Drug Saf (2015) 38:55–64
DOI 10.1007/s40264-014-0244-x

REVIEW ARTICLE

Aristolochic Acid Nephropathy: Epidemiology, Clinical Presentation, and Treatment

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Published online: 2 December 2014

Abstract Aristolochic acid (AA) is a compound extracted from the *Aristolochia* species of herbs. It has been used for centuries as a remedy for various illnesses and diseases. However, in the early 1990s in the setting of a weight loss herbal remedy, AA exposure was associated with a syndrome of kidney injury, termed aristolochic acid nephropathy (AAN). This entity is marked by elevated serum creatinine, significant anemia, and histopathologic changes demonstrating a hypocellular interstitial infiltrate with severe fibrosis. Progression towards end-stage renal disease (ESRD) is rapid, with most patients having chronic kidney disease for less than 2 years. In addition, AAN is associated with a 40–45 % prevalence of urothelial carcinomas. Treatment of AAN is limited to glucocorticoids that have been shown to delay progression in non-randomized trials. As most patients progress to ESRD, need for renal replacement therapy, as either dialysis or kidney transplant, usually ensues. However, given the high malignant potential, care must be taken to minimize future development of upper urinary tract cancers by performing prophylactic bilateral nephroureterectomies and aggressive cancer surveillance.

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Key Points

Aristolochic acid exposure leads to kidney injury characterized by progressive interstitial fibrosis leading to the need for dialysis or transplant, with associated urothelial malignancy occurring after kidney failure.

Treatment of aristolochic acid nephropathy includes glucocorticoids and pre-emptive bilateral nephroureterectomies at the time of transplant or end-stage renal disease.

Balkan-endemic nephropathy is also related to aristolochic acid exposure; however, time course to kidney failure is substantially longer.

1 Introduction

Traditional Chinese medicines have been used for thousands of years to treat numerous ailments and diseases in China and surrounding countries [1]. Over the last several decades, Chinese herbal medications have been used with increasing frequency in Western countries. With this increased use, concerns over efficacy and safety of some of these herbal medications have arisen. One such traditional Chinese herb that has contributed to this need for increased scrutiny, due to catastrophic worldwide complications, is from the *Aristolochia* plant.

Aristolochic acids (AAs) are compounds derived from the genus *Aristolochia*, from the plant family *Aristolochiaceae* (Fig. 1), which contains more than 500 species that have been used for centuries for medicinal purposes

