

Diagnosis and Management of Obstructive Uropathy in the Setting of Advanced Pelvic Malignancies

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Abbreviations

AKI: Acute Kidney Injury

ANP: Atrial Natriuretic Peptide

BOO: Bladder Outlet Obstruction

BPH: Benign Prostatic Hypertrophy

BUO: Bilateral Ureteral Obstruction

CT: Computed Tomography

GFR: Glomerular Filtration Rate

MRI: Magnetic Resonance Imaging

MUO: Malignant Ureteral Obstruction

PCN: Percutaneous Nephrostomy Tube

RBF: Renal Blood Flow

RI: Resistive Index

RPF: Retroperitoneal Fibrosis

RPG: Retrograde Pyelogram

SPT: Suprapubic Tube

Tm DTPA: Technetium Diethylenetriaminepentaacetic Acid

Tm MAG: Technetium Mercaptoacetyltriglycine

TUU: Trans-ureteroureterostomy

UDS: Uroynamics

UP: Ureteral Pressure

UTO: Urinary Tract Obstruction

US: Ultrasound

UUO: Unilateral Ureteral Obstruction

ABSTRACT

Obstructive uropathy is a common urological problem, with a variety of etiologies, ranging from benign to malignant processes, extrinsic to intrinsic conditions. Its presentation depends largely on the location of the obstructive lesion and the acuity of the obstruction. Lower versus upper urinary tract obstruction present differently. A wide variety of imaging tools can aid in diagnosing the obstructive process and help delineate the etiology and the location of the obstruction. Treatment is geared towards alleviating the obstruction, either by restoring the normal urinary flow within the urinary tract by utilizing a ureteral stent for upper urinary tract obstruction or urethral catheters for lower urinary tract obstruction, or by diverting the urine by placing a percutaneous nephrostomy tube or suprapubic catheters. Pelvic malignancies are a subset of the many causes of obstructive uropathy and have unique considerations in treatment. Future directions in the realm of management of obstructive uropathy should focus on maximizing urinary drainage while minimizing the morbidities associated with the current available treatment options.

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INTRODUCTION

Urinary tract obstruction (UTO) is a common urological problem. It is caused by blockage of urinary flow, which is secondary to benign

or malignant processes and can be a result of extrinsic or intrinsic conditions. In a review of autopsy findings, Bell *et al*^[1], found that hydronephrosis was discovered in 3.1% of 59,064 autopsies. Out of the 37,477 males, the most common etiology was benign prostatic hypertrophy (BPH) and prostatic adenocarcinoma. Out of the 21,587 women, the most common etiology was pregnancy or gynecologic malignancies – typically cervical or uterine cancer.

The true overall incidence of ureteral obstruction as a result of pelvic malignancies is unknown but it is clinically encountered commonly as a progressive pathology resulting in urinary blockage and poses a risk of renal functional decline^[2]. Only 21% with this condition will be caused by a primary urological tumor. Ureteral stents and percutaneous nephrostomy tubes (PCN) are tools to help adequately drain the upper urinary tracts^[3]. Recovery after obstruction studied in canine models by Leahy *et al*^[4] showed complete recovery of kidney function if the obstruction was relieved in 14 days. This decreased to 31% after 28 days, and 8% in 60 days. Therefore, timely recognition of the obstruction and treatment providing relief of the obstruction by using either ureteral stents or PCNs is critical to preserving kidney function.

PATHOPHYSIOLOGY

Renal blood flow (RBF), ureteral pressure (UP), and glomerular filtration rate (GFR) all vary in different phases of obstruction, and the pattern of change among the three defined phases are different in unilateral ureteral obstruction (UUO) and bilateral ureteral obstruction (BUO)^[5].

