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Lesson 12 Volume 40

Complex Infections of the Urinary Tract*

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to describe complex and rare infections of the genitourinary tract, including etiology and pathophysiology, as well as diagnosis and management.

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INTRODUCTION

Urinary tract infections are a common problem for men and women. When host immune defenses are lowered, or when organism counts increase, infections can take hold and cause significant morbidity and even mortality. Infection can involve the lower urinary tract or can extend to the upper urinary tract, including the ureters and kidneys. In addition, other rare organisms can cause infections in the bladder and even systemically. In this Update, we review the pathophysiology, clinical manifestations, diagnosis and management of several less common and rare—yet important to recognize—infectious processes of the urinary system.

LOBAR NEPHRONIA, RENAL ABSCESS AND PERINEPHRIC ABSCESS

Description, epidemiology and pathophysiology. Lobar nephronia is an infective process of the kidney limited to one or more renal lobules, which is characterized by local leukocytic infiltration.[1] The condition was originally described in 1979 in a radiological context.[2] LN sits on a spectrum between acute pyelonephritis and renal abscess, and if left untreated may develop into a renal abscess. The mechanism of infection is often thought to be hematogenous spread.

Renal and perinephric abscesses, on the other hand, are characterized by the liquefactive necrosis absent in LN.[3] Reports have demonstrated that most inoculation is by gram-negative organisms for both of these conditions. The mechanism is likely ascending infection due to tubular obstruction from prior infection or calculi.[4] Perinephric abscesses differ from renal abscess in that the collection is in the perinephric space as opposed to the renal parenchyma, often extending into Gerota's fascia. It is important to note, though, that some abscess may be classified as mixed, existing in the renal parenchyma and perinephric space simultaneously.

In one of the larger series reported in adults comprising 57 cases of acute focal bacterial nephritis, those diagnosed with LN by imaging tended to be younger than those with pyelonephritis (mean age 44 vs 55 years), and there was a 3:1 ratio of females to males in incidence.[5] Diabetes and obstructive uropathy both also predispose patients to develop abscesses.

Clinical manifestations. Overall, presentation of these conditions can be quite similar. Severity of illness on presentation has been linked to outcomes for these illnesses.[6] **The most common clinical manifestation is fever, which is present in approximately 55% to 85% and 80% of patients with abscesses and LN, respectively**.[6–9] Reported cohorts have demonstrated that fever in LN can be prolonged when compared to acute pyelonephritis.[10] Flank pain and nausea/emesis are present in approximately 45% to 75% and 10% to 30% of patients with abscesses, respectively, and 80% and 20% of those with LN.

Urinalysis may be negative in a significant number of patients with either perinephric or renal abscess as compared to LN.[5,10] Blood cultures may provide useful information in these patients, but mixed data on concordance between blood and urine cultures have been reported. Cultures are most often positive for organisms commonly found in other urinary tract infections, with *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis* and *Pseudomonas aeruginosa* being most common.[11,12] If left untreated, a renal abscess can follow a severe course, with an overall mortality rate reported at around 8%.[8]

Diagnosis. **The diagnosis of renal infection or abscess is confirmed with radiological findings and sometimes culture results in the presence of clinical signs.[1,2]** On computerized tomography, LN is characterized by an intraparenchymal mass, which is similar in density to normal tissue without any rim enhancement (fig. 1, ***A***). Contrast medium is often necessary to identify the lesion, as the differential diagnosis includes a renal mass. In comparison, renal abscess is characterized by a defined fluid collection (fig. 1, *B*). CT is the preferred diagnostic modality as it provides good visualization of tissue planes for treatment planning compared to ultrasound.

