Arterio-Ureteral Fistula: Systematic Review of 445 Patients

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Study Need and Importance: Arterio-ureteral fistula (AUF) is a rare, but potentially lethal, clinical entity. In spite of an increase in reported cases and clinical awareness, AUF is not always recognized in time. Delay between first presentation and treatment may adversely affect clinical outcome.

What We Found: In this systematic review we found 245 published articles with 445 patients and 470 AUFs. Most patients had a medical history of chronic indwelling ureteral stents (80%), pelvic oncology (70%), irradiation (53%) or vascular surgery (26%), presenting with intermittent (micro) hematuria or building up to massive hematuria. The pathophysiologic hypothesis is presented in the figure. AUF was located at the crossing between ureter and artery, mostly the common iliac artery. The best modality to diagnose this entity was an angiography, with a sensitivity of 62%. Endovascular stent graft placement is preferred over open surgical repair in terms of AUF-related mortality (4% vs 11%). AUF-specific mortality before 2000 vs after 2000 is 19% vs 7%, coinciding with increasing use of endovascular stent graft placement.

Limitations: The retrospective nature of this study, including many single case reports, results in a low level of evidence and high risk of bias. Furthermore, report bias could impact our findings such as better medical registration, electronic patient files, better imaging tests, less invasive treatment options, and better outcome.

Interpretation for Patient Care: Clinical awareness as well as multidisciplinary approach is important to decrease unnecessary delay between first presentation and treatment of AUF. The best diagnostic tool is an angiography and the preferred treatment is endovascular stent graft placement.
Arterio-Ureteral Fistula: Systematic Review of 445 Patients

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Purpose: Arterio-ureteral fistula (AUF) is an uncommon diagnosis, but increasingly reported and potentially lethal. This systematic review comprehensively presents risk factors, pathophysiology, location and clinical presentation of AUF aiming to increase clinical awareness of this rare but life-threatening condition, and to put this entity into a contemporary perspective with modern diagnostic tools and treatment strategies.

Materials and Methods: This review was performed according to the PRISMA (Preferred Reporting Items for a Systematic Review and Meta-Analysis of Individual Participant Data) guidelines. A literature search in PubMed® and EMBASE™ was conducted. In addition, retrieved articles were cross-referenced. Data parameters included oncologic, vascular and urological history, diagnostics, treatment, and follow-up, and were collected using a standard template by 2 independent reviewers.

Results: A total of 245 articles with 445 patients and 470 AUFs were included. Most patients had chronic indwelling ureteral stents (80%) and history of pelvic oncology (70%). Hematuria was observed in 99% of the patients, of whom 76% presented with massive hematuria with or without previous episodes of (micro)hematuria. For diagnosis, angiography had a sensitivity of 62%. The most predominant location of AUF was at the common iliac artery ureteral crossing. AUF-specific mortality before 2000 vs after 2000 is 19% vs 7%, coinciding with increasing use of endovascular stents.

Conclusions: AUF should be considered in patients with a medical history of vascular surgery, pelvic oncologic surgery, irradiation and/or chronic indwelling ureteral stents presenting with intermittent (micro)hematuria. A multidisciplinary consultation is necessary for diagnosis and treatment. The most sensitive test is angiography and the preferred initial treatment is endovascular.

Key Words: hematuria, stents, urinary fistula, endovascular procedures, angiography

Arterio-ureteral fistula (AUF) is an uncommon but potentially lethal clinical entity. AUF is defined as a pathological connection between a ureter and an artery, most commonly the iliac artery or previously implanted graft.

Between 1908 and 1994, only 33 cases were described. From there, an increase in reports on AUF has been
observed, with up to 139 cases in 2008. Since then, many more reports have appeared, including series with a substantial number of cases.

Well-known risk factors for developing AUF are a history of pelvic irradiation, pelvic oncologic surgery, vascular surgery and/or chronic indwelling ureteral stent. First clinical presentation is often hematuria without any additional symptoms, which frequently ceases without any treatment. Although according to the guidelines hematuria necessitates urological evaluation, the lack of awareness of AUF may delay diagnosis. Even with a clinical suspicion of AUF, there is still a great difficulty in confirming this entity despite several imaging tests. Management of AUF has historically performed by open surgical repair but has shifted to endovascular treatment since first described in 1996.