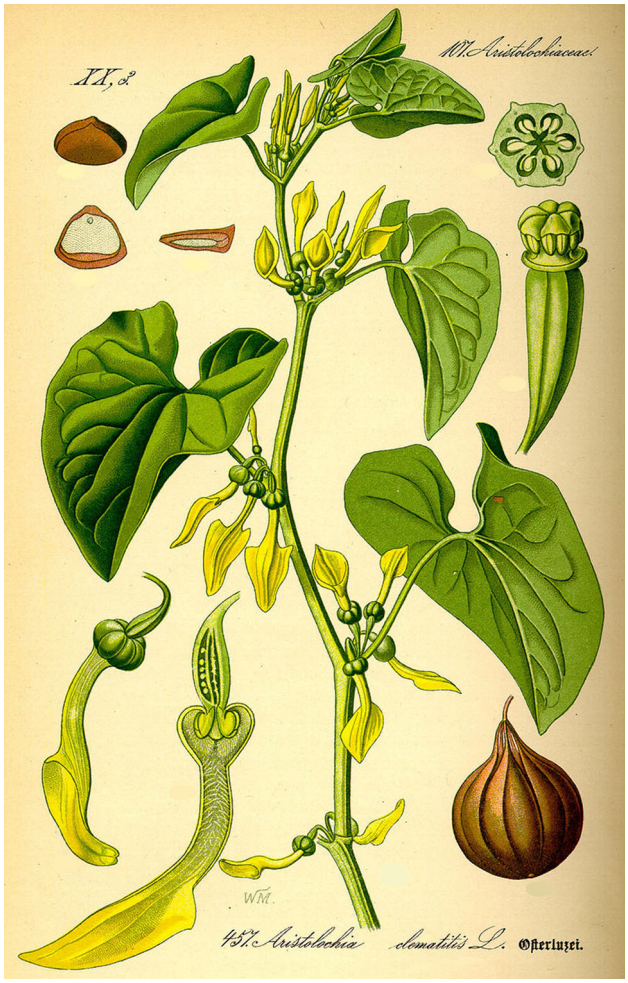

Fig. 1 Drawing of *Aristolochia clematis*

[2]. Extensive lists of AA-containing compounds have been published previously and are reviewed elsewhere [3–5]. AA-containing compounds have been used in obstetrics, as antiviral and antibacterial agents, as anti-inflammatory agents for arthritis, as topical skin agents for eczema, as diuretics, as anti-neoplastic agents for a variety of malignancies, and as components of herbal weight-loss agents [2, 3]. The effects of these compounds can range from relatively benign to significantly toxic. Two species, *Aristolochia clematis* and *Aristolochia fangchi*, with common names of birthwort and Fang chi, have gained unwanted attention as compounds responsible for kidney injury leading to progressive renal failure in a syndrome that was originally referred to as 'Chinese herb nephropathy,' but later became known as aristolochic acid nephropathy (AAN) [2]. In addition to kidney injury, urothelial malignancies also complicate AA exposure [6].

2 The Emergence of Aristolochic Acid Nephropathy

In Belgium, between 1991 and 1992, an increased incidence of patients presenting to the emergency department with signs and symptoms of renal failure was observed [7]. These patients were primarily women and it was found that they all had previously used slimming regimens from the same weight-loss clinic. Initially, nine patients were described with progressive renal failure that rapidly progressed to end-stage renal disease (ESRD); however, the number quickly rose to more than 100 affected individuals [8, 9]. In addition, other cases of AAN from ingestion of AA-containing compounds were reported in the USA, Europe, Australia, Japan, Korea, Taiwan, China, and Hong Kong [10–18].

An investigation into the cause of the initial outbreak demonstrated that, during the production of the weight-loss supplement, one herb was accidentally substituted for another, reflecting problems associated with a lack of regulatory oversight of these products [3]. The supplement had undergone an ingredient substitution in 1990, with the introduction of *Stephania tetranda* and *Magnolia officinalis*, two herbs that had no known nephrotoxicity. As the workup progressed, it was determined that *Stephania tetranda* had been accidently replaced with *Aristolochia fangchi*, as both belonged to the 'fang ji' family of traditional Chinese herbs and had very similar names. This was subsequently supported through phytochemical analysis, which demonstrated that the supplements did not contain tetrandrine from *Stephania tetranda*, but instead contained AA [3, 8, 19].

3 Mechanism of Action

AA is the active chemical extracted from the *Aristolochia* species. AA itself is a mix of structurally similar nitrophenanthrene carboxylic acids: 8-methoxy-6-nitro-phenanthro-(3,4-d)-1,3-dioxolo-5-carboxylic acid (AAI) and 6-nitro-phenanthro-(3,4-d)-1,3-dioxolo-5-carboxylic acid (AAII) [19]. Under aerobic conditions, AAI is demethylated into AAIa and then reduced to aristolactam Ia, which is a very stable end product. AAII is not metabolized aerobically, but instead, during anaerobic conditions is reduced to aristolactam II (Fig. 2).

The reduction forms of AAI and AAII can form covalent adducts with DNA, which can block transcription and DNA replication, leading to cell cycle arrest and apoptosis in a p53-dependent manner [20, 21]. These DNA adducts have been identified in the kidneys of AAN patients. These mutations have also been observed in urothelial cancer from patients with AAN. These transversions seem to be very rare in cancers caused by other carcinogens.

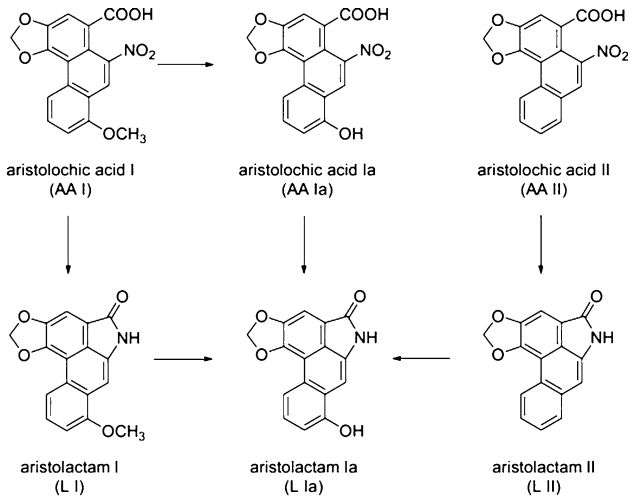

Fig. 2 Biotransformation of aristolochic acid in humans

The specific mechanism by which AAN develops is not currently known. AAN can be preceded by acute tubular necrosis (ATN); however, unlike other forms of tubular injury, there is no tubular regeneration but instead progressive tubulointerstitial fibrosis. In vitro studies have demonstrated the effects of AA on proximal tubules. At high doses, AA exposure leads to proximal tubule cell apoptosis, resulting in cellular necrosis and causing severe dysfunction of tubular function, including re-absorption of filtered substances [22]. In vivo studies have demonstrated that these effects can be seen as early as 2 days after administration of AA [23].