Alternatively, US can be used to confirm a diagnosis of LN. On ultrasound the condition often appears as a poorly defined sonolucent mass with decreased blood flow (fig. 2, *A*).[1] US for abscess will often demonstrate a low density lesion with or without loculations and purulent debris (fig. 2, *B*). **US is faster and more cost-effective than CT for diagnosis.**

Treatment. **LN: No guidelines on the management of LN currently exist.** The mainstay of treatment is medical management with antimicrobial therapy. **Several reported series have shown that antibiotic therapy alone is adequate for resolution of LN in an overwhelming majority of patients.** Atypical presentations of LN, as well as the prolonged course of illness, are possible causes for unnecessary invasive procedures such as needle biopsy, partial nephrectomy and diagnostic laparoscopy. In a series of 3 patients who underwent invasive procedures for LN, Siegel et al noted that none were evaluated by a urologist prior to undergoing an invasive procedure.[13]

Renal and Perinephric Abscess: The management of abscesses is often divided by size. **Smaller abscesses (less than 3 cm)**

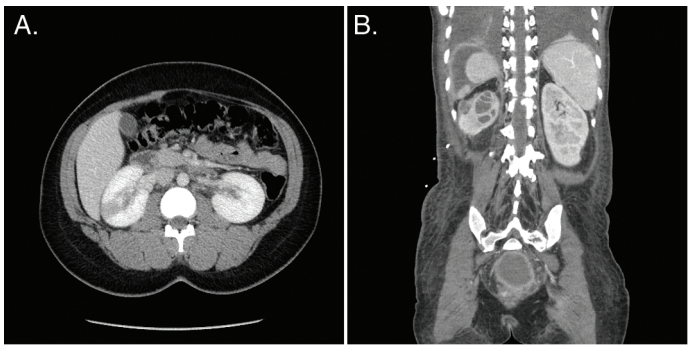

Figure 1. (A) On CT lobar nephronia in right kidney is characterized by intraparenchymal lesion similar in density to normal tissue that is poorly perfused on contrast enhanced imaging, with no rim enhancement. (B) Renal abscess in right kidney is characterized by defined fluid collection, often intraparenchymal.

ABBREVIATIONS: CT=computerized tomography, EC=emphysematous cystitis, EPN=emphysematous pyelonephritis, GUTB=genitourinary tuberculosis, LN=lobar nephronia, TB=tuberculosis, US=ultrasound, XGP=xanthogranulomatous pyelonephritis

