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Practice Guidelines

# Nephrotoxins and acute kidney injury — The consensus of the Taiwan acute kidney injury Task Force

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The Taiwan Acute Kidney Injury (AKI) Task Force conducted a review of data and developed a consensus regarding nephrotoxins and AKI. This consensus covers: (1) contrast-associated AKI; (2) drug-induced nephrotoxicity; (3) prevention of drug-associated AKI; (4) follow up after AKI; (5) re-initiation of medication after AKI.

Strategies for the avoidance of contrast media related AKI, including peri-procedural hydration, sodium bicarbonate solutions, oral N-acetylcysteine, and iso-osmolar/low-osmolar non-ionic iodinated contrast media have been recommended, given the respective evidence levels.

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Regarding anticoagulants, both warfarin and new oral anticoagulants have potential nephrotoxicity, and dosage should be reduced if renal pathology exam proves renal injury. Recommended strategies to prevent drug related AKI have included assessment of 5R/(6R) reactions — risk, recognition, response, renal support, rehabilitation and (research), use of AKI alert system and computerized decision support.

In terms of antibiotics-associated AKI, avoiding concomitant administration of vancomycin and piperacillin-tazobactam, monitoring vancomycin trough level, switching from vancomycin to teicoplanin in high-risk patients, and replacing conventional amphotericin B with lipid-based amphotericin B have been shown to reduce drug related AKI. With respect to non-steroidal anti-inflammatory drug associated AKI, it is recommended to use these drugs cautiously in the elderly and in patients receiving renin-angiotensin-aldosterone system inhibitors/diuretics triple combinations.



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## Introduction

Drug-induced nephrotoxicity is a common etiology of acute kidney injury (AKI), leading to 20% of all community- and hospital-acquired events.[1] In an aging society, people have more comorbidities, and receive more diagnostic or therapeutic procedures with some degree of nephrotoxicity.[1] Therefore, knowledge of drug nephrotoxicity and early detection are helpful in successfully preventing drug-associated AKI and avoiding severe complications.[2]

The Taiwan Acute Kidney Injury Task Force was organized by the Taiwan Society of Critical Care Medicine (TSCCM), the Taiwan Society of Emergency and Critical Care Medicine (SECCM), the Taiwan Society of Nephrology (TSN), the Asia—Pacific Chapter of the Extracorporeal Life Support Organization (APELSO), the Nutrition Society of Taiwan, and the Taiwan Society for Parenteral and Enteral Nutrition (TSPEN). The Taiwan AKI Task Force conducted a review of data and developed a consensus regarding nephrotoxins and acute kidney injury. This consensus covers: (1) contrast-associated AKI; (2) drug-induced nephrotoxicity; (3) prevention of drug-associated AKI; (4) follow up after AKI; and (5) re-initiation of potentially nephrotoxic medication after AKI.

## Contrast-associated AKI

Contrast-associated AKI is one of the leading causes of iatrogenic renal insufficiency, along with widespread medical images containing contrast materials.[3] Pathophysiology of contrast-induced nephropathy included oxidative stress, apoptosis, immune/inflammation, epigenetic regulation, renal medullary hypoxia, and direct toxicity of contrast agents.[3] Chronic kidney diseases (CKD) may pronounce the risk of contrast-induced acute kidney injury (AKI), however, for patients with preserved renal function, the risk is marginal.[4] Since the prevalence of chronic kidney diseases is high in Taiwan,[5] it is critical to avoid the acute renal complications of contrast media in the Taiwanese population. Effective therapy for contrast-induced nephropathy is not obtained, thus risk prediction and preventive strategies are important to reduce its occurrence.[5] Several strategies, including appropriate use of contrast medium, individualized hydration, and high-dose statins may reduce the chance of contrast-induced nephropathy. Furthermore, the evidence of remote ischemia preconditioning and vasodilators in the prevention of contrast-induced nephropathy needs further investigation.[3]

**Q2-1.** What can be recommended for prevention and management of contrast-associated AKI according to current evidence?

**A2-1-1.** If there are alternative options, we suggest not to perform examinations using contrast media injections.[6,7] (Not graded)

**A2-1-2.** Iso-osmolar or low-osmolar non-ionic iodinated contrast media are preferable.[6] Iso-osmolar contrast media may protect better against contrast-induced acute kidney injury than low-osmolar non-ionic iodinated contrast media.[8] (Grade 1B).