The diagnostic and therapeutic options for AUF have importantly changed in the past 10–15 years. In spite of an increase in reported cases, diagnosis and treatment of AUF still tends to be a clinical conundrum.

The current review aims to put the entity of AUF into a contemporary perspective of modern diagnostic and therapeutic options with an analysis of the patient characteristics, the optimal diagnostic tools and outcomes of different treatments (endovascular, open vascular or urological surgery). Finally, the outcomes of these patients in relation to year of diagnosis and association with therapy are presented.

MATERIALS AND METHODS

This systematic review was performed according to PRISMA (Preferred Reporting Items for a Systematic Review and Meta-Analysis of Individual Participant Data).

Search Strategy

A literature search was conducted in May 2021 in 2 bibliographic databases from 1908 to 2021: PubMed® and EMBASE™. Different keywords and derivates of keywords were used: ureteroarterial OR uretero-arterial OR uretero-iliaic OR ureteroiilial OR uretero-iliaic OR uretero-liial OR arterioureteral OR artery-ureteral OR arterio-ureteral OR arterio-ureteric OR arterio-ureteric OR ilioureteral OR ili-ureteric AND fistula.

AUF was defined as a pathological passage between an artery or previously implanted vascular graft, with the same function as an artery, and a ureter. Inclusion criteria were: 1) adult population 18 years and older, 2) written in English or German, 3) observational studies (including case series or case-reports) and 4) AUF as defined above, full-text or conference abstract. Articles were excluded based on the following criteria: 1) systematic reviews or meta-analyses, 2) animal study, 3) absence of individual case data, 4) fistulas other than described above, 5) post-traumatic fistulas or 6) articles that include overlapping patient populations (most recent publication was used). After the search, cross-referencing of all included articles was applied. Studies or abstracts that were not available in full-text or missing key details were extracted using Google Scholar or obtained through personal contact. Extracted data included oncologic, vascular and urological clinical medical histories, clinical presentation, diagnostic tests, fistula location, treatment and followup. We used a standardized template (Excel® 2016, Microsoft®, Redmond, Washington) for individual case data extraction, which was performed by 2 independent reviewers (K.K. & T.L.).

Definitions and Classification

Hematuria was classified as: intermittent without clinical consequences; first intermittent, followed by more massive bleeding; and massive hematuria at first presentation with ≥3.22 gm/dl (≥2 mmol/L) drop in hemoglobin, clot retention and/or hemorrhagic shock. Diagnostic tests were grouped according to confirmative and not-confirmative of AUF. Sensitivity was calculated for each test, defined as positive tests/total tests = sensitivity (%). Ureteroscopy classification was classified as confirmative if there was a pulsatile bleeding from the ureteral orifice. Ureteropyelography, computerized tomography angiography and angiography were classified as confirmative if contrast extravasation was observed. Treatment of AUF was categorized as primary endovascular, primary open repair, combined endovascular/open repair and solitary urological treatment.

Outcomes were classified as non-lethal outcome versus AUF-related death, defined as death due to massive hemorrhage or postoperative deaths (<30 days) or directly related to the treatment of AUF.

The standard care rapidly changed to minimally invasive endovascular treatment in the 21st century, and therefore characteristics and outcomes of patients diagnosed before 2000 and after 2000 were compared.

No risk of bias assessment was performed because the majority of the included articles were case reports. The PICOs criteria are presented in supplementary Appendix 1 (https://www.jurology.com). Descriptive statistics were used (SPSS® version 27.0).

RESULTS

Literature Search

Our literature search included a total of 245 articles with 445 patients and 470 AUFs. Figure 1 shows the PRISMA flow diagram. Publication year ranged from 1908–2021. A complete reference list is presented in supplementary Appendix 2 (https://www.jurology.com).

Demographics

Demographics are shown in table 1.