Histopathologic studies have demonstrated severe tubular cell degeneration and necrosis, with completely naked tubular basement membranes, in patients exposed to AA [24]. In one histopathologic study, tubular injury was compared in eight patients with AAN with patients with antibiotic-mediated ATN [25]. In those with AA-induced ATN, markers of tubulointerstitial injury, including proliferating cell nuclear antigen and epidermal growth factor, demonstrated a decreased expression pattern relative to those patients with antibiotic-mediated ATN. In addition, the interstitium of patients with AA-induced ATN was positive for fibronectin and collagen deposition, whereas that of patients with antibiotic-induced ATN was devoid of fibronectin and collagen. Also, patients with AA-induced ATN exhibited decreased expression of vascular endothelial growth factor (VEGF), expression of which was directly related to tubular regeneration [25].

4 Presentation and Diagnosis

Patients with AAN typically present incidentally with an elevated serum creatinine on routine laboratory evaluation

Table 1 Presenting signs and symptoms of aristolochic acid nephropathy

Elevated serum creatinine
Hypertension
Anemia
Glucosuria
Proteinuria
White blood cell casts
Small kidneys with irregular cortical outlines

(Table 1). Patients may display mild to moderate hypertension with an otherwise normal physical exam. In addition to an elevated serum creatinine, a profound anemia that is out of proportion to the degree of renal failure may be seen. This is most likely secondary to destruction of the peritubular erythropoietin-producing cells. Dependent on the degree of proximal tubular dysfunction, patients may also demonstrate normal glycemic glucosuria and mild tubular proteinuria on urinalysis. Urine sediment may demonstrate sterile pyuria with the presence of white blood cell casts, although a bland urine sediment is also possible. Ultrasonography of the kidneys often shows small kidneys with irregular cortical outlines, with asymmetry seen in upwards of 50 % of cases [26].

Kidney injury from AA exposure falls into one of three clinical–histopathological patterns (Table 2) [27]. The most common presentation is a chronic pattern of decreased glomerular filtration rate (GFR) and elevated serum creatinine that is associated with the lowest daily AA intake but the largest cumulative dose. GFR tended to decline at an average rate of −3.5 ml/min/year in these patients. Of interest, patients demonstrated persistent AA end products at up to 12 months post exposure. Another injury pattern is acute AAN, demonstrated by an acute rise in serum creatinine that tended to return to normal yet was associated with progression to chronic kidney disease (CKD) in the next 1–7 years. These patients with acute AAN tended to have the highest daily intake of AA-containing compounds. The last clinical–histopathological subtype is acute tubular dysfunction. These patients generally display a Fanconi syndrome [15]. Serum creatinine and markers of proximal tubular injury improve upon discontinuation of AA exposure. These patients had the lowest daily intake of AA and, in an 8-year follow-up period, normal serum creatinine. In addition, these patients did not develop urothelial malignancies (Fig. 3) [28].

Diagnosis of AAN is confirmed by renal biopsy (Fig. 4). Renal histology demonstrates a hypocellular infiltrate with significant interstitial fibrosis. Predominantly proximal tubular cells demonstrate loss of brush border and atrophy progressing from the superficial to the deep cortical regions. Glomeruli may be relatively spared in acute

Table 2 Renal syndromes associated with aristolochic acid exposure

Pathology	AA exposure	AA dose	Progression to ESRD	Malignancy
CKD	Chronic	Low daily dose	<2 years	High prevalence
AKI	Acute	High daily dose	1–7 years	Intermediate prevalence
Tubular dysfunction	Acute	Low daily	None	None

AA aristolochic acid, *AKI* acute kidney injury, *CKD* chronic kidney disease, *ESRD* end-stage renal disease