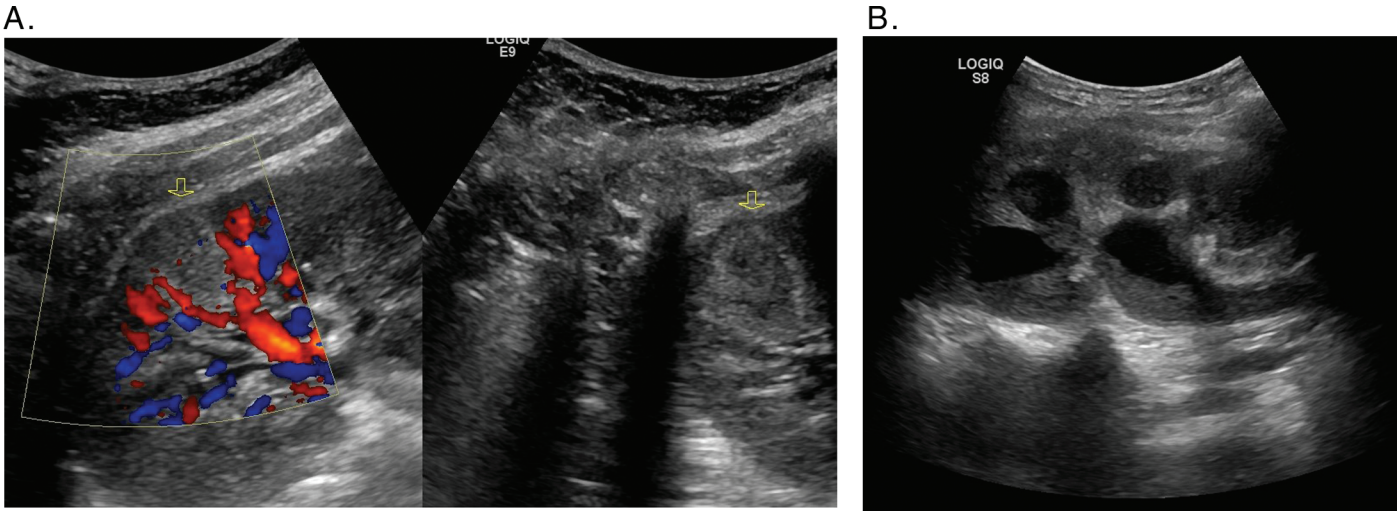

Figure 2. (A) On US lobar nephronia (arrows) appears as poorly defined, heterogeneous mass with decreased or no blood flow. (B) Intrarenal abscess can demonstrate purulent material within dilated calyces with loculated fluid.

are often managed conservatively. The literature suggests that antimicrobial therapy alone provides adequate treatment for the overwhelming majority of these abscesses. In a series of 49 patients with perinephric abscesses measuring up to 5 cm (19 cases with 3 to 5 cm abscesses), all were managed with antibiotics alone, with complete resolution of symptoms and lesions on imaging.[13] Other studies examining the use of percutaneous drainage for abscesses 3 to 5 cm have reported good outcomes. **While antimicrobials alone may be a viable option for abscesses greater than 3 cm, consideration should be given to percutaneous drain placement or surgical intervention.**

With regard to large abscesses (greater than 5 cm), intervention by way of percutaneous drainage, surgical drain placement or nephrectomy in addition to antimicrobial therapy is recommended. It is not uncommon for these patients to require multiple interventions before resolution of the illness, with more than one-third of patients requiring 2 or more percutaneous or surgical interventions.[13] When choosing between percutaneous vs surgical drainage, limited data suggest they are equal in efficacy.[6] Thus, surgeons may opt for the management they deem appropriate for each patient. Involvement of the interventional radiology department for percutaneous drainage may be a less invasive first step, with placement of a second drain or progression to surgical drainage for patients who fail to improve. These patients with complex infections also benefit from consultation with an infectious disease specialist to ensure optimal choice of agents that maximize tissue penetration while accounting for other comorbidities such as renal insufficiency. Nephrectomy should be reserved for patients with diffuse involvement or cortical damage, or those whose clinical condition requires immediate resolution of disease.

EMPHYSEMATOUS CYSTITIS AND PYELONEPHRITIS

Description, epidemiology and pathophysiology. The following conditions are acute and serious infections that result from the spread of gas-forming bacteria within the urinary tract. Emphysematous cystitis is characterized by a gas-forming infection within either the urothelial lumen or bladder wall.[14] Emphysematous pyelonephritis refers to gas-forming infection within the renal parenchyma, collecting system or perinephric space.[14,15] Infection is often the result of facultative anaerobes (organisms able to grow in both aerobic and anaerobic conditions), which include common uropathogens such as *E. coli*, *K. pneumoniae* and *Proteus mirabilis*, among others.

Overall, these conditions are rare in incidence. Reports have demonstrated that female gender and diabetes mellitus are risk factors for both conditions. With regard to EC, neurogenic bladder, chronic catheterization and chronic bladder outlet obstruction are additional risk factors.[15] EPN has a predilection to affect patients with recurrent pyelonephritis and those with recurrent, obstructive or chronically infected nephrolithiasis or urolithiasis.[1,14] Like EC, diabetes mellitus is a major risk factor for infection in EPN, and may be involved in up to 90% of reported cases.[15,16]

Clinical manifestations. **EC presents on a spectrum ranging from acute cystitis to septic shock**. The most common symptoms include dysuria, suprapubic tenderness and pneumaturia. However, in a review of 158 cases, the authors reported that up to 7% of patients were asymptomatic at presentation. The overall mortality for EC ranges up to 7%.[15,17]