Unilateral Ureteral Obstruction

In a canine model by Moody *et al*^[6] the relationship between the three factors is triphasic: (1) both the UP and RBF increased within the first 1.5 hours; (2) RBF declined while UP continued to increase for the next 3.5 hours; and (3) finally both RBF and UP decreased progressively. Glomerular filtration rate is maintained in phase 1 because of the increased RBF, however GFR declines in phase 2 since RBF declines, and finally GFR declines further in phase 3 as RBF and UP declines^[7]. These effects are mediated by multiple biochemical factors such as angiotensin II^[8], nitric oxide^[9-11], and endothelin^[12-14], all of which facilitate the vascular tone patterns associated with each phase of the process (afferent arterioles vasodilation in phase 1, efferent arterioles vasoconstriction in phase 2, and efferent and afferent arterioles vasoconstriction in phase 3)^[15,16].

Bilateral Ureteral Obstruction

The hemodynamic changes in BUO or obstruction in a solitary kidney system are different compared to UUO^[5,17]. Renal blood flow initially increases for the first 90 minutes, then progressively declines. Ureteral pressures increase and remain elevated for a prolonged period compared to UUO^[5]. Instead of afferent arteriole vasodilation, efferent arteriole vasoconstriction, followed by afferent vasoconstriction as seen in UUO, BUO has persistent afferent vasodilation leading to persistently elevated UPs. This was documented well in a micropuncture study by Yarger *et al*^[6], revealing increased hydrostatic pressures in rats with BUO compared to rats with UUO. The GFR in both UUO and BUO decreases, where UUO is due to increased afferent resistance, and BUO is related to its elevated intratubular pressures^[12].

Postobstructive Diuresis

Relief after obstruction can often have a profound effect on the

electrolyte balance and mechanisms of urinary concentration and dilution ability. Postobstructive diuresis occurs more commonly after BUO and is not seen as often in UUO given the compensatory up regulation of ion channels within the contralateral kidney^[19,20]. BUO causes overall retention of sodium, water, urea, and other osmolar substances as well as increased Atrial Natriuretic Peptide (ANP) production^[21] leading to profound diuresis. The body's intravascular volume status and the total body exchangeable sodium is correlated with the level of diuresis that often occurs after post obstruction relief. Muldowney *et al*^[22] discovered that the amount of exchangeable sodium after BUO is elevated and the diuresis did not lead to any clinical sodium depletion. They concluded that this was a result of physiological diuresis. Gulmi *et al*^[23] compared volume resuscitated dogs with BUO to volume deplete dogs with BUO and found that the volume resuscitated dogs had an elevated ANP leading to prolonged diuresis.

Another consequence of postobstructive diuresis involves an impairment of urinary concentration, which manifests itself through an increase in free water clearance and increased solute excretion. The concentration defect comes from an inability to maintain medullary tonicity due to impaired sodium reabsorption, which directly impacts the kidney's ability to reabsorb water^[24]. McDougal and Wright^[25] demonstrated this concentrating defect in ligated rats, which demonstrated a defect in urinary concentration and sodium reabsorption after relief of BUO. Potassium balance is also impacted, its fractional excretion increases after BUO release, which could be due to the increased delivery of sodium to the tubules and overall increased tubular flow rates^[25].

CLINICAL PRESENTATION

The clinical presentation for obstructive uropathy is widely variable^[21] and often depends on the location of the obstruction and the acuity of presentation^[2,12]. In pelvic malignancies, both acute and chronic presentations of obstructive uropathy are possible, with etiologies ranging from stricture disease from pelvic surgery^[26], radiation induced scar tissue formation within the ureter or extrinsically in the retroperitoneum^[27,28], chronic, insidious extrinsic tumor compression of the ureter either from the primary tumor, a recurrent mass, or metastasis^[2,29].

Lower Urinary Tract Obstruction

Obstruction at the level of the bladder neck, also known as bladder outlet obstruction (BOO), could be caused by benign processes such as BPH or malignant processes such as invasion of the bladder at or distal to the trigone. Patients often complain of obstructive and irritative voiding symptoms, such as urinary urgency, frequency, decreased force of stream, and incomplete bladder emptying^[30,31]. Examination can often reveal a large, palpable distended bladder, and patients can often present with anuria^[30].