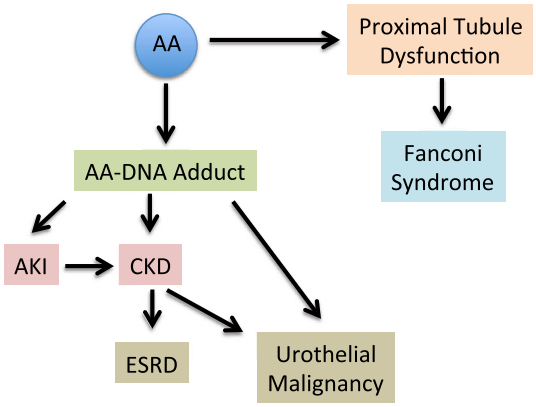

Fig. 3 Diagram of histopathologic variants from aristolochic acid exposure. Aristolochic acid exposure can lead to proximal tubular dysfunction, which can result in a Fanconi syndrome. This is self-limiting and does not lead to end-stage renal disease or urothelial malignancy. Aristolochic acid exposure can also lead to DNA adducts. The aristolochic acid-DNA adducts can lead to an acute kidney injury that will eventually progress to chronic kidney disease. Aristolochic acid exposure can also lead to chronic kidney disease, which can progress to both end-stage renal disease and urothelial malignancy. Aristolochic acid exposure, through AA-DNA adducts, has also been reported to lead to urothelial malignancy without known acute kidney injury or chronic kidney disease. *AA* aristolochic acid, *AKI* acute kidney injury, *CKD* chronic kidney disease, *ESRD* end-stage renal disease

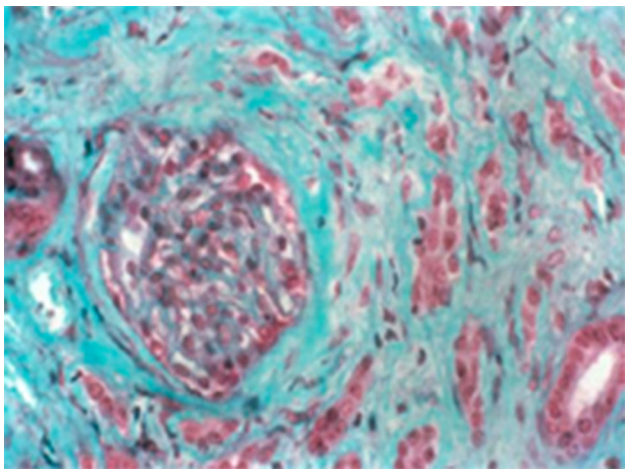

Fig. 4 Biopsy specimen showing aristolochic acid nephropathy. Hypocellular fibrosis and tubular trophy (magnification × 400). With permission from Debelle et al. [3]

disease, but with more chronic and progressive disease, there is endocapillary collapse and basement membrane corrugation.

Diagnostic criteria for AAN require an estimated GFR (eGFR) <60 ml/min/1.73 m^2, and two of the three following histopathological criteria: (1) hypocellular interstitial fibrosis decreasing from the outer to the inner cortical regions; (2) ingestion of an AA-containing product, confirmed by phytochemical analysis; (3) presence of DNA adducts in the renal tissue or urinary tract (Table 3) [8]. Phytochemical analysis of supplements suspected of containing AA, and identification of DNA adducts in tissues of patients with AAN, can be undertaken with a variety of methods, including mass spectroscopy and high-performance liquid chromatography [29–32]. DNA adducts can persist in renal tissue for more than 20 years after AA exposure [33]. It is important to have a definitive (rather than probable) diagnosis of AAN, as exposure has a high rate of malignancy (see below). As such, management of these patients with prophylactic surgical interventions is critical and necessary to prevent future cancer formation.

5 Aristolochic Acid Exposure and Malignancy

The carcinogenic potential of AA has been known for quite some time through animal models. In a study examining chronic AA toxicity in rats, 3 months of treatment with 1 and 10 mg/kg of AA resulted in severe gastric papillomatosis that progressed to metastatic squamous cell carcinoma if left untreated [34]. The use of AA-containing supplements poses a high risk for urothelial malignancy in patients with AAN. This association was first noted in patients who underwent nephroureterectomies at the time of transplant. Four tissue samples of surgical specimens from three patients with AAN demonstrated moderate atypia and hyperplasia in urothelial cells [35]. One patient, a 28-year old woman with a previous left nephrectomy, underwent a right nephroureterectomy and a distal left ureterectomy. Examination of the resected tissue demonstrated three World Health Organization (WHO) grade 1 and one WHO grade 2 transitional cell carcinomas in the bladder wall and right and left ureters [6]. Around this time, a patient with CKD stage V from the original Belgian

Table 3 Diagnostic criteria for aristolochic acid nephropathy

eGFR <60 ml/min/1.73 m^2
Two of the following:
Hypocellular fibrosis decreasing from the outer to the inner renal cortex
Known ingestion of an AA-containing compound confirmed by phytochemical analysis
Presence of AA-DNA adducts in kidney or ureter tissue

AA aristolochic acid, *eGFR* estimated glomerular filtration rate

cohort presented with hematuria just 1 year after being diagnosed with AAN. Clinical–histopathological evaluation demonstrated a WHO grade 2 transitional cell carcinoma of the right uretero–pelvic junction [36]. These cases provide strong support for the carcinogenic potential of AA.