EPN may present similarly to acute pyelonephritis. Pneumaturia will only be present in cases where infection involves the collecting system. The classic triad is fever, flank pain and vomiting, although presentation is variable (present in up to 80%, 70% and 20% of patients, respectively).[18] Historically, this condition has had an extremely high mortality rate, nearing 70% overall. However, more contemporary reports have demonstrated improved outcomes, with mortality rates approaching 20%. Several clinical factors, such as lowered systolic blood pressure (<90 mm Hg), altered level of consciousness, acute kidney injury, hyperglycemia and acid-base abnormalities, have been associated with increased mortality.[19]

Diagnosis. **Diagnosis of EC and EPN is confirmed with radiological findings in the presence of clinical signs.** Plain films, US or CT can diagnose both conditions. However, presence of gas in the bowel may result in difficulty diagnosing these conditions on plain film. The extent of gas invasion will ultimately guide therapy. Therefore, CT is the modality of choice for both detecting and planning treatment for these conditions.[1]

EC is characterized by gas within the bladder lumen or within the bladder wall itself. Cystoscopy has been utilized in case reports to confirm diagnosis or to examine for bladder wall necrosis.[15,17] With regard to emphysematous pyelonephritis, CT will demonstrate nephric or perinephric gas patterns (fig. 3). However, reports have described gas extending into the spermatic cord and scrotum.[20] Three main classification systems exist to describe CT findings. The first was created by Michaeli et al in 1984 based on findings on plain films and intravenous pyelograms.[21] Wan et al were the first to create a classification system based on CT findings, dividing findings into 2 classes.[22] Finally, the classification system described by Huang and Tseng divides EPN into 4 classes based on CT findings.[16] These 3 classifications are summarized in Appendix 1.

Treatment. **The available data have shown that the vast majority of EC cases can be managed conservatively with Foley catheter placement and antibiotic therapy.[15]** In diabetic patients, tight glycemic control is of high importance, and involvement of an endocrinologist may be necessary. Broad-spectrum therapy should be initiated until final cultures and sensitivities are available. In extreme cases of extensive bladder wall necrosis despite antibiotics, several case reports have described surgical intervention with debridement or cystectomy.[15]

The treatment of EPN may vary depending on the radiographic classifications. Cases with Huang class I or II infection had 100% survival when treated with a combination of tight glycemic control, intravenous antibiotic therapy, and percutaneous drainage or ureteral stent for patients with obstructive uropathy.[18]

Although there are extremely limited data on outcomes, patients with Huang class III and IV infections likely require radical nephrectomy. Huang and Tseng reported that class III infections had a failure rate of 39% despite percutaneous drainage, and class III and IV infections together had an overall mortality rate of 28%.[16] Elawdy et al reported that 2 of 6 patients and 2 of 2 patients required radical nephrectomy for resolution of Huang class IIIa and IIIb infections, respectively.[18] Thus, clinicians may have a lowered threshold to proceed with surgical management in cases of class III or IV infections.

Long-term management of these patients will likely be multifaceted. Since up to 90% of this population has diabetes mellitus, it is imperative to push for improved glucose control. Followup with an endocrinologist is recommended. For patients with obstructive uropathy, relieving stone burden and regular followup to monitor for formation of new stones may aid in preventing recurrence. It is important to note that no data exist regarding the recurrence of gas-forming infections.

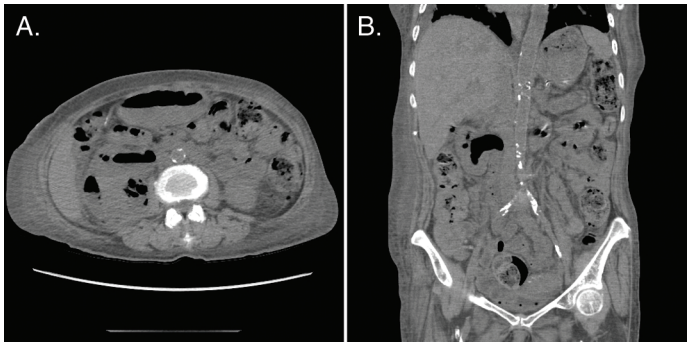

Figure 3. CT of right renal emphysematous pyelonephritis demonstrates gas within renal pelvis (A) and renal collecting system (B).