**A2-1-3.** Before the injection of contrast media, intravenous infusions of isotonic normal saline or sodium bicarbonate solutions are recommended.[6,9–11] (Grade 1A)

**A2-1-4.** Routine oral or intravenous N-acetylcysteine are not recommended to use for the prevention of contrast-induced acute kidney injury.[6,9,11,12] (Grade 1A)

**A2-1-5.** Routine prophylactic intermittent hemodialysis or hemofiltration is not suggested to prevent contrast-induced acute kidney injury.[6,13,14] (Grade 2C)

**A2-1-6.** High-dose statins, remote ischemic preconditioning, and vasodilators have potential benefits for the prevention of contrast-induced nephropathy.[3] (Not graded)

**A2-1-7.** Other novel antioxidants (quercetin, febuxostat, and recombinant klotho) might be promising clinical candidates for the prevention of contrast-induced nephropathy.[3] (Not graded)

## Drug-induced nephrotoxicity

There are three clinical syndromes associated with drug-induced nephropathy, including acute renal failure, chronic interstitial nephritis and the nephrotic syndrome. Table 1 described potential nephrotoxic agents and their effects on kidney[15] Main causes consist of prerenal problems, acute interstitial nephritis, acute tubular necrosis and intratubular obstruction.[15] The most important offending drugs related to prerenal failure are non-steroidal anti-inflammatory drugs (NSAIDs), captopril and cyclosporin.[15] Acute interstitial nephritis is usually self-limiting, with spontaneous renal recovery after offending drug withdrawal, and steroids may promote the recovery,[15] Drugs involved in acute interstitial nephritis are listed in Table 2.

According to one systematic review and meta-analysis, observational studies on the use of warfarin among patients with atrial fibrillation (AF) showed that the prevalence of warfarin related nephropathy (WRN) was 31%, and the 5-year mortality rate for WRN was 1.91 times that of non-warfarin related nephropathy.[16] The risk of AKI caused by warfarin in patients with CKD is significantly higher than in those without kidney diseases.[17]

The literature on WRN mostly consists of observational studies.[18–22] The ethnic heterogeneity between the studies is high, and the diagnostic criteria are also inconsistent (Table 3). Retrospective observational studies have shown that new oral anticoagulants (NOACs) carry a lower risk of AKI in patients with AF than warfarin does.[17,23,24] In post-hoc analysis of randomized controlled trials (RCT), nevertheless, the risks of AKI caused by different NOACs were inconsistent (Table 4).

Given that NOAC-related RCTs have hitherto excluded patients with CKD stage 4–5,[25–27] there is a lack of evidence on the risk of AKI caused by NOACs among patients with eGFR lower than 30 ml/min/1.73 $m^2$. In a review article published in the *Journal of the American Society of Nephrology*, Brodsky et al. suggested that if renal pathology tests reveal typical anticoagulant-related nephropathy (with unexplained profuse glomerular hemorrhage; abnormal thin or thick glomerular basement membrane), anticoagulant strategy should be switched to NOACs for initial warfarin users, while dosage should be reduced for initial NOAC users.[28] Absorption, metabolism, and NOACs dosing in chronic kidney disease were described in Table 5.

Regarding the impacts on AKI caused by different etiologies, an observational cohort study of 618 patients with AKI from intensive care units in 5 medical centers in the USA found that there was no statistically significant difference in a combined outcome of in-hospital mortality and non-recovery (dialysis dependence at discharge) among different etiologies. Moreover, whether early removal of nephrotoxins or early dialysis might improve patient prognosis also cannot be properly investigated.[29] Another study from Spain demonstrated that at least 54% of acute renal failure cases were potentially drug-related, moreover, compared with other etiologies, drug-related AKI has higher peak serum creatinine and lower mortality, despite the severity of AKI (According to the RIFLE classification)does not reach statistical significance.[30]

Drugs-induced AKI consists of several causes, including interstitial nephritis, intrarenal obstruction, nephrotic syndrome, electrolytes disorders, and acid-base and fluid. Certain drugs altered intraglomerular hemodynamics, caused inflammatory changes in renal tubular cells, and lead to tubulointerstitial disease and renal scarring.[31] No systematic review or meta-analysis has been published that can confirm the hypothesis that different etiologies of AKI might lead to distinguishable outcomes, such as in renal recovery rate, the reversibility of the etiology, the effect of dialysis or rates of dialysis dependence. More studies are required to address these unknowns.