Two larger case series demonstrate the high prevalence of urothelial malignancy in patients with AA exposure. In one series of cases, 19 kidneys and ureters from ten patients were examined for malignant lesions [37]. In four of the ten patients, high-grade multifocal transitional cell carcinoma (prevalence 40 %) was observed. In addition, histological samples from all ten patients revealed moderate cellular atypia in the medullary collecting ducts, pelvices, and ureters. All samples with carcinoma in situ and urothelial atypia cells demonstrated p53 over-expression, as demonstrated by immunohistochemistry. In those patients with mild urothelial atypia, p53 expression was low, while it was low to intermediate in patients with moderate atypia. In patients with carcinoma in situ or transitional cell carcinoma, p53 expression was low to intermediate compared with low in patients without cancer.

In a second study, the tissue specimens of 39 patients who underwent pre-emptive bilateral nephroureterectomies were analyzed [38]. Of the 39 patients, 18 demonstrated urothelial carcinomas (prevalence of 46 %), with 17 of the cases identified as carcinoma of the ureter, renal pelvis, or both; one case was noted as a papillary bladder tumor. Of the remaining patients, 17 had mild to moderate urothelial dysplasia and two patients had normal tissue. AA-related DNA adducts were observed in all tissue samples analyzed. In addition, the authors demonstrated that a cumulative dose of more than 200 g of AA-containing compounds resulted in a higher risk of urothelial carcinoma.

A 15-year longitudinal study in 38 of the previously discussed patients was performed to evaluate the risk of subsequent bladder cancer, except for one patient who was excluded out of the 39 for previously identified bladder cancer [39]. In the 17 patients who were found to have upper-tract urothelial carcinoma, 12 developed bladder carcinoma (71 %). This is in contrast to only three of 21 patients who developed bladder carcinoma with no previously identified upper-tract urothelial cell carcinoma, a prevalence of 14 %. In the patients with bladder cancer, there was no association with amount of AA ingestion and future development of cancer. Of the patients who developed bladder cancer, three died from metastatic disease, with two belonging to the group with prior upper tract carcinoma and one having no prior evidence of upper tract cancer.

An isolated case of urothelial carcinoma without overt AAN was reported in a patient exposed to a cumulative dose of 189 g of AA for a 1-year period for the purposes of weight loss [40]. The patient did have an acute kidney injury from presumed partial obstruction at the time of diagnosis of a left ureteral carcinoma. Surgery revealed extension of tumor into the surrounding lymph nodes. The patient eventually died from septic shock in the setting of pneumonia. Post mortem evaluation demonstrated DNA adducts in the kidney, lymph nodes, liver, and spleen, consistent with AA exposure. It is unclear why this patient had no renal involvement despite DNA adducts in kidney tissue. Unfortunately, there was no histologic description of the kidney tissue to determine whether there were any changes consistent with mild AAN. To date, no other case of isolated urothelial malignancy without kidney involvement has been reported.

Recent studies looking at genome-wide analysis in AAN patients with known urothelial cancers have led to the identification of a mutational fingerprint of AA-induced carcinogenesis [41, 42]. The genes identified in the two studies were similar and included those involved in chromatin modification, a mechanism of carcinogenicity that was not previously known to be involved in urothelial cancers. In addition, the average mutation rate in AA-associated cancers was 150 mutations/Mb, much greater than the rates of smoking-associated lung carcinoma (8 mutations/Mb) and ultraviolet-associated melanoma (111 mutations/Mb). This makes AA one of the most potent carcinogens discovered to date. One group used the mutational fingerprint to correlate possible involvement of AA exposure with other cancers. In a subset of patients with known hepatitis B-induced hepatocellular carcinoma, mutational patterns were similar to that of AA-induced malignancy, leading the authors to suggest that prior AA exposure may have occurred in some patients [42]. However, there is no comment on the differences in presentation, pathology, or progression of hepatocellular carcinoma with and without this unique molecular fingerprint.

A recent report of B-cell lymphoma in a patient with known AAN who underwent bilateral nephroureterectomy and subsequent transplant raises the question as to whether non-urothelial cancers can be the associated with AA exposure [43]. The patient in this case had primary splenic lymphoma that developed in the setting of chronic

immunosuppression administered for 18 years for renal allograft. The treatment course consisted of splenectomy and adjuvant chemotherapy. Unfortunately, the splenic tissue was not analyzed for AA-DNA adducts, and therefore this can only be deemed as an association and not a consequence of AA exposure. In patients with previously reported urothelial cancers associated with AA exposure, only one documented case of a non-urothelial cancer has been reported. The patient developed a hepatocellular carcinoma, but the malignancy was thought to be secondary to hepatitis C [39]. In light of the aforementioned association of an AA molecular fingerprint with hepatitis B-induced hepatocellular carcinoma, the question does arise as to whether this patient with hepatitis C-associated hepatocellular carcinoma had a carcinogenicity pattern that was more typical of AA exposure as opposed to hepatitis C exposure.