Acute Upper Urinary Tract Obstruction

Urolithiasis is the most common cause of acute upper UTO^[7]. However, in pelvic malignancies, obstruction can result from stricture formation from recent surgery, or radiation induced strictures^[26,27]. Patients often complain of renal colic, which is a cyclical pain associated with acute ureteral obstruction, caused by activated collecting system mechanoreceptors that lead to activated spinothalamic C fiber excitation^[32,33]. Other symptoms often associated with acute obstruction include: anorexia, nausea,

vomiting, abdominal pain, cramping, or a vague feeling of fullness^[2,34].

Chronic Upper Urinary Tract Obstruction

Slowly progressing, chronic obstruction can result from benign conditions such as idiopathic retroperitoneal fibrosis (RPF) or more insidious processes such as extrinsic compression due to an enlarging pelvic malignancy^[2,29]. These patients are more likely to present less severely with vague, poorly localized, dull abdominal pain^[2,12]. This was demonstrated by Shafik *et al*^[34] in 14 healthy individuals who experienced less severe symptoms with slow distension of the renal pelvis compared to their counterparts who underwent rapid pelvic distension. Long term effects of chronic obstruction of bilateral ureters or of a solitary kidney may present with symptoms related to volume status and electrolyte abnormalities, such as heart failure, altered mental status, hypertension, or anorexia^[12].

EVALUATION

After obtaining a thorough history and physical examination and obtaining basic laboratory studies such as serum electrolytes and urinalysis, further imaging can be considered. Certain exam findings and patient complaints can help guide the differential diagnosis. For example, if the patient presents with a palpable bladder, obstructive voiding symptoms, and elevated bladder volumes based on bladder scan, lower UTO may be suspected. On the other hand, if a patient presents with a non-palpable bladder, decreased urine output with no sense of urinary urgency or frequency, then an upper UTO is more likely^[31]. A variety of imaging modalities are available to diagnose obstructive uropathy and help delineate the location of the obstruction, a number of which are discussed below.

Ultrasonography

Renal ultrasound (US) is one of the first line imaging modalities and has been studied as a possible first line imaging study to evaluate hydronephrosis in the emergency department setting^[35]. It has benefits of being widely available, inexpensive, and free of ionizing radiation, making it safe for pediatric, pregnant patients, or people with renal insufficiency^[12]. However, caution must be exercised since hydronephrosis is different from pelviectasis, which can exist without any physical obstruction^[21] and abnormalities such as parapelvic cysts can often lead to a false diagnosis of hydronephrosis^[36]. Renal US can only assess anatomical dilation of the pelvic system and cannot discover any functional obstructions^[21]. Licurse *et al*^[37] looked at a group of 200 individuals with acute kidney injury (AKI) and was able to stratify patients based on risk factors to help identify patients with hydronephrosis. Otherwise, without any stratification, Laing *et al*^[38] reported a false negative rate of 35% in their patients, underscoring the need for clinical correlation.

Doppler US can look at more detailed factors such as renal resistive index (RI), which can potentially discern between an obstructive or non-obstructive etiology for the observed pelviectasis. Although the studies have been conflicting in terms of the sensitivity and specificity of using RI, they all do suggest that an elevated RI can correlate with the degree of obstruction^[39,40,41]. Therefore, the use of RI should be correlated with clinical information.

Further information can be gained about the upper urinary tracts by assessing the bladder. For example, doppler US of the bladder can visualize ureteral jets, which was found to be reliable by De Bessa *et al*^[42] to look for hydronephrosis in children.

Nuclear Medicine Renography

While renal US can evaluate the anatomical aspect of obstruction, nuclear renography is the primary functional study. Technetium Diethylenetriaminepentaacetic acid (Tm DTPA), and Technetium Mercaptoacetyltriglycine (Tm MAG) are the two agents that are commonly used. Tm DTPA is freely filtered and is not secreted nor reabsorbed and Tm MAG is eliminated purely by the proximal tubules without any reabsorption. These can both be used to assess renal function. Often times the study can be combined with diuretics. The half-life of the agents is used to evaluate renal function while considering the shape of the washout curves. A half-life less than 10 minutes is normal, greater than 20 minutes indicates obstruction^[12]. However the patient's baseline renal function can affect the tracer's clearance and change the overall interpretation of the study's results^[43].

