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The Epidemiology, Diagnosis, and Management of Aristolochic Acid Nephropathy

A Narrative Review

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It has been 20 years since the first description of a rapidly progressive renal disease that is associated with the consumption of Chinese herbs containing aristolochic acid (AA) and is now termed aristolochic acid nephropathy (AAN). Recent data have shown that AA is also the primary causative agent in Balkan endemic nephropathy and associated urothelial cancer. Aristolochic acid nephropathy is associated with a high long-term risk for renal failure and urothelial cancer, and the potential worldwide population exposure is enormous. This evidence-based review of the diagnostic approach to and management of AAN draws on the authors' experience with the largest and longest-studied combined cohort of patients with this condition. It is hoped that a better understanding of the importance of this underrecognized and severe condition will improve epidemiologic, preventive, and therapeutic strategies to reduce the global burden of this disease.

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Between 1990 and 1992, an epidemic of rapidly progressive interstitial renal fibrosis was observed in a cohort of young female patients in Belgium (1). The cause of the epidemic was tracked to a weight-loss clinic that had treated the women with a combination of Chinese herbs and other medicines. The causative agent was identified as aristolochic acid (AA) (2), and renal disease after AA exposure is now formally recognized as aristolochic acid nephropathy (AAN). It also became apparent that damage due to AA can persist for several years and that AA is associated with an extremely high incidence of urothelial cancer (3).

Aristolochic acids are a family of compounds found in the *Aristolochia* genus of plants, many of which are commonly known as birthwort or Dutchman's pipe. These plants have long been used for various medicinal purposes (4). *Aristolochia* species and herbs that can be mistaken or substituted for them in herbal remedies have now been banned in many countries. However, there is evidence that large-scale exposure to AA continues in Asia, with potentially devastating public health implications (5). Indeed, since the initial description of AAN, it has become clear that AAN is a global disease and that AA exposure is also the cause of Balkan endemic nephropathy (BEN), a disease first described in the 1950s whose cause was undefined until recently.

This review covers the latest data on the epidemiology of AAN, explains the pathophysiologic basis and clinical presentation of the disease, and proposes diagnostic criteria and management strategies to help clinicians better identify and treat patients with the disease.

Methods

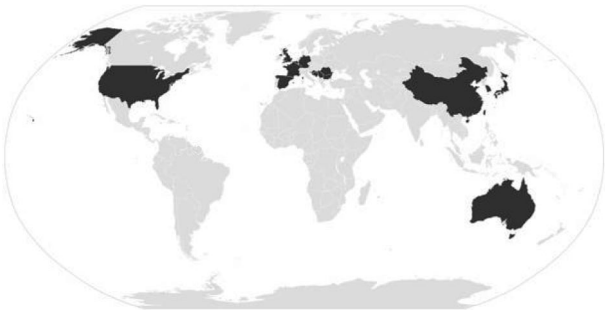
We searched PubMed using the terms *aristolochic acid*, *Chinese herbs/herb/herbal nephropathy*, and *Balkan endemic nephropathy* and examined reference lists of relevant articles. Studies published after 1960 were included; when possible, non–English-language publications were also included. We duplicated the searches on the search engines of the World Health Organization, U.S. Food and Drug Administration (FDA), and European Union and the Web sites of regulatory bodies in countries in which cases of AAN have been reported. We identified 35 case reports and series, 7 cohort or case–control studies pertaining to the epidemiology of AAN, and 1 nonrandomized trial relating to management. In the many areas of AAN management that lack good-quality evidence, we offer our consensus opinions, having shared extensive clinical and research experience in AAN and related fields.

Epidemiology

High-quality epidemiologic data on the incidence and prevalence of AAN are lacking, given the absence of agreed-upon diagnostic criteria and the low awareness of the disease globally. The initial report of the first recorded outbreak of AAN in Belgium in the early 1990s described 9 women who had received the same herbal weight-loss regimen and presented with renal failure (1). That epidemic eventually involved more than 100 patients. An investigation revealed that a constituent in the regimen (*Stephania tetrandra*) had been replaced by *Aristolochia fangchi*. Phytochemical analysis confirmed the presence of AA (6), and detection of AA–DNA adducts in renal tissue from these patients has since confirmed AA exposure (3, 7).