To date, no known non-urothelial malignancies are attributed to AA exposure, as confirmed by the presence of AA-DNA adducts in cancerous tissue. However, in animal models with AA exposure, gastric carcinoma, lung carcinoma, renal cell carcinoma, and malignant lymphoma have all been reported [44]. With all of these malignancies, diagnosis was made via histologic changes, without identification of AA-DNA adducts, raising the possibility of a different mechanism of carcinogenicity. The presence of newer methods of molecular identification of cancer raises the possibility that non-urothelial cancers may be identified in patients with AA exposure but without documented AAN.

6 Treatment and Management

Given the high prevalence of AAN and urothelial malignancy with AA exposure, the sale and distribution of AA-containing supplements has been prohibited in an attempt to prevent future cases. In the USA, the FDA has issued a strict warning against the use of any supplements containing AA. The agency permits the seizure of any substance known to contain AA. Since 2004, the EU has not approved any herbal medications with AA, limiting the availability of this toxic substance [8]. In Hong Kong, Taiwan, and China, the use of most, but not all, AA-containing plants has been prohibited [8]. However, despite these efforts, products containing or suspected of containing AA have still been available on more than 100 websites [45]. In addition, AA is often found in herbal products when tested, due to the lack of regulatory oversight of these products.

The only therapy that has shown any efficacy in delaying progression of AAN to ESRD has been glucocorticoids. In a small study, 12 female patients with biopsy-proven AAN and baseline serum creatinine of 1.8–3.9 mg/dL were treated with the steroid prednisolone at a dose of 1 mg/kg for 1 month, followed by a 0.1 mg/kg taper every 2 weeks. At 1 year, only two of the 12 steroid-treated patients required dialysis [46]. This is in contrast to the development of ESRD at 1 year in 16 of 23 patients who made up the retrospective untreated control group. The groups were followed for a total of 8 years. In follow-up at 3 years post diagnosis, eight of the 14 patients treated with steroids required renal replacement treatment (RRT) and 11 of 14 patients required RRT at 8 years. In contrast, 21 of the 23 non-steroid-treated patients required RRT at 3 years, while 22 of the 23 patients developed ESRD requiring RRT at 8 years of follow-up [47]. Given the beneficial effect on delaying progression to ESRD in the setting of steroid administration, it is reasonable to use steroids in patients with biopsy-proven AAN with an eGFR >20 ml/min/1.73 m^2.

Apart from the limited data available in humans to treat AAN, many animal studies have examined various compounds and their effect on progression of kidney injury and disease. The potential renoprotective effects of darbepoetin-α on AAN in mice exposed to this toxic substance have been studied [48]. Administration of darbepoetin-α 0.1 μg/kg protected against acute tubular damage and was associated with a reduction of interstitial fibrosis in the acute setting. In another animal model, mice were exposed to AA with or without prophylactic probenecid at a dose of 150 mg/kg [49]. Mice treated with probenecid manifested less histopathological damage, including fewer AA-DNA adducts than placebo-treated mice. However, this therapy was only used in the setting of acute exposure. It is likely that the mode of action is related to the effect of probenecid on organic acid transporter function. It is unclear whether this drug would have any effect on tubulointerstitial fibrosis and/or progression of AAN with chronic AA exposure.

In another animal model, rats were exposed to AA with or without concomitant losartan at a dose of 33.3 mg/kg/day [50]. Histologic interstitial fibrosis, tubular injury, and molecular involvement of microvasculature injury were decreased in losartan-treated mice [50]. The renal effects of single (enalapril) and combined (enalapril and candesartan) renin-angiotensin-aldosterone system (RAAS) inhibition were also evaluated in rats exposed to AA [51]. RAAS blockade in these animals did not demonstrate a statistical difference in kidney failure, as measured by elevations in serum creatinine concentration, or histopathological changes characteristic of AAN.