Computed Tomography and Magnetic Resonance Imaging

Computed tomography (CT) scans provides greater anatomic detail compared to US and is the imaging modality of choice for any patient with acute ureteric colic^[12]. Vieweg *et al*^[44] found that a non-contrasted CT scan had a sensitivity and specificity of 98% of diagnosing ureteral stones. A CT urography scan visualizes the genitourinary system with (1) a non-contrasted phase; (2) nephrogenic phase; and (3) excretory phase^[45]. This is the ideal study to evaluate hydronephrosis since it will be able to delineate stones and calcifications in the non-contrasted portion and evaluate for any intrinsic filling defects in the excretory phase^[12], with the addition of being able to evaluate for any extrinsic anatomic abnormalities that may be contributing to the patient's symptoms.

Magnetic Resonance Imaging (MRI) provides similar anatomic information and does not utilize any ionizing radiation, which makes it safer in pregnant women or children. In patients with renal insufficiency, MRI is a viable alternative, since the risk of contrast induced nephropathy is 10% in patients with a GFR of less than 65, while the risk of nephrogenic systemic fibrosis is less than 5% in patients with GFR less than 30^[46,47].

Urodynamics

Urodynamics (UDS) is a series of diagnostic tests that observes the functional patterns of bladder filling, urine storage, and emptying^[48,49]. Current literature providing level 1 evidence regarding its use is limited, though recent studies do endorse its use in stress urinary incontinence^[50,51]. Nitti and Brucker^[49] suggest that UDS is most useful if the initial workup including the history and physical examination along with simple diagnostic tests, such as the above imaging or functional modalities, were not sufficient in guiding the diagnosis and treatment. It is important keep the limitations of UDS in mind, as UDS is performed in an unnatural setting and may not duplicate real life symptomatology and can lead to false negatives and positives.

BOO on UDS classically presents with high pressure and low flow voiding^[49]. UDS can help differentiate between detrusor underactivity from BOO using pressure-flow dynamics^[48,49]. Griffith *et al* reported a 68% positive predictive value of pressure flow studies in identifying BOO^[52]. In addition, video UDS, which fluoroscopically follows the voiding patterns, the location of the BOO can often be defined, which is particularly useful in women with BOO^[49]. Multiple studies report that pressure flow studies can predict outcomes of surgical treatments of BPH, therefore recent updates to the AUA/SUFU guidelines suggest that patients about to undergo complex surgical interventions should undergo UDS testing to help uncover any

detrusor overactivity or impaired compliance^[48]. In conclusion, UDS is a useful tool, but it is not the first functional or imaging study that would be performed to workup obstructive uropathy.

TREATMENT

Despite treatment of pelvic malignancies and even with complete resolution of the disease process, patients can still develop obstructive uropathy, sometimes even as a result of the treatment itself. From surgical management to chemotherapy to radiation treatments, patients can develop a host of issues such as strictures or RPF and all of these processes can cause obstruction of the urinary tract that would require treatment^[26-28].

In patients with malignancies, post-renal AKI due to obstruction is more common compared to the general population^[53]. Outcomes for patients with chronic illness or malignancy who also have AKI have poorer outcomes compared to those without^[54]. Therefore, it is critical to provide some way to decompress the kidneys through either a ureteral stent or a PCN.

Treatment for obstructive uropathy varies widely depending on the etiology, ranging from palliative options to definitive, curative options. For the purpose of this review, we will focus on the treatment options for malignant cases of obstruction, with special emphasis on ureteral stents and PCNs.

Lower Urinary Tract Obstruction Relief

Bladder outlet obstruction is initially managed with bypassing the obstruction by placing a Foley catheter. If catheterization proves difficult, a suprapubic tube (SPT) can be placed either at the bedside or in the operating room. Further treatments after the initial decompression should focus on the acute derangements, such as post obstructive diuresis and any electrolyte abnormalities that may result. Once the acute phase of obstructive uropathy resolved, definitive management is tailored towards the inciting disease process. For example, BPH would be treated with surgeries such as transurethral resection of the prostate (TURP) to facilitate better urinary flow, and pelvic malignancies could be treated with definitive or palliative objectives using surgery or possibly adjuvant hormonal, radiation, or chemotherapeutic options to decrease the overall tumor burden^[12,31].

