Overview of aristolochic acid nephropathy: an update

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Aristolochic acid nephropathy (AAN) is a rapidly progressive renal interstitial fibrosis caused by medical or environmental exposure to aristolochic acid (AA). Since the outbreak of AAN in Belgium was reported nearly 30 years ago, the safety of herbal remedies has drawn considerable attention, and AAN has become a global public health problem. Breakthroughs have been made to better understand the disease, including the toxicity of AAs, the possible mechanisms of AAN, the disease patterns, and the pathological features; however, some critical problems remain unresolved. Because of the insidious onset of the disease, the incidence of AAN and the prevalence of exposure to AAs are unknown and might be largely underestimated. During the past decades, AA-containing herbs have been strictly administered in many regions and the occurrence of AAN has declined sharply, yet cases of AAN are still sporadically reported. Despite the progress in the understanding of the disease’s pathogenesis, there is no effective treatment for delaying or reversing the renal deterioration caused by AAN. Therefore, the risk of exposure to AAs should be taken seriously by public health workers and clinicians. In this review, we updated the latest data on AAN, summarized the advances throughout these years, and put forward some challenges for future research.

Keywords: Aristolochic acids, Aristolochic acid nephropathy, Herbal therapy, Interstitial nephropathy, Renal tubular dysfunction

Introduction

In 1964, a Chinese doctor named Songhan Wu first described two patients with acute renal failure after excessive intake of Aristolochia manshuriensis, yet the nephrotoxicity of Aristolochia was not taken seriously at that time [1]. In the early 1990s, a group of Belgian scholars reported that a cohort of young female patients suffered from rapidly progressive interstitial renal fibrosis [2]. The onset of the epidemic was attributed to continuous consumption of the same slimming pills containing Chinese herbs; therefore, this new type of kidney disease was initially termed “Chinese herbs nephropathy” [2]. Very soon after, researchers revealed that roots of Stephania tetrandra (Pin Yin: Han Fang Ji), an original component in the slimming regimen, were mistakenly replaced with...
roots of an aristolochic acid (AA)-containing herb called *Aristolochia fangchi* (Pin Yin: Guang Fang Ji), because they both belong to the “Fang Ji” family in traditional Chinese medicine and share similar names in Pin Yin [3,4]. Further studies then identified AA as the causative agent, leading to the renaming of this renal tubulointerstitial disease as “aristolochic acid nephropathy” (AAN) [5]. Furthermore, AA exposure has been proven to be associated with a high incidence of urothelial carcinoma [6,7]. Since its discovery, cases related to AA intoxication have been reported all over the world, and AA exposure has received considerable attention [8]. Due to its hidden onset, the incidence of AAN could be largely underestimated, especially in Asia [8]. As traditional medicines are extremely popular in Asia, the wide application of *Aristolochia*, as well as the frequent substitution of botanical products by AA-containing herbs, increased the potential risk of AAN [8-10]. Despite the banning of *Aristolochia* in many countries, botanical remedies containing AA are still accessible and sporadic cases are occasionally reported, reminding clinicians not to overlook the harm of AA exposure [11].

**Epidemiology of aristolochic acid nephropathy**

The outbreak of AAN in Belgium first reported in the early 1990s included nine female patients [2], but the number of patients involved rose to more than a hundred in 1998 [12]. Cases with similar or different phenotypes related to AA nephrotoxicity were reported thereafter in Europe [13-16], the United States [17], China [18,19], Japan [20,21], Korea [22], Australia [23], and Bangladesh [24], illustrating that AA-containing herbs were widely used for treating an assortment of diseases. Due to its insidious onset, low awareness, as well as lack of strict diagnostic criteria, the prevalence of AAN remains largely unknown and is probably underestimated, especially in Asia [8]. Thousands of cases have been reported in China in the past decades among patients previously diagnosed with chronic tubulointerstitial nephritis of unknown origin [25]. At our center in Beijing, 300 patients were diagnosed with AAN between 1997 and 2006 [18]. As for Korea and Japan, the number of persons affected by AAN appears to be relatively lower than in China [21,22]. Although no cases of AAN have been reported in India, the high proportion of patients with chronic interstitial nephritis among the chronic kidney disease (CKD) population might be associated with dietary and environmental AA exposure [26,27]. In the Balkan region, so-called Balkan endemic nephropathy is regarded as an endemic type of AAN with similar clinical and pathological features; it occurs after the chronic ingestion of food made from flour contaminated by the seeds of *Aristolochia clematitis* [28].