**Q3-1.** Is there sufficient evidence to classify potential nephrotoxins in a clinically useful way?

**A3-1-1.** Some biomarkers are promising candidates for earlier detection and intervention for AKI, such as Kidney Injury Molecule-1, Beta-2 microglobulin, Clusterin, and Cystatin C.[32] (Not graded)

**A3-1-2.** When using warfarin, it is necessary to evaluate the potential occurrence of AKI, including risk factors of age, diabetes mellitus, heart failure, hypertension, and nephrotic syndrome.[18] (Grade 1A)

**A3-1-3.** In patients with an eGFR higher than 30 ml/min/1.73 $m^2$, the use of NOAC may carry a lower risk of AKI than warfarin (Grade 1A).[33,34]

**Q3-2.** Compared with other causes, such as insufficient renal perfusion, shock, or infection, does drug-related AKI result in different outcomes?

**A3-2.** No systematic review or meta-analysis has been published that confirms the hypothesis that different etiologies of AKI might lead to distinguishable outcomes. More studies are required to address this question (Not graded).

**Table 1** Potential nephrotoxic agents and their effects on kidney.

| Drug category | Medication | Renal toxicity | Outcome |
|---|---|---|---|
| Non-narcotic analgesic | Acetaminophen | Chronic interstitial nephritis, acute tubular necrosis | ↙ Cause papillary necrosis in animals<br>↙ Important cause of end-stage renal disease |
| | Aspirin | Chronic interstitial nephritis | ↙ Self-limiting<br>↙ Steroids may promote recovery |
| | Non-steroidal anti-inflammatory drugs | Prerenal problem, acute interstitial nephritis | ↙ Self-limiting<br>↙ Steroids may promote recovery.<br>↙ High risk of acute renal failure for the combined use of an NSAID and methotrexate; NSAID with triamterene |
| Carbonic-anhydrase inhibitor | Acetazolamide | Proximal renal tubular acidosis | |
| Antiviral | Acyclovir | Acute interstitial nephritis, crystal nephropathy | ↙ Self-limiting<br>↙ Steroids may promote recovery |
| Immunosuppressive agent | Cyclosporin | Prerenal problem, acute tubular necrosis, Chronic nephritis | ↙ Drug induced nephrotic syndrome, membranous glomerulonephritis and minimal change glomerular disease<br>↙ Reversible after withdrawal of the drug |
| Hypouricemia agent | Allopurinol | Acute interstitial nephritis | ↙ Self-limiting<br>↙ Steroids may promote recovery |
| Antidepressant | Amitriptyline | Rhabdomyolysis | |
| Antimicrobial | Aminoglycosides | Acute tubular necrosis | ↙ Outcome is usually good; recovery after withdrawal of the drug in almost all cases (about 10 days) |
| | Beta lactams | Acute interstitial nephritis | ↙ Self-limiting<br>Steroids may promote recovery |
| | Carbenicillin | Metabolic alkalosis | |
| | Colistin | Increased permeability of the cell wall and consequent edema and lysis; acute tubular necrosis | ↙ Good renal prognosis after discontinuation of the drug |
| Antifungal | Amphotericin B | Acute tubular necrosis, distal renal tubular acidosis | ↙ Renal function usually improves after cessation of therapy<br>↙ Irreversible damage may occur, especially at a cumulative dose above 5g. |
| Antihypertensive | Angiotensin-converting enzyme inhibitors | Acute kidney injury | |
| | Angiotensin receptor blockers | Acute kidney injury | |
| Sedative-Hypotonic | Benzodiazepines | Rhabdomyolysis | |

## Prevention of drug-associated AKI and timing of re-initiation

Drug-induced nephrotoxicity is a frequent adverse event which leads to higher morbidity and increased healthcare utilization.[35] Early detection of AKI via an electronic sniffer or electronic-alert could be achieved by recording individual creatinine or urine output, which are typically available in the integrated electronic health record or intensive care clinical information system.[36] Electronic surveillance presents a powerful tool to identify susceptible populations, early recognition of events, timely response with preventative strategies or early intervention