Ureteral Stent

Zimkand *et al*^[55] described the first ureteral stent in 1967, which allowed a means of bypassing the narrowed portion of the ureter to effectively drain the kidney. Ureteral stents have a broad range of clinical uses. They can be used in the short term, such as in the case of obstructing stones or after a urological procedure, to allow a scaffolding to facilitate the patent healing of the ureter. They can also be used in the long term, in patients with some intrinsic or extrinsic reason for obstruction^[56]. However, though ureteral stents can effectively treat intrinsic ureteral defects^[57], extrinsic etiologies are more prone to stent failure. This was described as early as 1989 by Docimo *et al*^[58], where there was a significantly higher rate of failure among extrinsic compression compared to the intrinsic etiology. These findings are echoed in multiple other studies^[59-61]. Without stent failure, chronic stent exchanges are an effective treatment for malignancy related obstruction in maintaining renal function^[62].

Several techniques have been attempted to alleviate the stent failure, such as using tandem stents for maximal drainage^[63] and expanding the research in the biomaterials being incorporated

into stents. The knowledge and technology developed has grown significantly and now there are a wide variety of biomaterials that are being tested for possible stent use with the goal of retaining flow and minimizing irritability^[64,65]. Now, other stent designs such as metallic stents are being used and have very promising results in decreasing the number of stent failures in patients^[56,66]. Christman *et al*^[67] show that the tensile strength of metallic stents is greater than the conventional double-J stent, which is promising to overcome the extrinsic compressive forces. Metallic stents also have the benefit of needing less frequent exchanges^[56], which has cost benefits for the patient. Taylor *et al*^[68] did a cost analysis and found that patients save approximately \$9,000 per year using metallic stents.

Unfortunately, ureteral stents are not without morbidity. Using a questionnaire, Joshi *et al*^[69] found that out of their 85 patients, 80% had urinary symptoms that affected their overall quality of life. Symptoms such as hematuria, urgency, frequency, nocturia, decreased sexual satisfaction, or discomfort with activity, have made patients unhappy or dissatisfied, with some even describing their stent as "terrible."^[69] Factors such as stent length and whether or not it is crossing midline can impact the severity of the associated symptoms^[70]. Despite the multitude of stent-related discomfort, a review of PCN compared to ureteral stents does not show a difference in the quality of life^[71].

Percutaneous Nephrostomy Tube

Percutaneous nephrostomy tubes are an alternate method to draining the kidneys, by placing a catheter through the back directly into the renal pelvis allowing the kidney to drain maximally^[2]. It can be used for urgent decompression in patients with hydronephrosis and severe UTI or in patients who have failed stent therapy and need chronic decompression. Pearle *et al*^[72] showed there was no difference between ureteral stent and PCN for rapid recovery.

Open placement of nephrostomy tubes traditionally leads to high rates of major complications between 45-53%^[73,74], though recent advances now have low morbidity rates^[26,75,76] and may have surpassed ureteral stents in terms of efficacy and complication rates^[77]. In a study by Romero *et al*^[78], 60% of a 43-patient population were readmitted for catheter related complications. Patients also have quality of life issues related to urinary leakage around the tube and skin excoriations at the tube exit site^[79]. Despite the associated morbidities with PCN, it may still be appropriate for patients, as it may alleviate the ureteral obstruction to reverse renal insufficiency to transition patients off of hemodialysis, resolve pulmonary edema, and reverse electrolyte abnormalities^[78]. It can also alleviate the discomfort associated with symptomatic ureteral obstruction^[80]. It also has the benefit of requiring only local analgesic and sedation with initial PCN placement^[81] and can be performed over wire seldinger technique with just one puncture^[79]. Routine exchanges require even less sedation support.