When it comes to risk factors, the cumulative dose of AA ingestion has been proven to be correlated with progressive renal dysfunction [25]. According to a survey conducted in China, regular use of nephrotoxic medications (analgesics or AA-containing pills) increased the risk of renal impairment (odds ratio [OR], 2.19) [29], and a cumulative dose of over 0.5-g aristolochic acid I (AA-I) intake was tightly associated with a higher CKD incidence (OR, 5.625) [30]. In recent years, the number of patients with newly diagnosed AAN has reduced sharply because of the warning and strict supervision of AA-containing herbs in many countries, yet sporadic cases are reported occasionally, reminding clinicians to take AA exposure seriously.

**Aristolochic acid: the culprit**

**Herbs containing aristolochic acids**

AAs are found in the plants of the genus *Aristolochia* and *Asarum* belonging to the *Aristolochiaceae* family, which are widely distributed worldwide [31]. Herbal remedies of *Aristolochia* can date back to more than 2,500 years ago in Europe, and at least 1,500 years ago in China [32]. Throughout the long history, AA-containing medications have been utilized to treat various diseases and indications, including eczema, headaches, colds, chronic pain, infections, inflammatory diseases, snake bites, as well as obstetrical and gynecological diseases [31,33-35]. At least seven species of *Aristolochia*, as well as four species of *Asarum*, are used medicinally (Table 1) [36,37]. In the clinical practice of traditional Chinese medicine, dozens of AA-containing herbs have been reported, including Ma Dou Ling (*Aristolochiae Fructus*), Guan Mu Tong (*A. manshuriensis* Caulis), Qing Mu Xiang (*Asarum Radix*), Ma Xia Tang (*A. clematitis* Caulis), Guang Fang Ji (*A. fangchi* Radix), Tian Xian Teng (*Aristolochiae Herba*), Xi Xin (*Asari Radix et Rhizoma*), etc. [31,38]. A number of Chinese patent medicines have been tested with the content of AA, some of which were associated with AAN in previously reported cases [31].
Metabolism of aristolochic acids

AA is a generic term for a family of structurally related nitrophenanthrene carboxylic acids [39]. Among all those compounds, AA-I and aristolochic acid II (AA-II) are the most common components extracted from the Aristolochia species (the structures of AA-I and AA-II are shown in Fig. 1) [40]. In human cells, AA-I and AA-II are mainly reduced to aristolactams (ALs), including AL-I, AL-Ia, AL-II, etc. (Fig. 1) [41]. During the metabolic process, AA-I and AA-II are activated to reactive cyclic nitrenium ions with delocalized charge, which then preferentially react with purines in the DNA to form AL-DNA adducts (predominantly dA-AAI and dG-AAI) [39,40,42]. The AL-DNA adducts, mainly located in the renal cortex and urothelium, might give rise to mutations in the TP53 tumor-suppressor gene, leading to urothelial malignancies [40].

The pharmacodynamics of AAs has been studied in animal models. After oral administration or intravenous injection, AAs are promptly absorbed in blood circulation and bind to plasma proteins, and are then distributed throughout the body [43,44]. AAs are first concentrated in the liver, and they are then transferred to the kidneys. The AA-albumin binding components are not filtrated through the glomerulus but flow further through the peritubular