XANTHOGRANULOMATOUS PYELONEPHRITIS

Description, epidemiology and pathophysiology. First described by Schlagenhaufer a century ago, XGP is a suppurative infection of renal parenchyma. It is thought to be caused by chronic infection and obstruction. Histologically, it is characterized by invasion of renal parenchyma with lipid-laden macrophages.[1] Patients often have a history of recurrent infection and obstruction secondary to nephrolithiasis.[1,23]

With regard to age, XGP most often affects those in the fifth to seventh decade of life.[1,23–25] Women appear to be at a much higher propensity than men to suffer from XGP, with some reporting a 4:1 female-to-male ratio.[24–26] Those with staghorn calculi are at particularly high risk.[23,24] However, XGP remains quite rare, accounting for less than 1% of upper tract infections in patients who receive imaging as part of their workup.

Clinical manifestations. Unlike other infections of the upper urinary tract, a significant fraction of patients with XGP may not present with overt signs of upper tract infection. This is likely attributable to the fact that **XGP develops due to a recurrent cycle of infection and obstruction.** Patients will often have a history of obstructive uropathy, likely secondary to structural abnormalities (ie ureteropelvic junction obstruction or duplicated system), recurrent stones or infection, or persistent staghorn calculi, and/or evidence of a nonfunctional kidney.[1,23] The most common symptoms are persistent flank pain and fever. Physical examination may be significant for a palpable abdominal mass in close to 50% of patients.[23] Urinalysis for patients with XGP is indicative of infection in 40% to 60% of cases with common urinary tract pathogens, especially stone-forming bacteria, likely to be found on culture.[1,27,28]

Diagnosis. The diagnosis of XGP is suggested radiographically and confirmed with final pathology of surgical specimens. **CT is often characterized by diffuse disease with thinning of the renal cortex.** Loffroy et al reported that up to 90% of patients have concurrent nephrolithiasis and/or hydronephrosis, with a strong predilection for staghorn calculi.[27] **Additionally, structural abnormalities of the ureteropelvic junction, loss of renal parenchyma and poor excretion of contrast material are commonly seen**. The disease may also be found to invade the perinephric space or present with concurrent perinephric or retroperitoneal abscesses. In cases where the disease is focal and without concurrent stone disease, it may be difficult to differentiate from renal neoplasm. Clinical history along with discussion with an experienced radiologist is key. Ultrasound will often demonstrate an enlargement of the kidney and a large hypoechoic intraparenchymal mass.[27]

It is important to note that XGP is often not the suspected diagnosis at time of nephrectomy. While some literature has suggested that the diagnosis is accurately made in 85% to 90% of patients preoperatively, others have found this to be true in as few as 25% of cases.[23,24,29]

Treatment. **The management of XGP is nephrectomy, with the aim of removing all inflamed tissue from the abdomen.** Surgeons should be advised that this operation is not without tangible risk. The reported literature places overall perioperative complication rates between 20% and 45%.[23,24,28]

Routine management with surgically placed drains for isolated XGP is not advised, as limited data have demonstrated that up to 100% of patients managed with initial drain placement ultimately required nephrectomy.[27] However, for patients presenting with concurrent abscess, prompt treatment of the abscess (as discussed previously) should be undertaken prior to nephrectomy. In addition, many surgeons advocate a cooling off period with antibiotics and supportive care in clinically stable patients prior to nephrectomy.