Bardoxolone methyl (BARD) was also examined as a protective agent in AA-exposed mice [52]. Mice received BARD at a dose of 10 mg/kg/day or placebo 2 days prior to and 5 days after exposure to AA. BARD-treated mice

demonstrated lower serum creatinine concentrations, decreased interstitial fibrosis, and decreased renal tubular damage. In addition, BARD increased Nrf2, a transcription factor that has anti-oxidant effects and enhances expression and up-regulation of downstream targets. However, given the mortality risk associated with BARD use in patients with diabetic nephropathy and CKD that were brought to light in the BEACON trial, it is highly unlikely that further research with this therapy will progress in human subjects [53].

Reduction of AA levels after acute exposure as a way to reduce or modify renal injury has also been studied. Induction of cytochrome P450 (CYP)-1A, a hepatic CYP enzyme known to detoxify AA, has been observed in mice treated with Tanshinone I, 3-methylcholantrene, and beta-Naphthoflavone [54–56]. All three compounds were associated with decreased aberrant histopathologic changes after AA exposure, relative to control animals. The effect of AA nitro-reduction has also been observed in mice treated with dicoumarol prior to AA administration [57]. Dicoumarol, an inhibitor of an enzyme responsible for AA activation, led to improved kidney function, decreased histopathologic changes characteristic for AAN, and improved survival as compared with placebo. However, although all of these treatments have demonstrated effects in animal models, they only alter AA levels and improve the renal complications of AAN in the acute setting and have not been evaluated with chronic AA exposure. However, given the presence of AA-related end products detected in patients at up to 12 months after AA exposure, it is unclear whether these therapies would have any potential in sub-acute or chronic disease management of AAN [27]. Currently, no therapies have demonstrated an ability to decrease the incidence of urothelial cancers. Table 4 lists the therapies utilized to treat AAN and their clinical outcomes.

In view of the data that support that AAN progresses very rapidly to ESRD, routine CKD management should be initiated for all patients at the onset of diagnosis. This involves blood pressure management with a goal target of <140/90 mmHg, attention to and management of cardiovascular risks, strict potassium and phosphorous regulation, and metabolic acidosis correction to serum bicarbonate >22 mEq/L. Anemia management should also include erythropoietin-stimulating agents (ESAs), as there are no studies that demonstrate increased progression of urothelial cancers with ESA administration, and only one animal model showing no increase in tumor size in ESA-treated rats [58]. Patients should also be counseled early for potential RRT options and access placement should be timely. There are no disease-specific contraindications in choosing hemodialysis versus peritoneal dialysis in these patients. Furthermore, kidney transplant should be offered to all eligible patients with AAN, as there currently are no documented cases of post-transplant recurrence of disease [26].

Since AAN has a high degree of urothelial and bladder carcinoma development, lifelong surveillance should be initiated at the time of diagnosis (Table 5). Surveillance should include a yearly computed tomography scan, cystoscopy with ureteroscopy, and biannual urine cytology [8]. At the time of RRT initiation and prior to kidney transplantation, the patient should be counseled significantly on the benefits and risks of cancer prevention associated with bilateral nephrouterectomy.

7 Similarities to Balkan Endemic Nephropathy

Balkan endemic nephropathy is a chronic kidney disease observed in patients living in countries of the Balkan territories along the Danube River—Bulgaria, Bosnia,

Table 4 Treatments for aristolochic acid nephropathy in human and animal models

Therapy	Human data	Follow-up	Outcome	References
Prednisolone	Yes	1 year	ESRD: 16.7 vs. 69.6 % (control)	[44]
Prednisolone	Yes	3 years	ESRD: 57.1 vs. 91.3 % (control)	[45]
Prednisolone	Yes	8 years	ESRD: 78.6 vs. 95.7 % (control)	[45]
Darbepoetin-a	No	Acute	Decreased interstitial fibrosis	[46]
Probenecid	No	Acute	Decreased AA-DNA adducts, fewer histopathologic changes	[47]
Losartan	No	Acute	Decreased interstitial fibrosis, decreased tubular injury	[48]
Enalapril/candesartan	No	Acute	No histopathologic difference	[49]
Bardoxolone methyl	No	Acute	Lower serum creatinine, decreased interstitial fibrosis, decreased tubular damage	[50]
CYP1A inducers	No	Acute	Decreased histopathologic changes	[52–54]
Dicoumarol	No	Acute	Decreased histopathologic changes, improved survival	[55]

AA aristolochic acid, *ESRD* end-stage renal disease

Table 5 Screening recommendations for urothelial cancer associated with aristolochic acid nephropathy

Yearly pelvic CT with contrast and cystoscopy with ureteroscopy
Biannual urine cytology
Bilateral nephroureterectomy at time of transplant or ESRD
Biannual cystoscopy and urine cytology post-transplant