Other cases and case series have since been reported in Europe (2, 8–12), the United States (13), Australia (14), Japan (15), Korea (16), China (17, 18), Taiwan (17), and Hong Kong (19) (**Figure 1**). These reports attest that AA-containing remedies have been, and continue to be, used for various indications, including eczema, acne, liver symptoms, arthritis, and chronic pain. However, the number of

Figure 1. **World map showing the epidemiology of AAN or BEN.**



Countries in which cases of AAN or BEN have been reported in the literature are highlighted. It is likely that the true worldwide distribution of the diseases extends beyond the countries highlighted, especially in the Far East and South Asia. AAN = aristolochic acid nephropathy; BEN = Balkan endemic nephropathy.

persons affected by AAN worldwide remains unclear. Investigators from China have reported that thousands of cases have been identified among patients previously labeled as having chronic tubulointerstitial nephropathy of unknown origin, and they describe 300 cases identified between 1997 and 2006 in 1 center in Beijing (18). Up to 40% of Taiwanese persons are likely to have consumed products containing AA in recent years, indicating that there will probably be a large emerging disease burden (20). In addition, *Aristolochia* species are known to be used in many regions where AAN has not yet been reported, including Africa, South America, and the Indian subcontinent (4, 21).

The only risk factor for development and progression of renal disease that has been defined with any certainty is cumulative AA dose. Patients in the Belgian cohort received many pharmaceutical products (including fenfluramine and acetazolamide) in addition to herbal products. The ingested dose of *A. fangchi* emerged in multivariate analysis as the only substance associated with rate of renal failure progression (22). Retrospective cohort and case–control studies in China and Taiwan have reported median doses of AA associated with renal impairment (18, 23). However, in light of variations in AA concentration in different herbal preparations, a "safe dose" of these products is unlikely to exist. Genetic studies may provide insight into the inherited factors conferring risk to persons exposed to AA (24).

Association With Cancer

Case reports of urothelial cancer associated with consumption of herbal remedies containing *Aristolochia* species began to emerge soon after the original description of AAN (17, 25–28). Two prevalence studies went further in defining the cancer risk among patients with AAN. In one, multifocal high-grade carcinoma in situ was seen in 4 of 10 patients (29). This was confirmed in a larger study of 39 patients with AAN who had prophylactic removal of kidneys and ureters (3). The latter study found that the risk for urothelial tumors was related to the dose of *A. fangchi*. A 15-year follow-up study reported a similar rate of upper urinary tract cancer and an increased incidence of late-onset bladder tumors (30, 31). Other reports support the strong association between ingestion of products containing AA and cancer of the upper urinary tract and bladder (32). An exceptionally high incidence of upper urinary tract urothelial cancer (UUC) has been reported in Taiwan (33), particularly in association with chronic kidney disease (CKD) (34). A case–control study of urinary tract cancer that used the Taiwanese National Health Insurance database found a marked dose-dependent association between consumption of AA-containing herbal products and risk for urinary tract cancer (35). This association was found to be independent of arsenic exposure, which has previously been implicated in the high rates of urothelial cancer in Taiwan (36). The connection between AA exposure and UUC has more recently been shown at the molecular level in a study involving 151 Taiwanese patients with UUC (37), which reported hallmark aristolactam–DNA adducts and A:T→T:A base transversions in the *TP53* gene in most tissue samples.

Association With BEN

Balkan endemic nephropathy is a chronic tubulointerstitial kidney disease found in farming villages close to tributaries of the Danube River in Bosnia, Bulgaria, Croatia, Romania, and Serbia (38). It is the cause of kidney disease in up to 70% of patients receiving dialysis in some of the most heavily affected regions (39); at least 25 000 individuals are known to have the disease (40). First described in the 1950s (41), BEN has a familial but not inherited pattern of distribution and a strong association with urothelial cancer (24).

Environmental exposure to AA was first suggested as a cause of BEN in 1969, when Ivic (42) found contamination of wheat flour by the seeds of *A. clematitis*, a weed that is common in wheat fields in endemic areas. More recently, definitive proof of AA exposure in patients with BEN has come from detection of aristolactam–DNA adducts and hallmark A:T→T:A base transversions in renal cortical and urothelial malignant tissue (43–47). It is now clear that BEN represents a form of AAN, from which it is pathologically indistinguishable.

Pathophysiology and Mechanisms of Carcinogenesis

The exact mechanisms of AA-induced nephrotoxicity are not fully characterized. Many animal models of AAN have been developed and are reviewed elsewhere (48, 49). It is unclear whether the nephrotoxic and carcinogenic effects of AA are dissociated; there has been at least 1 report of AA-associated urothelial cancer in the absence of severe renal impairment (50).