With regard to approach, reported cohorts demonstrate that both laparoscopic nephrectomy and open nephrectomy are options for management of the disease. Limited data exist comparing the 2 approaches, although Guzzo et al reported on a cohort of 26 patients who underwent nephrectomy for XGP (laparoscopic in 14, open in 12).[28] They found that laparoscopy was associated with decreased mean hospital stay (11 vs 3 days), reduced blood loss (900 vs 300 cc) and decreased transfusion rate. In contrast, Vanderbrink et al. found no such differences between groups when comparing the 2 techniques for XGP.[24] Given that no strong evidence exists to guide this decision, surgeons should exercise caution with regard to proper patient selection for laparoscopic nephrectomy. Similarly, very limited data exist on the utility of partial nephrectomy in this context.

RARE INFECTIONS

Malakoplakia. **Description, epidemiology and pathophysiology:** Malakoplakia is a granulomatous disease of infective etiology that most commonly affects the genitourinary tract but has also been reported in the gastrointestinal tract, central nervous system, skin, lung, brain, lymph nodes and retroperitoneum.[26,30,31] There are only around 500 cases reported in the literature.[26] Malakoplakia involves the urinary tract in more than 75% of reported cases, most commonly the bladder, but also including the kidney and ureter.[32] Involvement of the testis, kidney and prostate has also been rarely reported.[33] Although often self-limiting and benign, the condition has a variable presentation and can mimic cancer, especially in the bladder, thus making it important for the urologist to recognize.

The word "malakoplakia" originates from the Greek word for soft plaques, describing its clinical presentation as yellow, soft, friable plaques.[34] Histologically, it is characterized by the presence of histiocytes called von Hansemann cells and calcified intracytoplasmic Michaelis-Gutmann bodies, which are remnants of partially digested bacteria. The pathogenesis is not well understood, but it is thought to be associated with an immunosuppressed state and chronic disease such as long-standing diabetes mellitus.[33] This is associated with reduced levels of cGMP, which impairs bacterial killing by macrophages. In more than 50% of cases, malakoplakia occurs in patients with autoimmune disorders, myelodysplastic syndromes or on immunosuppressive drugs such as after organ transplant.[35] Nearly 90% of patients have chronic urine infections with coliform bacteria such as *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *Staphylococcus aureus*.[36] In addition, bacterial infections in other parts of the body have been implicated in the pathogenesis of the condition.[35]

Clinical Manifestations: Malakoplakia in the bladder can be varied in presentation and may mimic inflammation or neoplasm, or even cause obstruction of the ureter. Inflammation of the bladder can present with dysuria, frequency/urgency or other irritative symptoms.[35] Accumulation of macrophages containing Michaelis-Gutmann bodies in the lamina propria of the bladder causes intraluminal protrusion that mimics bladder cancer and can lead to hematuria.[32] In addition, malakoplakia can coexist with malignancy.[35]

Renal malakoplakia may present with clinical signs of pyelonephritis, with flank pain, fever and leukocytosis. There may be a visible tumor-like renal mass that mimics a malignancy, or there could be a diffuse involvement that does not appear to be a mass on imaging. Other symptoms can include abdominal or low back pain with no laboratory test evidence of infection.[37]

Diagnosis: Clinical presentation and gross appearance are not adequate to ensure the diagnosis, and microscopic examination is required. Appendix 2 lists differential diagnosis of malakoplakia. **Tissue shows von Hansemann cells with Michaelis-Gutmann bodies that contain calcium and iron**. Additional histochemical stains for periodic acid-Schiff, alizarin red, von Kossa and variably for Prussian blue, as well as positive CD163 and CD68 immunomarkers, can confirm the diagnosis. Cystoscopy can be helpful for urinary malakoplakia in the bladder to distinguish from bladder carcinoma, and appropriate biopsy and diagnostic maneuvers should be performed. Imaging techniques are unable to distinguish malakoplakia from malignancy with precision.