Table 1. Common aristolochic acid-containing herbs in medicinal use

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
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<tbody>
<tr>
<td>Aristolochia</td>
<td>Aristolochia clematitis L. (known as birthwort, located in Europe)</td>
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<td>Aristolochia serpentaria L. (virginia snakeroot, North America)</td>
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<td>Aristolochia indica L. (Indian birthwort, Asia)</td>
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<td>Aristolochia debilis Sieb. et Zucc. (China)</td>
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<td>Aristolochia bracteolata Lam. (Africa)</td>
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<td>Aristolochia acuminata Lam (India)</td>
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<td>Aristolochia triolobata L. (Central/South America, Caribbean)</td>
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<tr>
<td>Asarum</td>
<td>Asarum heteropoides f. mandshuricum (Maxim.) Kitag (China)</td>
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<td>Asarum sieboldii Miq. (China)</td>
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<td>Asarum europaeum L. (Europe)</td>
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<td>Asarum canadense L. (North America)</td>
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Figure 1. Metabolism of aristolochic acids in human cells.
capillaries, where AAs are transferred to the nearby proximal tubular epithelial cells (PTECs) via organic anion transporters (OATs) \[44–46\]. A study demonstrated that the distribution ratio of AA in the liver went down several days later, yet it remained high in the kidneys even after 40 days, implying its accumulation and slow elimination in the kidneys \[46\]. In humans, AA and its metabolites could be detected in the plasma of approximately half of AAN patients even after over 18 months of AA withdrawal \[18\]. Taken together, the organ-specific accumulation and the slow elimination of AAs shed light on possible mechanisms of how AAs persistently do harm to the kidneys and ultimately result in chronic AAN.

**Toxicity of aristolochic acids**

Although AA-I is regarded to be responsible for AA-related diseases in previous studies, other members of the AA family, as well as their intermediates in the process of metabolism, also show nephrotoxicity. A few *in vitro* and *in vivo* studies demonstrated that compounds like AL-I, 7-methoxy-AL-IV, AL-Iva, etc., also do harm to PTECs \[47–50\]. More interestingly, some of them even show much stronger nephrotoxicity than AA-I in several studies \[47,49,50\]. Structurally, the nitro and methoxy groups play crucial roles in AA-mediated intoxication \[51,52\]. These findings indicate that some nephrotoxic constituents of the AA family, besides AA-I, might contribute to the pathogenesis of AAN in AA-containing herbs or other species, which remind researchers that more attention and stricter supervision of such compounds are required in the future for the sake of herbal safety.

**Clinical manifestations and pathology**

**Clinical patterns of aristolochic acid nephropathy**

The initial presentation of AAN turns out to be silent, and renal dysfunction is often discovered by routine blood tests \[8\]. Nonspecific symptoms including nausea, fatigue, poor appetite, and edema occur in some AAN cases \[18,22\]. According to a previous study conducted by our center including 300 patients diagnosed as AAN between 1997 and 2006 with 2 to 156 months of follow-up, three clinical subtypes were defined \[18\]: chronic AAN, acute AAN, and renal tubular dysfunction (Table 2).

**Chronic aristolochic acid nephropathy**

Over 90% of patients were reported to suffer from chronic AAN with decreased estimated glomerular filtration rate (eGFR) at different degrees, and most of them developed rapid progression to end-stage renal disease (ESRD) (me-

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<th>Table 2. Clinical patterns and pathological features of AAN</th>
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<td>Pathological features</td>
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AA-I, aristolochic acid I; AAN, aristolochic acid nephropathy; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Scr, serum creatinine; TBM, tubular basement membrane.

\(a\)Patients who had history of long-term AA-I ingestion and presented with persistently elevated Scr level and decreased eGFR at different degrees for over 3 months, or accompanied by kidney atrophy revealed by ultrasound examination though the duration of abnormal Scr level was imprecise were defined as chronic AAN. \(b\)Patients presenting with AKI or a sudden elevation of Scr level within 3 months after termination of AA-I intake were defined as acute AAN. \(c\)Patients with normal Scr level and obvious renal tubular dysfunction after AA-I intake were defined as renal tubular dysfunction AAN.
Acute aristolochic acid nephropathy
Approximately 5% of patients were shown to present with nonoliguric acute kidney injury and developed acute or subacute renal failure, which is often caused by continuous or excessive use of Chinese medicine decoctions containing AA in a short period of time.

Renal tubular dysfunction aristolochic acid nephropathy
Less than 3% of patients with intermittent and lowest cumulative AA-I intake showed varying degrees of renal tubular dysfunction or Fanconi syndrome.

In addition, hypertension, elevated serum creatine, as well as anemia presenting earlier and more severe than anticipated from the progression of renal failure, are usually seen in physical examinations and laboratory tests. Urinalysis is unremarkable in most cases. Mild proteinuria and glycosuria can be detected in some patients. Tubular-derived proteinuria is confirmed by the increased level of five kinds of low molecular weight proteins in urinalysis, including β2-microglobulin, α1-microglobulin, cystatin C, retinal-binding protein, and Clara cell protein. Furthermore, levels of urinary neutral endopeptidase, a 94-kDa ectoenzyme of proximal tubule brush border, decrease significantly in patients with moderate renal failure and are almost undetectable in those with ESRD, indicating the loss of integrity of proximal tubules. Taken together, all these findings imply that proximal tubules are the main target of AA-containing herbs.