After metabolic activation, AA-derived aristolactam nitrenium ions form covalent adducts with purine bases in DNA (**Figure 2**). These adducts lead to A:T→T:A transversion mutations in the tumor-suppressor *TP53* gene, which have been seen in urothelial tumor cells from UUC cases in the United Kingdom, Taiwan, and the Balkans (25, 37, 47). Such mutations are rarely seen in other types of human cancer, including series of UUC unrelated to AA exposure (51).

Natural History

Most patients diagnosed with AAN show an unusually rapid progression toward end-stage renal disease. In a follow-up study of the original Belgian cohort, the 2-year actuarial renal survival rate was 17% compared with 74% in a control group with other tubulointerstitial nephropathies (52). The experience in other centers has been similar, with a median rate of change in estimated glomerular filtration rate (eGFR) of −3.5 mL/min per year in the largest Chinese case series (18). Patients with relatively preserved GFR at presentation (serum creatinine level <176 μmol/L [<2 mg/dL]) seem to have a reduced risk for progression to stage 5 CKD (52).

The rate of progression of renal impairment is considerably slower in BEN; the decline in renal function to stage 5 CKD occurs over 15 to 20 years (53). The most likely explanation for this is relatively low exposure to AA over a prolonged period (54).

These observations are consistent with the idea that cumulative AA dose is associated with the degree of renal insufficiency and the rate of decline in renal function (18); patients with AAN may progress to end-stage renal disease in as little as 1 month in high, sustained exposures (55). Small numbers of patients presenting with reversible acute kidney injury or with a Fanconi syndrome of tubular dysfunction have also been reported (8, 15, 18, 56). The available evidence does not allow determination of the extent and duration of AA exposure in these patients.

Almost all documented cases of urothelial cancer have been in patients with AAN who required renal replacement therapy, perhaps because cumulative AA dose is a shared risk factor for renal impairment and cancer. However, the published literature suggests a wide variation in the timing of AA-associated urothelial cancer; extensive urothelial cell atypia is a common finding in biopsy specimens from patients with early disease and less severe renal impairment (3) and late-onset bladder tumors detected up to 15 years after cessation of AA intake (30). Thus, exposure in patients with cancer who do not have obvious renal impairment may go unrecognized.

Diagnosis

Most patients with AAN present with renal insufficiency, anemia, a urine sediment with few erythrocytes and leukocytes, and mild proteinuria (typically <1.5 g/2d). In both Chinese herb–associated AAN and BEN, the observed degree of anemia has been noted to be out of keeping with the decrease in GFR, perhaps as a result of early destruction of erythropoietin-producing peritubular cells (51). Renal tract ultrasonography reveals shrunken kidneys, which can be asymmetrical and irregular in cortical outline.

No serum or urinary biomarkers have thus far been shown to have clinical utility in the diagnosis of AAN or BEN. Although many recent studies have reported that levels of various urinary proteins are elevated in patients with AAN (57, 58), whether these findings simply represent nonspecific tubular damage is not yet clear.