Risk Factors. The most common risk factor was the presence of chronic indwelling ureteral stent (357 patients, 80%) with a mean duration of 36 months before first suspicion of AUF. Furthermore, 311 patients had an oncologic history (70%), predominantly
cervical cancer in 114 patients (26%), colorectal cancer in 77 (17%) and bladder cancer in 57 (13%). Oncologic pelvic surgery was performed in 289 patients (65%) with previous total, anterior or posterior exenteration in 51 patients (16%). Previous pelvic radiation therapy was documented in 238 patients (53%) with a mean of 52 Gy. A medical history with predominantly open vascular surgery was present in 114 patients (26%).

In a total of 18 patients (4%), none of the above risk factors were present. In 7/18 patients (1.6%) AUF was caused secondary to kidney transplantation (3/18) or urological treatment such as Acucise® or laser endopyelotomy (4/18). The other 11/18 patients (2.5%) had a spontaneous AUF caused by a pseudoaneurysm or true aneurysm (9/18), arteriovenous malformation (1/18) or aberrant vessels of the common iliac artery (1/18).

**First Presentation.** Hematuria was present in 99% of the patients; 1% presented without hematuria, but with vascular symptoms (claudication or leg ischemia) or with hydronephrosis at routine imaging. As shown in table 1, the majority of patients (61+277 patients, 76%) had massive hematuria with or without previous episodes of intermittent (micro)hematuria. Some reports stated the presentation of general hematuria without further elaboration. Associated symptoms were hemorrhagic shock and/or clot retention in 77 patients (17%); pain, mainly flank pain, in 57 patients (13%); and other symptoms such as infection and bleeding other than hematuria in 44 patients (10%).

**Diagnosis**
In total, 972 imaging tests were performed to diagnose AUF, with a mean of 2.2 per patient. Of those imaging tests only 46% effectively confirmed the presence of AUF. The sensitivity of all tests is shown in table 2. Angiography is the best modality for confirming AUF with a sensitivity of 62%.

In 25 case-reports “provocative angiography” was described and defined as manipulation of ureteral stent or vascular catheter at the site of the suspected AUF. This provocative maneuver can confirm the AUF and cause massive hemorrhage. For this reason the maneuver should only be performed under controlled circumstances. In 20/25 cases “provocative angiography” was helpful to confirm the AUF. However, it is not a standardized procedure, and therefore sensitivity (%) could not be calculated.

In 34 patients none of the diagnostic tests could definitively confirm the diagnosis, but AUF treatment was initiated based on strong clinical suspicion. After the treatment hematuria stopped in these cases, confirming AUF (diagnosis per treatment). In 14 patients AUF was confirmed postmortem. A diagnostic algorithm is presented in figure 2.

**Fistula Location**
Figure 3 shows the AUF location in all patients. The side of the fistula and exact arterial branch were not detailed in the report of 10 and 6 patients, respectively. A total of 123 patients (28%) had an altered anatomy of the ureter because of previous urinary deviation (119 patients) or kidney transplantation (4 patients). Urinary deviation was mainly an ileal conduit. A total of 21 patients had bilateral AUFs and 4 patients had 2 AUFs on the ipsilateral side. Another 2 patients had AUF first, followed by an arterial-conduit fistula; those last 2 were not included in the total AUFs. The reported time between 2 fistulas were <8 days in 6 patients and between 1.5 and 84 months (mean 17 months) in 14 patients.

**Intervention and Outcome**
Unnecessary treatment was performed in 44 patients: 26 nephrectomies of healthy kidneys, 14 renal artery embolizations and 11 other treatments.
Treatment and outcomes are shown in table 3. The endovascular treatment group had more patients and a substantially decreased AUF-related mortality compared to the open vascular treatment group. Untreated AUF is associated with high mortality rate. There were no AUF-related deaths reported in the combined endovascular/open and the urological treatment group. In 85 patients the internal iliac artery was embolized using coils or vascular plugs, mostly in addition to introduction of an endovascular stent. The most frequently used covered stents were: VIABAHN® (26%), Advanta V12®/iCast® (22%), FLUENCY® (17%), WALL-GRAFT™ (6%) and GORE® EXCLUDER® (6%).