Pathology of aristolochic acid nephropathy
Macroscopically, the kidneys of patients with chronic AAN are detected as shrunken and asymmetric, with the thinning of renal parenchyma on ultrasound testing. Microscopically, the renal pathology of AAN often has certain characteristics. The immunopathological examination of renal tissue biopsy is usually negative. In patients taking excessive drugs containing AA, light microscopic examination shows severe injury of tubular epithelial cells similar to acute tubular necrosis, including severe cell degeneration and necrosis or disintegration with naked tubular basement membrane. The lesions appear to be diffuse or multifocal and are characterized by the lack of regeneration of tubular epithelial cells. As for those with long-term intermittent AA consumption, the main pathological feature is extensive paucicellular interstitial fibrosis accompanied by apparent atrophy of proximal tubules, which starts predominantly from the superficial cortex and then progresses to the deep cortex, whereas little infiltration of interstitial inflammatory cells can be observed. The glomeruli remain relatively spared. Furthermore, loss of peritubular capillaries and ischemic shrinkage of glomeruli are detected in some cases. Apart from the lesions mentioned above, the swelling of organelles in the interstitial microvascular endothelial cells as well as the stratification or even rupture of the basement membrane are shown on electron microscopic examination.

Association with urothelial malignancies
Approximately 30% to 40% of AAN patients are accompanied by urinary translational cell carcinoma (TCC), which might be detected before or after the diagnosis of AAN, after over 10-year withdrawal of AA-containing herbs, or even after kidney transplantation. Tumors can be observed multifocally throughout the whole urinary system, including the renal pelvis, ureter, and bladder with a high recurrence rate. Visible or invisible hematuria is regarded as the most common initial symptom, and flank pain occurs in about 20% of patients. Abnormal urinary cytology, though not sensitive enough, indicates the existence of TCC. Computed tomography (CT) urography or magnetic resonance urography, as well as invasive examinations, including cystoscopy, ureteroscopy, and simultaneous biopsy, assist with accurate diagnosis and tumor staging. Furthermore, the long-term existence of AA-derived DNA adducts and the TP53 mutation spectra also serve as powerful biomarkers of AA exposure.

Pathogenesis of aristolochic acid nephropathy
Breakthroughs on the pathogenesis of AAN have been made in the last few decades. Possible mechanisms of how AAs damage the kidney tissues are concluded as follows (Fig. 2).
Direct nephrotoxicity

AAs exert dose-dependent damage to renal tubules, leading to apoptosis and necrosis of PTECs via p53-mediated signaling [65].

Impairment of cell repair

Under normal circumstances, the tubular epithelial cells have strong capability for self-repair. After renal tubules are injured by nephrotoxic drugs, those spared or slightly injured tubular epithelial cells soon start their self-repair procedures by proliferating. However, renal biopsy shows lack of cell regeneration in patients with AAN, suggesting that AAs might somehow disrupt the self-repair process. Previous studies have demonstrated that exposure to AAs results in epithelial cell cycle arrest in the G2/M phase and reduced expression of epidermal growth factor, yet such inhibition cannot be reversed even after removal of extra-cellular AAs [66,67].

Chronic hypoxia and ischemic injury

Pathologically, a severe loss of peritubular capillaries (PTCs), as well as disrupted PTC lumina, strongly suggest that the injury of vascular endothelial cells might participate in AAN pathophysiology [58]. Cytotoxicity of AAs, decreased expression of vascular endothelial growth factor, as well as imbalance between the vasoactive factors, are associated with upregulation of hypoxia-inducible factor alpha and reduction of vascular network, illustrating that chronic hypoxia and ischemic injury might partially give rise to interstitial fibrosis and defect of cellular proliferation [58,68–71].