Renal Histology

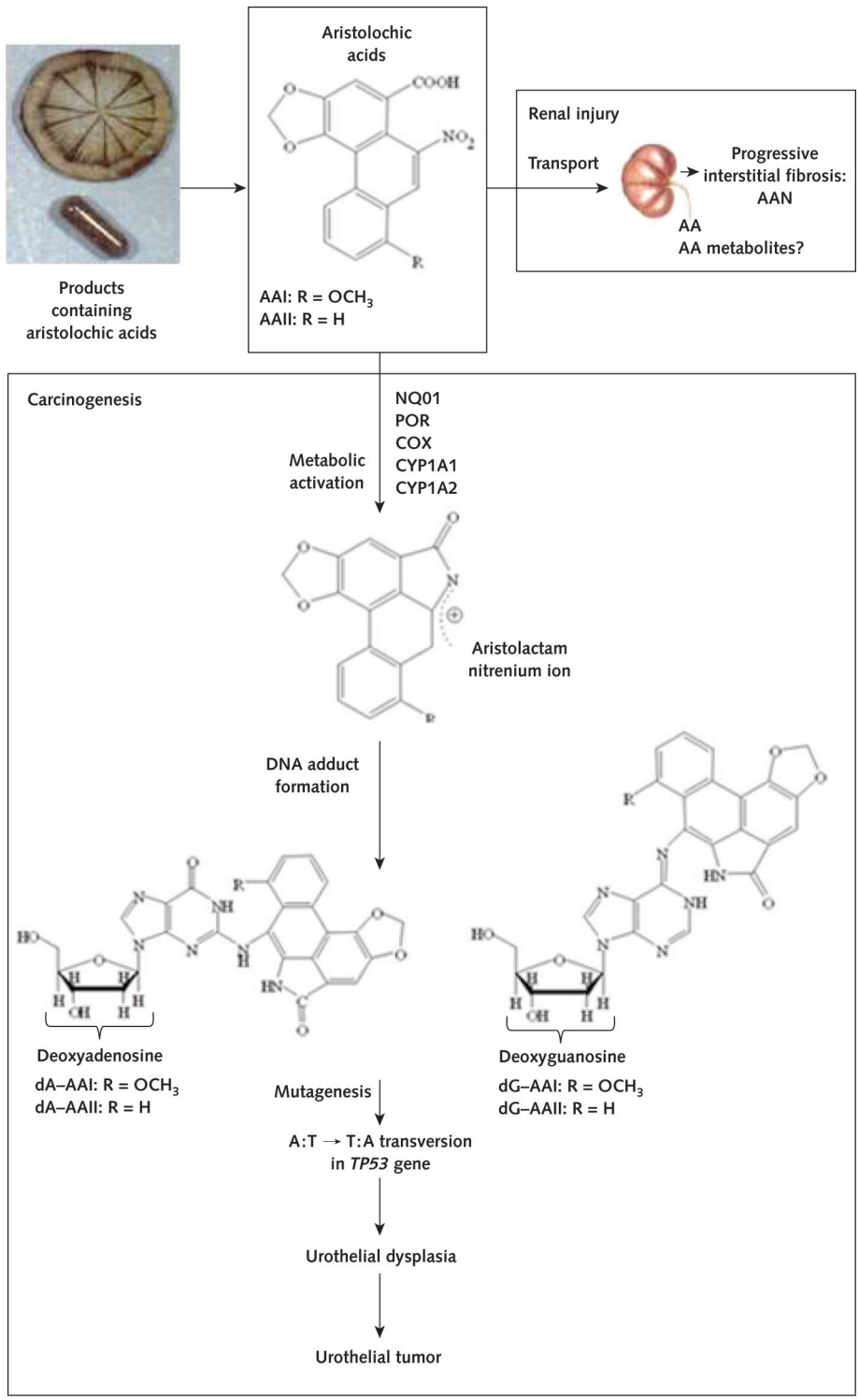
Histologic examination remains the mainstay for diagnosis of AAN. The most striking finding is extensive interstitial fibrosis associated with tubular atrophy and low numbers of chronic inflammatory cells decreasing from the outer to the inner cortical labyrinth (**Figure 3**) (59–61). Virtually all patients have associated multifocal urothelial atypia, and 40% to 46% of patients have multifocal, often bilateral transitional cell carcinoma in situ, usually located in the upper urinary tract (3, 29). Glomerular and vascular lesions secondary to the progressive kidney destruction by the tubulointerstitial fibrotic process are also usually evident. At the end stage, the entire cortex may be replaced by fibrous tissue, reducing and even abolishing the corticomedullary gradient.

The interstitial fibrosis that characterizes analgesic nephropathy is morphologically distinguishable from AAN and BEN by its multifocal transcortical development and substantial infiltration by inflammatory cells in often-calcified areas of papillary necrosis, leading to corrugated atrophic kidneys (62).

Botanical Diagnosis

The genus *Aristolochia* (Aristolochiaceae family) includes 120 species, of which 99 are known to be used for medicinal purposes (4). The AA content and nephropathy risk associated with ingestion of most of these species are unknown. Species of *Aristolochia* still included in the *Pharmacopoeia of the People's Republic of China* (63) are those used in medicinal preparations traded under their Chinese pinyin names, "Fang Ji" and "Mu Tong" (64). These terms can refer to innocuous plant species, such as *Stephania tetrandra*, or toxic species, such as *A. fangchi*, as shown by the Belgian outbreak (65). Although comprehensive lists of botanicals known to contain AA have been published by the International Agency for Research on Cancer and the FDA (64, 66), substantial risk is also likely to be posed by products with unknown AA content. Given the problems of nomenclature and substitution of different herbal products, the detection of AA by phytochemical analysis remains the gold standard for confirming AA content (6).