After initial treatment, 25 patients (2 initial open repairs, 23 initial endovascular) had recurrence of hematuria after a mean of 6 months. Secondary treatment included open (9 patients), endovascular (13 patients), first endovascular and later open because of graft infection (2 patients), and 1 conservative treatment. Other reported complications were secondary AUF (ie occurrence of AUF in a new location; 25 patients), graft infection (14 patients) and stent thrombosis (16 patients). Secondary AUFs were mostly treated with endovascular stent placement in addition to the first endovascular stent (19/25 patients). Six patients underwent open surgical repair; 5 patients with open repair were dated before 2001 and the last open repair was performed because stent graft removal was indicated, and segmental small bowel resection was performed.

The overall survival rate was 71% with a mean followup of 22 months. The AUF-related mortality was 9%, which decreased from 19% before 2000 to

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Sensitivity</th>
<th>No.</th>
<th>Total No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiography (best modality)</td>
<td>169/272</td>
<td>62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ureteropyelography</td>
<td>60/118</td>
<td>51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Computerized tomography angiography</td>
<td>68/141</td>
<td>48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urethrocystoscopy/ureterorenoscopy/pouchoscopy</td>
<td>40/142</td>
<td>28</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Diagnostic test sensitivity**

![Figure 2. Diagnostic algorithm. CT, computerized tomography. UCS, urethrocystoscopy.](image)
7% after 2000. The main reason for AUF-associated mortality was massive hemorrhage. The time between first presentation and AUF-related death was less than 10 days in 52% of the patients and more than 10 days (30–426 days) in 48% of the patients. The other causes of death were advanced cancer in 34 patients (8%), sepsis in 10 patients (2%), cardiac arrest in 7 patients (2%), pulmonary cause in 5 patients (1%), other causes in 11 patients (2%) and unknown in 13 patients (3%). Deaths occurred a mean of 15.7 months after AUF diagnosis.

DISCUSSION
This review comprehensively presents risk factors, pathophysiology, location and clinical presentation of AUF aiming to increase clinical awareness of this rare but life-threatening condition, and to put this entity into a contemporary perspective with modern diagnostic tools and treatment.

The main risk factors for development of AUF are chronic indwelling ureteral stents, history of pelvic oncology with predominantly cervical cancer, irradiation therapy and vascular pelvic surgery. Other associated causes that were found are pseudoaneurysm (fig. 4), true aneurysm, arteriovenous malformation, kidney transplantation and urological treatment. The urological treatment, eg laser or Acucise endopyelotomy, is not being used in modern medicine and was last described in 2009.11 Since the main risk factors are based in different medical disciplines, the diagnosis requires a multidisciplinary approach with expertise of vascular surgeon, interventionist radiologist and urologist.12 Bergqvist et al suggested that 15% of AUFs are considered primary fistulae and 85% are secondary
to other diseases. In the current review we identified 97.5% secondary AUFs and only 2.5% primary AUFs caused by pseudoaneurysm, true aneurysm, aberrant vessels and arteriovenous malformation.

Although the exact pathophysiology is still uncertain, a few hypotheses exist on how AUF develops and the contributing risk factors (fig. 5). Under normal conditions the pulsatile artery does not affect the ureter since the ureter can move freely (fig. 5, A). However, pelvic surgery and radiation therapy could cause fibrosis and ischemic injury to the artery. At the ureter crossing point these injuries could lead to fixation of the ureter to the adjacent arterial branch and could cause ureter obstruction (fig. 5, B). In case the ureter is fixed due to indwelling ureteral stents and/or retroperitoneal fibrosis, it could cause friction due to the pulsatile artery. Fibrosis, ischemia and/or friction could cause localized necrosis and eventually AUF (fig. 5, C). In addition, indwelling ureteral stents and endovascular stent grafts are associated with urinary tract infections and graft infections, respectively. These infections may weaken the ureteral or arterial wall due to edema which eventually could result in AUF.

Location of AUF is at the crossing between ureter and artery, mainly the common iliac artery. The crossing is altered in patients with urinary deviation, diseases such as aortitis or retroperitoneal fibrosis and kidney transplantation. In patients with a urinary deviation the left ureter crosses the midline, including the aorta, to a right sided stoma and therefore is more vulnerable to make a fistula with the aorta or right common iliac artery. In patients with aortitis or retroperitoneal fibrosis the ureter diverts medially and therefore forms more fistulas with the aorta.