Infiltration of inflammatory cells

Though some cases are characterized by little infiltration of interstitial inflammatory cells, recent studies show that the immune system participates in AAN progression [72]. Innate immune cells, such as monocytes/macrophages, as well as adaptive immune cells, including both T lym-
phocytes and B lymphocytes, are detected in the medul-
lar rays and in the outer medullae [72–74]. Inhibition of
immune cell infiltration or suppression of relative inflam-
matory signaling pathways dramatically attenuates renal
fibrosis [72,73,75]. Besides, the fact that steroid therapy
might slow down the deterioration of renal dysfunction in
AAN patients provides evidence for this immune-related
process [76,77].

Activation of profibrotic signaling

Overexpression of profibrotic factors and massive pro-
duction of extracellular matrix deposition are detected,
suggesting that activation of profibrotic signaling plays an
indispensable role in renal firosis [58,66]. After stimulation
of AA, the tubular epithelial cells that were arrested in the
G2/M phase tend to transfer to a profibrotic phenotype by
excreting transforming growth factor beta 1 (TGF-β1) and
connecting tissue growth factor, which further promote the
activation of fibroblasts into myofibroblasts, and the pro-
duction of collagen via TGF-β/Smad3-dependent and JNK/
MAP kinase-dependent mechanisms [66,78,79].

Diagnosis

No universally accepted diagnostic criteria of AAN have
been reached worldwide so far. In clinical practice, the
diagnosis of AAN is usually based on the history of AA-con-
taining medication intake, clinical manifestation of renal
tubular injury or impaired renal function, and typical renal
histopathology displaying hypocellular interstitial fibrosis
[25]. Additionally, the detection of AA-derived DNA ad-
ducts in patients’ renal/urinary tract tissues as well as AA
and its metabolites in the blood/ urinary samples support
AA exposure [64]. Tubulointerstitial diseases caused by
other reasons should be evaluated and differentiated from
AAN in every suspected patient before a definite diagnosis
is made. For patients with complex history of using several
nephrotoxic medications (including AA-containing herbs,
analgesics, antibiotics, etc.), different drug-induced ne-
phropathies should be discriminated by the combination
of clinical course and pathological manifestations.

Management

Treatment and surveillance

Unfortunately, there is no effective treatment for AAN. Several studies have demonstrated that steroid therapy de-
layed the progression of renal failure in some cases [76,77],
supporting the hypothesis that immune factors could be
involved in the progression of AAN [74]. Nevertheless, the
long-term effect of steroid therapy on AAN and whether
the benefits outweigh the side effects remain ambiguous.
Renin-angiotensin system modulation by salt depletion
and pharmacologic blockade with angiotensin-converting
enzyme inhibitors (ACEIs) or angiotensin-receptor block-
ers are indispensable to managing CKD, yet no evidence
supports that this strategy might improve renal function or
slow down disease progression in AAN patients [80].

The principles of AAN management are similar to CKD
patients of other causes, which include controlling blood
pressure, treating complications, preventing infection, and
time preparing for renal replacement therapy [25]. Because
of the high incidence and recurrence rate of TCC in AAN
patients, simultaneous bilateral nephroureterectomy has
been recommended when performing renal transplanta-
tion surgery or at the start of dialysis [7,25,61]. Since the
occurrence of TCC in bladder turns out to be much lower
than that in renal pelvis and ureter, routine cystectomy
seems unnecessary in most cases [7].

For further surveillance, routine urinary cytologic eval-
uation should be performed in all patients with AAN, yet
more invasive methods are required due to its poor sensi-
tivity. It has been suggested that yearly CT and ureterosco-
py should be performed on patients who do not undergo
the removal of bilateral native kidneys and ureters, whereas
regular cystoscopy and bladder biopsy should be offered to
patients every 6 months after nephroureterectomy [25]. If
AA-derived DNA adducts are positive in the bladder spec-
imens, which suggests a much higher risk of developing
TCC in the bladder, cystectomy should be considered [25].