Figure 2. **AA metabolism and proposed mechanism of AA-induced urothelial carcinogenesis in humans and metabolic activation and DNA adduct formation of AAI and AAII.**



After reductive metabolic activation mediated by cytosolic and/or microsomal nitroreductases or COX, 7-(deoxyadenosine-N^6-yl) aristolactam I or II (dA–AAI or dA–AAII) and 7-(deoxyguanosine-N^6-yl), aristolactam I or II (dG–AAI or dG–AAII) is formed. The presence of these adducts has been associated with characteristic A:T→T:A transversion mutations in codon 139 of the *TP53* gene. The relationship between the molecular mechanisms of carcinogenesis and those of AA-induced nephrotoxicity is still poorly characterized. AAI = aristolochic acid I; AAII = aristolochic acid II; AAN = aristolochic acid nephropathy; COX = cyclooxygenase; CYP = cytochrome P450; NQO1 = NAD(P)H:quinone oxidoreductase 1; POR = P450 oxidoreductase.

DNA Adduct Analysis

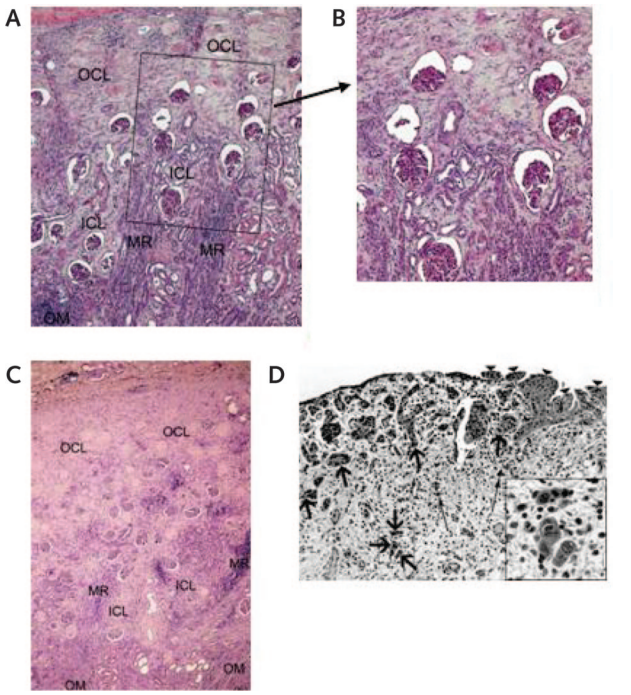
We suggest that, when possible, identification of AA–DNA adducts form an essential part of establishing the diagnosis of AAN. In most cases, this requires extraction of DNA from a fresh (unfixed) biopsy core of renal tissue. Alternatively, a "probable" diagnosis can be confirmed after identification of adducts in nephrectomy specimens. The ^{32}P-postlabeling technique for this analysis has been described elsewhere (67, 68).

Diagnostic Criteria

There are no strict criteria for diagnosing AAN. In our practice, any patient with suspected AAN is evaluated for other causes of possible renal impairment. If no alternative cause is identified, we make a *definite* diagnosis of AAN in any patient with impaired renal function (eGFR <60 mL/min per 1.73 m^2) and any 2 of the following 3 criteria: hypocellular fibrosis decreasing from the outer to the inner renal cortex, as shown by histologic evaluation of the kidney; ingestion of products confirmed by phytochemical analysis to contain AA; or the presence of AA–DNA adducts in renal or urinary tract tissue. We make a *probable* diagnosis of AAN in patients with impaired renal function and only one of the criteria together with urothelial cancer at the time of presentation. Although the presence of cancer is not a requirement for a diagnosis of AAN, given the particular association between AA exposure and cancer risk we believe that the presence of upper urinary tract cancer in the appropriate clinical context is highly suggestive of AA-induced disease. Any patient with impaired renal function, no alternative explanation for renal dysfunction, and a history of use of herbal remedies likely to contain AA but without phytochemical confirmation could be considered to have *possible* AAN. However, given the important implications of a diagnosis of AAN, we believe that either phytochemical confirmation of the presence of AA in ingested products or detection of AA–DNA adducts in pathologic specimens must form an essential part of any definitive diagnosis.

Specific diagnostic criteria will assist in the further study of AAN and will be essential in capturing robust epidemiologic data. A diagnosis of AAN has potential legal ramifications, as highlighted recently by a High Court case in the United Kingdom (69).