CT computed tomography, *ESRD* end-stage renal disease

Croatia, Romania, and Serbia. Balkan-endemic nephropathy has been known as a cause of kidney disease in this area for more than 50 years [59, 60]. This nephropathy occurs in patients older than 18 years and has a non-familial, geographic predilection with members of the same village to be affected over family members in geographically disparate regions. Histologically, Balkan-endemic nephropathy is similar to AAN, with a hypocellular interstitial infiltrate and marked tubulointerstitial fibrosis that decreases from the outer to the inner cortical regions. In addition, there is usually only mild glomerulosclerosis and significant tubular atrophy. However, the course of Balkan-endemic nephropathy varies significantly from AAN, with time to ESRD most often more than 20 years in this nephropathy compared with less than 2 years in AAN. In addition, Balkan-endemic nephropathy also has a high association of urothelial carcinoma, another feature similar to AAN; however, presentation of urothelial carcinoma may precede the diagnosis of apparent kidney disease [61].

Much effort has been put forth in the identification of the culprit substance responsible for Balkan-endemic nephropathy. Early theories focused on environmental factors, including hydrocarbons, heavy metals, or certain vitamin deficiencies [62]. However, the focus has more recently shifted to AA. The theory was actually put forth in the 1970s but resurfaced in the 1990s with the emergence of the AAN outbreak [59]. It was thought that Balkan-endemic nephropathy was due to contamination of bread from seeds of *Aristolochia clematitis*, a weed found growing in the wheat fields of endemic regions. Exposure through AA-contaminated bread was thought to cause the kidney disease observed in these patients.

Recently, a more definitive association was noted with the identification of AA-DNA adducts in both kidney specimens and urothelial tumors of patients with Balkan-endemic nephropathy [63]. In 78 % of patients with Balkan-endemic nephropathy studied, there was a specific A:T→T:A p53 mutation, which is ordinarily very uncommon to transitional cell cancers. The long progression of Balkan-endemic nephropathy to both ESRD and urothelial cancers is most likely the result of the much lower, yet chronic, levels of exposure to AA that occurs in the endemic disease. In contrast, higher acute and sub-acute exposure to AA occurs in patients with AAN and likely explains this time from exposure to disease difference.

Apart from the Balkan territories, chronic interstitial nephritis accounts for approximately 28 % of all CKD in India [64]. Traditional herbal Indian medicine incorporates many *Aristolochia* species, which may cause or exacerbate kidney injury in the CKD that is often attributed to an 'idiopathic interstitial nephritis' [65]. In Bangladesh, a recent study attempted to look at the risk of AAN, based on *Aristolochia indica*-containing compounds [66]. It was estimated that patients would consume between 25 and 180 g of AA compounds for various illnesses, with doses at times equivalent to those responsible for AAN. The authors suggest that AAN may be an under-represented form of kidney injury in Bangladesh. However, currently there are no histopathological studies examining kidney tissue for the presence of AA-DNA adducts in patients from these countries.

8 Conclusions

AAN is an aggressive form of kidney injury that is largely preventable by avoidance of AA-containing products. However, with more than 500 species of *Aristolochia*, it is difficult to regulate the supplements, especially with a lack of regulatory oversight for herbal and natural products. Once patients develop a chronic lesion, progression to ESRD is relatively rapid, with most patients requiring some form of RRT within 2 years. Glucocorticoids have been shown to delay, but not prevent, eventual progression to ESRD. Numerous animal studies have evaluated the utility of certain medications to prevent or reduce kidney injury in the acute setting. However, as yet, no therapies have been studied in the setting of chronic exposure or in affected humans. As a result, patients must undergo routine CKD care at the time of diagnosis and prepare for dialysis or either pre-emptive or post-ESRD kidney transplantation. Given the high malignant potential, all patients should be advised on the utility of bilateral nephroureterectomies. Balkan-endemic nephropathy is now known to result from chronic, low-level AA exposure. Urothelial cancers also complicate this toxin exposure, but in contrast to AAN, the course to ESRD and malignancy development is slower. Given these similarities, Balkan-endemic nephropathy should be included under the term AAN. This inclusion will raise clinician and public awareness of the root cause of Balkan-endemic nephropathy. Finally, it is likely that 'idiopathic interstitial nephritis' described in patients from other countries that are exposed to AA-containing herbal products is a form of AAN. Testing of renal tissue and urothelial cancers for AA-DNA adducts would be helpful in sorting out this issue. Newer molecular techniques and

genome-wide analysis may contribute to the diagnosis of AAN in patients with previously undefined CKD.

Conflict of interest No sources of funding were used to assist in the preparation of this study. Randy L. Luciano and Mark A. Perazella have no conflicts of interest that are directly relevant to the content of this study.

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