In recent years, advances have been made in under-
standing the pathogenesis of AAN, and new therapies
and pharmaceutical targets have been explored in animal
models. Drugs with the effect of inhibiting OATs can block
the entry of AAs into PTECs in animal models, leading to
prevention of cellular injury and AA accumulation [81]. A
recent study in rat model indicated that chymase-induced ACE-independent angiotensin II formation participates in kidney injury in AAN, and chymase inhibitor (with or without ACEI) significantly mitigates the progression of AAN, which might be a potential therapeutic target in the future [82]. In addition, the anti-renal fibrosis effects of some traditional Chinese formulas (such as Dahuang Fuzi Decoction [83], Fuzheng Huayu Recipe [84], Kangxianling [85], etc.) have been proven and might provide a viable approach for treating AAN as well as CKD induced by other causes [86]. Furthermore, the anti-fibrotic and regenerative effects of mesenchymal stem cells and their extracellular vesicles have been attested in animal models of AAN [87,88].

**Prognosis**

The prognosis of AAN is worse than tubulointerstitial renal diseases caused by other reasons, with irreversible renal dysfunction in most cases and a much lower 2-year kidney survival rate of only 17% [54]. In the light of follow-up data in our center, cumulative dose of AA ingestion turns out to be the decisive factor for the progression and outcome of AAN patients [18]. A small proportion of cases develop rapidly progressive renal failure to ESRD within a year. Some patients presenting with acute AAN and those with tubular dysfunction AAN might have a partial recovery after cessation of AA-containing medication and timely treatment. However, most patients undergo chronic deterioration of renal function and have to turn to renal replacement therapy after years of progression.

**Prevention**

Due to the nephrotoxicity and carcinogenicity of AAs, prevention of exposure to AAs has become a global public health priority. Regulatory authorities of many countries have sent out warnings against AA-containing remedies, and products with AAs have been banned and restricted in the drug markets. In the United States, the Food and Drug Administration issued an alert about the danger of AAs in 2001 [25]. In Europe, the enforcement of the 2004 European Directive on Traditional Herbal Medicinal Products in 2011 has imposed a ban on AA-containing remedies [25]. The Korea Food and Drug Administration has forbidden the use of AA-containing ingredients since 2005 in Korea [22]. Taiwan and Hong Kong laid embargoes on such herbal medications in 2003 and 2004, respectively. Here in mainland China, the medicinal standards for several species of Aristolochia, including Guan Mu Tong (A. manshuriensis Caulis), Guang Fang Ji (A. fangchi Radix), and Qing Mu Xiang (Aristolochiae Radix), were canceled from the “Chinese Pharmacopoeia” in 2004 [89,90], followed by the cancellation of Ma Dou Ling (Aristolochiae Fructus) and Tian Xian Teng (Aristolochiae Herba) in the latest version released in 2020 [91]. The National Medical Products Administration of China has stressed that the nephrotoxicity of AA-related patent medications must be marked clearly on the labels, and those AA-containing patent drugs and preparations are accessible only under the strict instructions given by licensed professional practitioners of traditional Chinese medicine [90]. Apart from official regulations, public education on the importance of rational use of herbal remedies is quite necessary for improving awareness of drug safety.

It is encouraging that the occurrence of AAN has decreased significantly, illustrating that those measures are quite effective in preventing exposure to AAs. Nevertheless, cases with newly-onset AAN are still occasionally detected nowadays, reminding clinicians not to let down their guard on AAN. Because of the poor prognosis and rapid progression of the AAN, it is important for doctors to identify the disease early and perform timely interventions.

**Conclusion and perspectives**

Since the first report of AA-related nephropathy, a great number of breakthroughs in understanding the pathogenesis of AAN have been made throughout these years. However, there still exist considerable challenges that require further investigation. The lack of universally accepted diagnostic criteria makes it harder for early and accurate diagnoses. Though specific biomarkers like AL-DNA adducts have been found, noninvasive biomarkers for AAN and exposure to AAs should be developed. Furthermore, potential therapeutic targets and remedies for reversing or delaying disease progression should be explored to improve the outcomes of patients with AAN. Lastly, strict regulation on AA-containing medications is required in the future to diminish this preventable disease. As such, there is still a long way to go to defeat AAN completely.
**Conflicts of interest**

All authors have no conflicts of interest to declare.

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**Data sharing statement**

The data presented in this study are available on request from the corresponding author.

**Authors’ contributions**

Conceptualization: QZ, GL, LY  
Project administration, Supervision, Validation: GL, LY  
Visualization: QZ, LJ  
Writing–original draft: QZ  
Writing–review & editing: LJ, TS, GL, LY  
All authors read and approved the final manuscript.

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