Figure 3. **Extensive hypocellular interstitial fibrosis associated with tubular atrophy decreasing from the outer to the inner cortical labyrinth of a patient with AAN associated with herbal medicine use (*A*) and BEN (*C*).**



AAN = aristolochic acid nephropathy; BEN = Balkan endemic nephropathy. **A** to **C.** Moderately cellular tubulointerstitial fibrosis and atrophy without corticomedullary gradients are visible in medullary rays and attending outer medulla. All images are stained with hematoxylin–eosin; obj. 4× for panels A and C and obj. 10× for panel B (insert of A at higher magnification). Image shown in panel C is courtesy of Professor Dusan Ferluga and Dr. Alenka Vizjak. **D.** Flat partially denuded grade II transitional cell carcinoma (*arrowheads*) from the right upper ureter in a patient with AAN (26) infiltrating the lamina propria as cords (*thick arrows*) and individual malignant cells (*thin arrows*). Hematoxylin–eosin stain, ×200; insert, ×500.

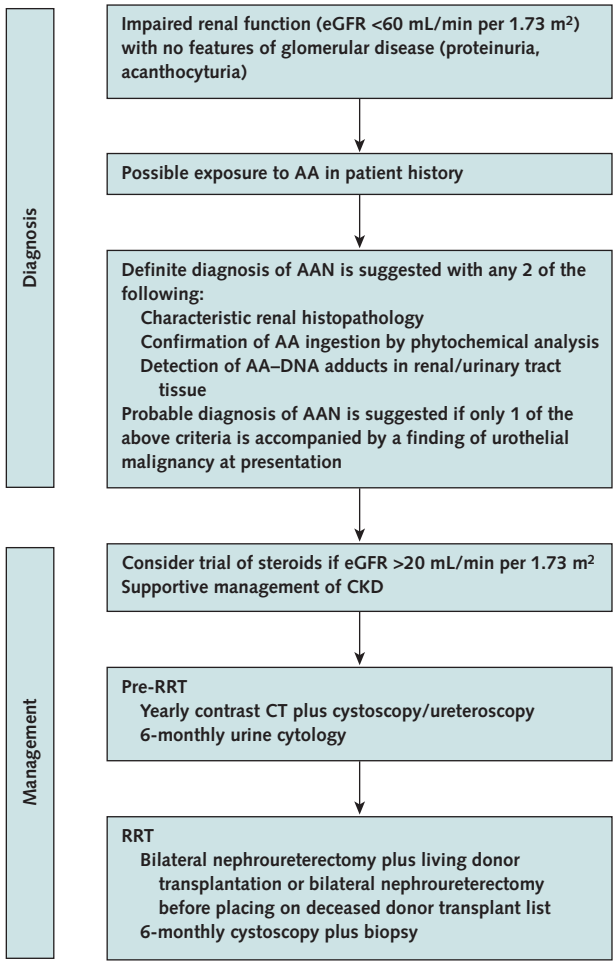
MANAGEMENT

Prevention

Prevention of exposure to AA is a key public health priority. In the European Union, the 2004 European Directive on Traditional Herbal Medicinal Products has, since 1 May 2011, required that all traditional herbal medicines be registered and approved; no products containing AA have been approved (70). In the United States, the FDA issued an alert in 2001 about the dangers of AA (71) and import alerts allowing the seizure of any product containing AA are in force. The medicinal use of most AA-containing plant species has been banned in Hong Kong, Taiwan, and mainland China, although certain AA-containing products are still permitted in China under the supervision of practitioners of Chinese medicine (19). Despite these regulatory measures, there is still cause for concern, with evidence that products containing AA remain available on the Internet (14, 19, 49, 72). Tighter local regulation of practitioners and outlets of alternative and herbal medicine is required, as well as a robust international system of surveillance to identify products containing AA.

Prevention of exposure to AA in parts of the Balkans where BEN is prevalent has not received sufficient attention since establishment of the etiologic relationship between AA and the disease. How persons in the Balkans are being exposed to AA and whether this is due to contamination of wheat production by *Aristolochia* species need to

Figure 4. **Proposed diagnostic criteria and management.**



AA = aristolochic acid; AAN = aristolochic acid nephropathy; CKD = chronic kidney disease; CT = computed tomography; eGFR = estimated glomerular filtration rate; RRT = renal replacement therapy.

be fully evaluated. An international panel has proposed that at-risk individuals in endemic areas be screened for renal disease with eGFR measurement and urine dipstick testing every 1 to 3 years (73).