**Table 2** Offending drugs related with acute interstitial nephritis.

| Antibiotics | NSAIDs | Diuretics | Antiepileptic drugs | Others |
|---|---|---|---|---|
| Amoxycillin | Fenclofenac | Chlorthalidone | Carbamazepine | Allopurinol |
| Benzylpenicillin (penicillin G) | Fenoprofen | Furosemide (frusemide) | Phenobarbital | para-Aminosalicylic acid |
| Carbenicillin | Ibuprofen | (Hydro)chlorothiazide | Phenytoin (diphenylhydantoin) | Azathioprine |
| Cefalexin | Indomethacin | Tienilic acid | | Captopril |
| Cefalothin | Mefenamic acid | Triamterene | | Cimetidine |
| Cefoxitin | Fenclofenac | | | Clofibrate |
| Cefradin | Naproxen | | | Glafenine |
| Ciprofloxacin | Phenylbutazone | | | Isoniazid |
| Cotrimoxazole (trimethoprim plus sulfamethoxazole) | Piroxicam | | | a-Methyldopa |
| Erythromycin | Sulindac | | | Propranolol |
| Methicillin | Tolmetin | | | |
| Nafcillin | | | | |
| Norfloxacin | | | | |
| Oxacillin | | | | |
| Rifampicin | | | | |
| Sulphonamides | | | | |
| Tetracyclines | | | | |
| Vancomycin | | | | |

**Table 3** Published literature on warfarin-related nephropathy.

| Authors | Study design | Inclusion criteria | Exclusion criteria | eGFR method | Definition of WRN | Duration of follow-up |
|---|---|---|---|---|---|---|
| An et al.[20] | retrospective, observational | >18-year-old, INR>3 | Have received RRT, baseline eGFR>175 ml/min | MDRD equation | Increased serum creatinine >50% of baseline or 0.3 mg/dL within one week after INR>3 | 23.3 ± 26.8 months |
| Brodsky et al.[18] | retrospective, observational | INR>3 | <18 yrs old, ESRD, major bleeding with INR>3 | CKD-EPI equation | Increased serum creatinine 0.3 mg/dL within one week after INR>3 | 5 years |
| Lim and Campbell[21] | prospective, observational | elderly people who have been in a specific care center for more than 1 day | Readmission within 28 days, INR<2, terminal status, urinary tract infection, dialysis | MDRD equation | Not available | 4–6 weeks |
| Brodsky et al.[19] | retrospective, observational | CKD stage 2–4, INR>3 | other etiologies of AKI | not available | Increased serum creatinine 0.3 mg/dL after INR>3 | 2 years |
| Brodsky et al.[22] | case series | AKI with hematuria | acute glomerulonephritis | GFR in ml/min | Biopsy-proven | 5 years |

Abbreviations: eGFR: estimated glomerular filtration rate; WRN: warfarin-related nephropathy; INR: international normalized ratio; RRT: renal replacement therapy; MDRD: Modification of Diet in Renal Disease; ESRD: end-stage renal disease; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CKD: chronic kidney disease; AKI: acute kidney injury.

once injury took place.[35] Moreover, 5R/(6R) framework was useful to identify and mange drug induced kidney injury: risk, recognition, response, renal support, rehabilitation and (research).[35,37] Current knowledge of drug induced kidney disease is limited due to inconsistent definitions of kidney injury, incomplete evaluations of concomitant risk factors and inadequate report of long-term outcome.[35]

**Table 4** Post-hoc analysis of clinical trials to compare the risk of acute kidney injury caused by warfarin and NOACs.

| Trials | Study patients | Treatment | Hazard ratio |
|---|---|---|---|
| RE-LY[27] | 18,113 | warfarin *v.s* dabigatran | 0.81 (0.69—0.96) |
| ROCKET[25] | 12,612 | Warfarin *v.s* rivaroxaban | Not reported but described as "consistent" with RE-LY |
| ARISTOTLE[26] | 16,869 | warfarin *v.s* apixaban | Not different from 1.0 |