Therefore, a discussion of patient goals and views must be conducted to determine if PCN is appropriate^[31,82]. Wilson *et al*^[83] studied 32 patients with malignant ureteric obstruction (MUO) and found that renal function did improve. However, these patients had limited life spans and did require an average of 1.6 admissions for PCN or stent related problems. On the other hand, Feng *et al*^[75] studied 37 patients and had more favorable results in that 84% of patients did not have any complications, were able to go home for 2 months, and had little to no pain.

Surgical Management for Refractory Cases

Often times, if conservative management of MUO is refractory,

then surgical options can be pursued to help alleviate the obstruction^[84]. Ureterolysis and ureteral reimplantation are both options to help restore urinary flow^[84-87]. Ureterolysis can be performed through a laparoscopic or open approach and has been described as an effective treatment option for refractory ureteral obstruction due to RPF^[85-87]. Styn *et al*^[85] in a cohort of 13 patients, observed an improvement in renal function with a mean creatinine level postoperatively at 1.1 in patients who underwent ureterolysis, showing that it is a good alternative treatment option for refractory cases.

Alternatively, ureteral reimplantation in patients with refractory MUO may not be a viable option as there are limitations such as active pelvic malignancy within the field or poor bladder tissue quality due to sequelae from radiation treatment^[84].

Urinary diversion is another treatment option for MUO, where the obstructed portion of the urinary tract can be diverted to a non-obstructed portion. Surgeries such as trans-ureteroureterostomy (TUU) or cutaneous ureterostomy have been described previously^[84]. Sugarbaker *et al*^[88] described using TUU in 11 patients and found no patients had any recurrent ureteral obstruction.

Special Considerations

Neither ureteral stents nor PCNs can remain in the urinary tract indefinitely and both require periodic changes. Prolonged retention can lead to problems with both ureteral stents and PCNs, including encrustation leading to stone formation or occlusion of the tube tract, breaking of the stent leading to difficulty with removal, and possible stent migration or PCN dislodgement^[81,89]. Most ureteral stents are made of synthetic polymers and can become encrusted with stone material and will require periodic exchanges every 3-4 months^[64]. Metallic stents are resistant to encrustation allowing for 12 month exchange time^[56]. Nephrostomy tubes are exchanged every 6-12 weeks^[90].

Patients with malignancies have unique characteristics that impact the timing and management of ureteral stents and PCNs. Those who are treated with chemotherapy are generally immunocompromised, have higher cell turnover, and have changes in overall tissue quality. Kehinde *et al*^[91] describes systemic disease to be a significant risk factor for developing stent related urinary tract infections and Bahu *et al*^[92] corroborated a similar risk factor for patients with malignancy related PCN placement, where 1 in 5 patients with malignancy developed infections after PCN placement. Multiple studies have reported higher stent failure rates in malignancy, either from extrinsic compression or encrustation^[2,59], though there are studies that do not reveal an identifiable factor^[71]. These noted factors can impact the frequency of stent exchanges and need for closer monitoring for stent failure.

From review of current literature, there is no standardized method to determine if the ureteral obstruction has resolved and the ureteral stent or PCN is ready to be removed. Adjunctive imaging modalities such as nuclear medicine studies or retrograde pyelograms (RPGs) can help with determining if the ureteral obstruction has resolved. Clinical findings such as clamping trials, to assess if the patient has any pain or discomfort with blockage of the flow out of the PCN, can help deduce whether the obstruction is still present and symptomatic. Caution must be exercised, however, with retrograde pyelograms (RPG) and monitoring for ureteral efflux, since re-obstruction may take hours to days to reform. Future studies are needed to determine the standardized method of assessing resolution of obstruction and to further evaluate the predictive success of the clinical findings.

CONCLUSION

Obstructive uropathy is a common condition, with both benign and malignant processes. Management is tailored to the overall etiology. For malignant processes, treatment is focused on decompression, utilizing ureteral stents or PCNs. For these patients, the treatment goals and views should be taken into account as both are not completely benign procedures without morbidity. Future directions should still be pursued to minimize the associated quality of life issues and facilitate maximal drainage.

CONFLICT OF INTERESTS

There is no conflict of interest.

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