Ungprasert, 2022; Sabatino et al., 2020).

2.5 Diagnosis and assessment

KDIGO defines AKI by any of the following: an increase in serum creatinine of at least 0.3 mg/dL within 48 hours; an increase to at least 1.5 times baseline within the preceding 7 days; or urine output below 0.5 mL/kg/hour for at least 6 hours (Khwaja, 2012). These criteria support early recognition even when symptoms are absent.

Assessment should compare current serum creatinine with the patient's baseline and review the timing of NSAID exposure, recent illness, fluid intake and losses, urine output, blood pressure, and concurrent medicines. Serum potassium and other electrolytes are important because impaired renal function and interacting medicines may increase the risk of hyperkalaemia. A single creatinine value without a known baseline may not fully reveal an acute change; repeat testing and clinical assessment may be needed (Khwaja, 2012; Nash et al., 2019).

The diagnosis should not be attributed automatically to NSAIDs. Dehydration, infection, obstruction, other nephrotoxic medicines, and underlying renal disease may also contribute. Persistent or unexplained dysfunction, suspected AIN, severe electrolyte disturbance, or significant reduction in urine output warrants prompt clinical evaluation and may require specialist input (Khwaja, 2012; Klomjit & Ungprasert, 2022; Sabatino et al., 2020).

2.6 Prevention, monitoring and clinical implications

Before recommending an NSAID, confirm that systemic treatment is necessary and consider non-pharmacological measures or suitable alternatives. Review previous AKI, CKD, hydration, cardiovascular and liver conditions, and all prescribed and over-the-counter medicines. Avoid duplicate NSAID therapy and carefully review the NSAID–diuretic–ACEI/ARB combination, especially in patients with additional risk factors (Dreischulte et al., 2015; Klomjit & Ungprasert, 2022; Lapi et al., 2013; Sabatino et al., 2020; Wongrakpanich et al., 2018).

When an NSAID is necessary, use the lowest effective dose for the shortest practical duration. In higher-risk patients, baseline and follow-up serum creatinine/eGFR and potassium assessment may be appropriate; the timing should be individualized according to baseline risk, clinical status, and treatment duration. Patients should seek professional advice during significant dehydration or acute illness and should not add another NSAID without advice (Khwaja, 2012; Klomjit & Ungprasert, 2022; Wongrakpanich et al., 2018).

If AKI is suspected, the potential NSAID should be promptly reviewed and generally withheld while the patient is assessed, unless the treating clinician decides otherwise. Evaluation should include renal function, electrolytes, urine output, volume status, concurrent medicines, and alternative causes. Management depends on the underlying cause and severity; correction of volume depletion and withdrawal of the precipitating medicine may allow

haemodynamic function to recover, but severe or persistent injury requires medical care (Khwaja, 2012; Klomjit & Ungprasert, 2022; Sabatino et al., 2020).

Pharmacists can contribute by identifying duplicate therapy and interactions, recognizing high-risk patients, checking non-prescription medicine use, counselling on safe use, and referring patients with symptoms or significant risk factors (Dreischulte et al., 2015; Klomjit & Ungprasert, 2022; Wongrakpanich et al., 2018).

2.7 Limitations and future considerations

The evidence includes observational studies, reviews, and clinical guidance. Differences in populations, AKI definitions, exposure measurement, follow-up, and adjustment for confounding limit direct comparison. Prescription databases may miss over-the-counter NSAID use, and observational associations cannot establish causation in every case. Therefore, relative estimates should be interpreted with absolute event rates and the patient's clinical context (Dreischulte et al., 2015; Lapi et al., 2013; Nash et al., 2019; Zhang et al., 2017).

Future studies should report both relative and absolute risks and examine outcomes by CKD stage, age, hydration, dose, duration, and concurrent medicines. Further research on pharmacist-led medication review and patient counselling may help identify practical prevention strategies.

3. CONCLUSION

NSAID-associated AKI is a clinically important and potentially preventable adverse event. Inhibition of renal prostaglandin synthesis can reduce afferent arteriolar dilation and GFR, particularly in people with CKD, older age, volume depletion, or cardiorenal disease. The NSAID–diuretic–ACEI/ARB combination warrants particular attention (Dreischulte et al., 2015; Lapi et al., 2013; Nash et al., 2019; Zhang et al., 2017).

Safer use depends on confirming the need for treatment, reviewing concurrent medicines, avoiding duplicate exposure, and using the lowest effective dose for the shortest practical duration. Renal function and potassium should be monitored when clinically appropriate. Individualized prescribing and pharmacist-led counselling can help reduce avoidable renal harm.

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