Glomerular filtration is determined by renal blood flow, hydraulic permeability of the glomerular basement membrane, and effective glomerular capillary pressure and. Angiotensin II preserves glomerular filtration rate in the situation of low blood flow, via vasoconstriction of the efferent arteriole. However, prostaglandin is antagonist for vasoconstrictive agents (such as norepinephrine, and cyclosporin), and it act as vasodilators of the afferent arteriole. Angiotensin-converting enzyme inhibitors (ACEI)/Angiotensin receptor blocker (ARB) block the formation of angiotensin II, and should be cautiously used in patients with stenotic renal arteries, NASID, and cyclosporin[15] This effect of ACEI/ARB appeared not to be dose related. Patients with renal artery stenosis maintain glomerular filtration rate of the stenotic kidney via angiotensin II-induced vasoconstriction of the efferent arteriole. Therefore, administration of an ACEI/ARB to may completely block glomerular filtration, and cause reversible acute renal failure if there are bilateral renal artery stenosis, or stenosis of a single functional renal artery, such as for renal transplant patients.[15]

Although ACEI and ARB have benefits, the risk—benefit ratio needs to be weighted in patients with AKD.[38] When to

**Table 5** Absorption, metabolism, and NOACs dosing in chronic kidney disease.

| | Dabigatran | Apixaban | Edoxaban | Rivaroxaban |
|---|---|---|---|---|
| Bioavailability | 3—7% | 50% | 62% | 66% (without food)<br>100% (with food) |
| Prodrug | Yes | No | No | No |
| Non-renal/renal clearance | 20%/80% | 73%/27% | 50%/50% | 65%/35% |
| CYP3A4 metabolism | No | Yes | Minimal (<4%) | Yes |
| Absorption with food | No effect | No effect | 6—22% | +3% |
| Intake with food? | No | No | No | Mandatory |
| Interaction with H2B/PPI | Yes (12—30%) | No | No | No |
| Asian ethnicity | +25% | No effect | No effect | No effect |
| GI tolerability | Dyspepsia | Well | Well | Well |
| Elimination of half-life | 12—17 h | 12 h | 10—14 h | 5—9 h (young)<br>11—13 h (elderly) |
| Approved for CrCl (mL/min) | ≥30 | ≥15 | ≥15 | ≥15 |
| Non-adjusted dosage, CrCl (mL/min); dosage | ≥50; 150 mg BID | ≥15; 5 mg BID | ≥50; 60 mg QD | ≥50; 20 mg QD |
| Adjusted dosage, CrCl (mL/min); dosage | ↙ 30—49; 150 mg BID (110 BID should be considered, ESC)<br>↙ 15—30; 75 mg BID (only in US)<br>*Dosage should be adjusted in concern of drug—drug interactions (e.g. verapamil) | 15-29+ ABC criteria*; 2.5 mg BID (*ABC criteria: adjusted dosage if two-put-of-three: age> 80; Body weight< 60 kg; serum creatinine ≥1.5 mg/dL | 15-49; 30 mg QD | 15-49; 15 mg QD |
| Contraindication, CrCl (mL/min); dosage | <30 | <15 | <15 | <15 |

Abbreviation: NOAC, new oral anticoagulants.

stop these drugs during periods of AKI/AKD and the timing of re-introduction had no conclusive consensus. In general practice, restart of ACEI/ARBs in acute illness is usually considered after GFR has stabilized and optimized volume status is achieved.[38]

**Q4-1. How can drug-induced acute kidney injury be recognized early and prevented?**

**A4-1.** 1) Early recognition and intervention can be achieved through the deployment of an electronic AKI alert system.[36,39–43] (Not graded)

2) Assess potential drug-induced acute kidney injury using the 5R/(6R) reactions: Risk, Recognition, Response, Renal support, Rehabilitation, and (Research).[35,44,45] (Not graded)
3) A systematic review indicated that utilizing a computerized decision support system (CDSS) to assist in drug prescription could reduce mortality, life-threatening events, and non-life-threatening events.[46–49] (Grade 1A)

**Q4-2. Could we lower the incidence of acute kidney injury by avoiding concomitant administration of vancomycin and piperacillin-tazobactam?**

**A4-2.** We suggest that clinicians be cautious of the incidence of acute kidney injury when simultaneously administrating vancomycin and piperacillin-tazobactam.[50–53] (Not graded)

**Q4-3. Could we avoid vancomycin induced AKI by monitoring serum drug level?**

1) We suggest monitoring serum vancomycin concentrations in patients receiving vancomycin therapy.[52] (Not graded)
2) We suggest monitoring serum vancomycin trough levels. If serum drug levels exceed 15 ng/ml, clinicians should be cautious of drug induced acute kidney injury.[50,51] (Grade 1C)
3) We suggest to use teicoplanin as an alternative for vancomycin in high-risk patients.[53] (Grade 1C)