Disease-Specific Management

Aristolochic acid nephropathy is notable for its rapid progression to end-stage kidney disease despite cessation of AA-containing products. No randomized clinical trials have been done to help inform optimum management of this condition; the best evidence comes from case series, expert opinion, and inferences from animal data.

Although renin–angiotensin system blockade with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers is important in managing CKD, no evidence shows that this strategy can improve renal function or delay progression in AAN. A study in a rat model of AAN showed no difference in outcome with sodium restriction or with treatment with enalapril or enalapril combined with candesartan (74). However, low-quality evidence has shown that steroid treatment can modify the course of the disease. A nonrandomized study of steroid therapy in the original Belgian cohort of patients with AAN showed statistically significant slowing in the progression of renal failure in 12 treated patients compared with well-matched historical control patients (75). On the basis of the available evidence, our practice is to consider a therapeutic trial of steroids for all patients with a diagnosis of AAN and an eGFR greater than 20 mL/min per 1.73 m^2, with a suggested starting dose of prednisolone of 1 mg/kg for 4 weeks followed by a gradual taper to a maintenance dose of 0.15 mg/kg. We recommend discontinuation of steroid therapy at 6 months if the eGFR continues to decrease.

Priorities in the management of AAN are similar to those of other causes of CKD: careful blood pressure control, cardiovascular risk reduction, management of metabolic complications, and timely preparation for renal replacement therapy.

Renal Replacement Therapy and Transplantation

We offer all patients with a definitive diagnosis of AAN the option of having bilateral nephroureterectomy at the point of considering renal replacement therapy, ideally in the context of planned living donor renal transplantation. Optimum surgical approaches for UUC have recently been subjected to a Cochrane review (76). We do not recommend routine cystectomy because the incidence of bladder tumors has been found to be lower than that of other urothelial tumors. The disease has not been found to recur after transplantation (52), and if bilateral nephroureterectomy is not done at or before transplantation, the post-transplantation risk for cancer in the native urinary tract has been reported to be as high as 52.9% over a median follow-up of 57 months (77).

Surveillance

Cytologic evaluation of urine can be done routinely on all patients with AAN, but we believe that it cannot replace a more invasive surveillance strategy owing to its poor sensitivity to tumors of the upper urinary tract. Therefore, in patients with AAN who do not yet require renal replacement therapy, we perform yearly surveillance with computed tomography imaging and ureteroscopy. After nephroureterectomy, we offer patients rigid cystoscopy and bladder biopsy every 6 months. Individuals may choose to undergo cystectomy if AA–DNA adducts are detected in bladder specimens. Recently published guidelines for diagnosis and management of UUC (78) are unlikely to be directly applicable to patients with known AA exposure or documented AA–DNA adducts in renal tissue, given the high risk for cancer.

Proposed diagnostic criteria and suggested management strategies are summarized in **Figure 4**.

Areas of Uncertainty

Although much progress has been made in understanding the epidemiology and molecular pathogenesis of AAN, many important areas of uncertainty remain. We see an urgent need for research addressing many key areas, including determining the true worldwide extent of exposure; defining genetic variants that might confer increased sensitivity or resistance to the nephrotoxic effects of AA; testing the accuracy and utility of diagnostic criteria and optimum screening strategies, including the use of noninvasive biomarkers; and developing therapeutic agents that can reverse or delay progression of the disease.

Given the geographic distribution of AAN, these questions can be addressed through a collaborative international approach, perhaps including establishment of a case registry. An international herbal reference center equipped to assess the composition and risks of products available to consumers would provide substantial public health benefit.

Conclusions

There have been many advances in our understanding of AAN since the first description of nephropathy associated with the ingestion of AA in the early 1990s, but considerable challenges remain. Products containing AA are still available, species of *Aristolochia* are still used in medicinal preparations in many parts of the world, and the sale and distribution of herbal medicinal products remain poorly regulated. As a result, the true extent of AAN worldwide remains unclear. We have attempted in this review to fill in the many evidence gaps about all aspects of this disease on the basis of our clinical experience and consensus, but future research should seek to determine noninvasive biomarkers of exposure and disease and optimum agents and surgical treatments that might alter the course of the disease. Perhaps most important, improved regulation of herbal medicines could help eradicate this entirely preventable illness.

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