Figure 4. AUF anatomy with pseudoaneurysm involvement.

Figure 5. Pathophysiology of AUF. A, normal condition—pulsatile artery does not affect freely movable ureter. B, fibrosis and ischemic injury due to pelvic surgery and/or radiation could cause ureter obstruction and fixation of ureter to arterial wall. C, ureteral stent placement to treat hydronephrosis which causes friction due to less freely movable ureter. In time, fibrosis, ischemia and/or friction could cause localized necrosis and eventually AUF.
Clinical presentation was mainly characterized by a long period of intermittent (micro)hematuria with initial remarkable findings at standard workup, promptly turning into massive hemorrhage, especially during routine ureteral stent replacement.

Diagnosis of AUF remains difficult because of the low sensitivity of imaging tests. Angiography seems to be the best modality, confirming diagnosis in 62%. However, a negative angiography could not exclude AUF because active bleeding is necessary for reliable angiography. In case of negative angiography, provocative angiography (ureteral or vascular manipulation at AUF site) should be considered under controlled circumstances.

Diagnosis is also difficult because of possibly misleading results of the imaging tests. These results could be renal clots suggesting renal bleeding instead of AUF. In a few cases, these results led to unnecessary treatment such as renal artery embolization or nephrectomy of a healthy kidney. For example, Moon et al presented a case with embolization of both renal arteries before correct diagnosis and treatment of AUF.

In the past few years, management of AUF has shifted from open surgical repair to minimally invasive endovascular treatment with covered stents. This is because AUF patients typically have a hostile environment for open repair because of previous extensive pelvic surgery and radiation therapy which causes adhesions and fibrosis. Thereby, endovascular is preferred over open surgical repair in terms of AUF-related mortality (4% vs 11%). Furthermore, endovascular treatment offers a lifesaving, rapid treatment in hemodynamically unstable patients. During followup, possible complications after endovascular treatment needing reintervention are recurrence of hematuria, endoleak, graft infection or stent thrombosis.

Compared to the period <2000, in the past 2 decades the overall AUF-related mortality seems to have decreased from 19% to 7%. This is probably the result of more awareness of this entity, better imaging techniques, shorter time interval between onset of complications and treatment and minimally invasive endovascular treatment. The AUF-specific mortality of combined treatment versus primary open treatment is 0% vs 11%. We suggest that in the acute setting, the first treatment should consist of endovascular stent placement, but elective open surgical repair may remain necessary in some cases, for example to remove an infected stent graft and perform an extra-anatomical bypass.

Preventive measures were rarely mentioned. Our view is that long-term indwelling ureteral stent placement should be avoided in patients with AUF risk factors. The risk of AUF formation should be taken into account when choosing between a percutaneous nephrostomy versus indwelling ureteral stent in high-risk patients. Also, risk factors for AUF formation should be taken into account when choosing specific surgical approaches in urinary diversion, pelvic or vascular surgery.

AUF reports seem to have substantially increased over the past few years. However, true incidence is likely to be higher when accounting for general underreporting, cohort studies without available individual data and numerous articles in other languages. It could be hypothesized that the increase in reported cases may be due to the increase in risk factors of AUF, in combination with overall increasing life expectancy.

Although this review describes a large number of AUF patients, the retrospective nature of this study, including many single case reports, results in a low level of evidence and high risk of bias. Furthermore, report bias could impact our findings such as better medical registration, electronic patient files, better imaging tests, less invasive treatment options and better outcome.

CONCLUSIONS
AUF is a rare cause of possibly life-threatening hematuria. Patients typically present with a long-lasting intermittent (micro)hematuria that can promptly deteriorate to massive hemorrhage. This presentation in combination with a medical history of vascular surgery, pelvic oncologic surgery, pelvic radiation therapy and chronic indwelling ureteral stents is highly suggestive for AUF. Clinical awareness as well as multidisciplinary approach is important to decrease unnecessary delay between first presentation and treatment. Endovascular treatment using covered stents is preferred, but not always possible. The reported AUF-specific mortality has decreased in the last 2 decades.

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