**Q4-4. Which form of amphotericin B could effectively reduce drug toxicity?**

**A4-4.** We suggest using lipid-based amphotericin B, such as lipid-emulsion or liposomal amphotericin B, instead of conventional amphotericin B, in order to reduce toxicity.[54,55]

**Q4-5. When can ACEI or ARB be re-initiated?**

**A4-5.** 1) We suggest that ACEI or ARB should be re-initiated after AKI among chronic kidney disease (CKD) patients who were regular users of ACEI or ARB before AKI.[38] (Grade 2D)

2) Serum creatinine and potassium concentration should be monitored one or two weeks after re-initiation of ACEI or ARB.[38] (Grade 2D)

**Q4-6. Should we stop the use of ACEI or ARB before surgery or cardiac catheterization in order to prevent acute kidney injury?**

**A4-6.** It is not necessary to stop the use of ACEI or ARB before surgery or cardiac catheterization.[38] (Grade 2D)

**Q4-7. Is it beneficial to use ACEI or ARB after AKI?**

**A4-7.** Use of ACEI or ARB after AKI may reduce the risk of mortality.[38] (Grade 2D)

## Follow up after AKI

Drug-associated acute kidney injury (DA-AKI) develops less than 7 days after exposure to offending drugs.[38] However, the median time from proton pump inhibitors (PPIs) use to event occurrence was 23 days for AKI, with the range of 14—28 days, and average time of 177 days for chronic kidney disease.[56] Other evidence demonstrated that PPI use was significantly associated with AKI outcomes after PPI use for 7 and 14 day, however, the associations between PPIs use and AKI outcomes gradually weakened after 28 days and 42 days of PPI use.[57] We suggest developing a framework for DA-AKI stage-based management from the acute stage through progressive kidney disease.[38] Persistent AKI is characterized by the continuance of AKI based on serum creatinine or urine output beyond 48 h from AKI onset, as defined by Kidney Disease: Improving Global Outcomes (KDIGO). Complete reversal of AKI within 48 h of AKI onset characterizes rapid reversal of AKI. Although the optimal duration of sustained AKI reversal is unknown, a minimum of 48 h is necessary to define an AKI event.[58,59] Acute kidney disease (AKD) is present if injury persists $\geq$7 days after an AKI initiating event. We suggest a 'layered' approach according to the severity of AKD, with different frequency and intensity of follow-up should be adopted. Nephrology or more frequent follow-up should be done for patients with more severe AKD and the presence of pre-existing chronic kidney disease, congestive heart failure, cirrhosis, and/or malignancy.[35]

Renal recovery in patients with AKI who have been treated with acute renal replacement is defined as more than 14 days sustained independence from RRT.[38] Moreover, remission of AKI for at least a 24-h period within 7 days following the first documented onset of AKI was defined as "early reversal"; for patient with AKI, a decrease in serum creatinine more than 150% compared to baseline, and the absence oliguria (UO $<$ 5 ml/kg/hr) longer than 6 h were coincidental with renal recovery.[60]

Future research should aim to determine the optimal time to define sustained independence from RRT and to develop and validate functional assessment tools for this population.[38] Most cases of nephrotoxicity resolve with discontinuation of the causal drug. However, AKI is a significant risk factor for the development of CKD, which is defined as renal injury persisting for more than 90 days.[38]

**Q5-1. How should follow-up be conducted after an episode of drug-associated AKI during hospitalization?**

**A5-1.** 1) We suggest a careful risk-benefit consideration before dose reduction or discontinuation of the offending drug, once DA-AKI develops. For dose-dependent renal toxicity, dose reduction may be sufficient to mitigate the injury, however, idiosyncratic nephrotoxicity often warrants drug discontinuation.[35] (Not graded)

2) We suggest initial reassessment of the underlying etiology of AKI, followed by precise measurement of kidney function.[35] Daily assessment of Scr and urine

output should be monitored.[35] Dose adjustments for kidney function should be made under the assistance of timed urine collections for clearance creatinine.[35] (Not graded)

3) We suggest re-evaluating hemodynamic and volume status, and adequacy of kidney perfusion. Complications of AKI, such as fluid overload, acidosis and hyperkalemia should be identified, and any need for renal replacement therapy evaluated, when persistent AKI is diagnosed [57]. Nephrology experts should be consulted if the etiology of AKI is not clear or subspecialist care is needed.[35] (Not graded)
4) We suggest timed urine creatinine clearance measurement to estimate kidney function for patients with persistent AKI in the steady state.[35] (Not graded)
5) We suggest not to use equations to estimate glomerular filtration rate for the assessment of renal function in persistent AKI.[35] We suggest daily assessment of serum creatinine and urine output.[35] Dose adjustments for kidney function should be made under the assistance of timed urine collection for clearance creatinine measurement.[35] (Not graded)
6) We suggest kidney biopsies to guide treatment decisions if the sub-phenotype of DA-AKI is difficult to distinguish through laboratory parameters (i.e. ATN vs. AIN).[35] (Not graded)
7) We suggest patients with more severe AKD (eGFR $<30$ ml/min/1.73 $m^2$) receive nephrology follow-up where feasible.[35,61] (Not graded)
8) We suggest more frequent follow-up and assessment of kidney function for patients with key modifiers, including pre-existing chronic kidney disease, congestive heart failure, cirrhosis, or malignancy.[35] (Not graded)
9) We suggest avoiding nephrotoxic medications or combinations in patients with DA-AKI. Given the clinically compelling reasons, nephrotoxic effects should be mitigated, and concomitant administering of multiple nephrotoxic drugs should be avoided whenever possible.[38] (Not graded)
10) We suggest avoiding concurrent risk factors for kidney injury, such as hypotension, hyperglycemia, anemia, etc., and minimizing nephrotoxins or drug interactions as much as possible.[35] (Not graded)
11) We suggest to continue monitoring therapeutic drugs even after drug discontinuation if supra-therapeutic drug concentrations are documented during the injury.[35]
12) We suggest to reserve renal replacement therapy (RRT) for severe injuries or to mitigate drug toxicity through dialysis.[35] RRT should be initiated if life-threatening changes in fluids, electrolytes, or acid-base balance emerge.[35] (Not graded)
13) We suggest to stop RRT based on changes in predialysis serum creatinine values, urine output, fluid status and acidosis. For drug dosing during the recovery, total renal clearance should be estimated to quantify intrinsic kidney function aside from dialysis therapy.[35] (Not graded)

**Q5-2. How to follow up after an episode of drug-associated AKI after discharge?**

**A5-2. 1)** We suggest to document the event to prevent future injury through subsequent exposure.[35] Furthermore, we suggest to inform patients about the event and educate them to inform other healthcare providers of their susceptibility to the drug.[35]

2) We suggest to use biomarkers and real-time assessment of glomerular filtration rate to accurately assess endogenous kidney function among patients receiving acute RRT.[38] (Not graded)
3) We suggest further follow-up in specialized clinics with repeated assessment of renal function to evaluate reversibility and delayed recovery.[35] (Not graded)
4) We suggest to report adverse events to national official organizations, and to avoid the use of offending drugs without consulting a nephrologist, drawing on information from past exposures.[35,38] In Taiwan, please complete the report of drug associated adverse reactions following the official instruction in Taiwan National Adverse Drug Reactions Reporting System. Please visit official network to get further information (https://www.fda.gov.tw/tc/siteContent.aspx?sid=4240) (Not graded)
5) We suggest the derivation and validation of a clinical risk score to predict RRT dependence at 90 days, or subsequent time points.[38] (Not graded)
6) We suggest future studies involving RRT interventions, focusing on kidney recovery as an important outcome measurement. Regarding kidney recovery end point, patients should be followed-up for a minimum of 90 days.[38] (Not graded)
7) We suggest to prioritize interventions that focus on ultrafiltration intensity, fluid balance, cardiovascular stability and optimal antibiotic dosage in consideration of the most plausible likelihood of effecting renal recovery.[38] (Not graded)

## Conclusions

CKD patients are at higher risk of AKI from associated drugs including contrast media, anticoagulants and antibiotics, and respective recommendations have been made, based on current evidence. A trend toward lower in-hospital mortality caused by AKI has been observed following the recommendation of prevention strategies such as the assessment of 5R reactions and the deployment of an AKI alert system and computerized decision support systems. Furthermore, follow-up after an episode of drug-associated AKI should be initiated during hospitalization, and continue after discharge, for up to 90 days. Re-initiation of drugs after AKI is an important issue, whereby serum creatinine and potassium concentration should be monitored after re-initiation of ACEI or ARB.

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## Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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