Treatment: The mainstay of treatment is medical management with prolonged anti-inflammatories or antibiotics. Due to the rarity of the disease, there are no standardized guidelines. Courses of quinolones and trimethoprim-sulfamethoxazole are effective and have been shown to improve survival.[38,39] These agents are taken up and concentrate within macrophages, resulting in improved efficacy. The optimal duration is not defined, but once initial treatment is successful, low doses of suppressive antibiotic can be used for long-term prevention. Furthermore, reducing the dose of immunosuppressive medications whenever possible has been shown to prevent recurrence.[40] Other medications such as bethanechol and vitamin C have been postulated to reverse malakoplakia pathogenesis by augmenting the ratio of cGMP to cAMP and improving lysosomal phagocytosis.[41,42] Persistent lesions in the bladder can be treated with transurethral resection.

When malakoplakia presents as a mass in the upper tract that mimics cancer or causes diagnostic confusion, surgical biopsy and/or excision can both clarify diagnosis and achieve cure. Upper tract involvement with malakoplakia is often persistent and associated with significant morbidity, so surgical treatment is frequently warranted. Renal involvement that does not resolve with antibiotics is often treated with nephrectomy. Combination of antibiotics in discussion with infectious disease colleagues and consideration of surgery may offer improved outcomes.[43] Furthermore, malakoplakia in the bladder that causes functional obstruction of the urinary tract should be excised.

Tuberculosis. **Description, epidemiology and pathophysiology:** TB is prevalent worldwide, affecting approximately 30% of the world's population through infection with *Mycobacterium tuberculosis*.[44] Despite advances in medical treatment, the incidence of the disease is rising, felt to be due in part to emergence of resistant organisms as well as AIDS and immunosuppressive conditions. It also still poses a significant threat in developing countries.[1]

In 2011 the World Health Organization reported 8.7 million new cases of TB globally, with 9,951 new TB cases in the United States in 2012, amounting to an incidence of 3.2/100,000 population.[45,46] Incidence rates are highest in foreign born persons

in the United States and are increased in non-Hispanic Asians, Hispanics and non-Hispanic Blacks.

Most cases of TB are confined to the lungs, but 15% to 27% of cases involve extrapulmonary TB. Of the cases 30% to 40% involve the urogenital system, making genitourinary TB the second most common extrapulmonary TB infection after lymphadenopathy.[47,48] In addition, 2% to 20% of patients with pulmonary TB subsequently develop urogenital involvement.[49,50] While 15% of TB patients are coinfected with HIV, as many as 75% of patients with GUTB are coinfected with HIV, suggesting that patients with a new TB diagnosis should be screened for HIV.[51] GUTB typically affects adults between the second and fourth decades of life with a mean age of 40.7 years, likely related to the long latent period between the original pulmonary infection and the appearance of genitourinary symptoms.[52]

M. tuberculosis is an intracellular aerobe that is spread by inhalation and induces a cellular immune response in the host, which leads to characteristic caseating granulomas and the purified protein derivative skin reaction. The immune system can keep the infection under control for years in a latent state (ie no active TB disease), and reactivation can be caused by biological stress such as malnutrition, diabetes mellitus, steroid or immunosuppressant use, and immunodeficiency.[53] HIV infection is associated with significant immunosuppression and has a higher death rate than any other type of TB infections.[54] **Approximately 10% of persons with latent disease will progress to active infection in their lifetime, with HIV being the greatest identifiable risk factor.[55]**

Hematogenous spread can occur to the genitals (including epididymis and prostate) and most commonly to the kidneys with subsequent urinary descent to the ureters and bladder. Colonization of the renal parenchyma leads to cortical and glomerular renal lesions that lie dormant in immunocompetent hosts. Reactivation is usually marked by single kidney involvement.[56] Genital involvement can be initiated either by hematogenous spread to the prostate and epididymis (with spread to adjacent seminal vesicles, vas deferens, penis and even testicles despite the blood-testis barrier) or by urinary spread via the prostate (into the ejaculatory ducts, seminal vesicles and epididymis; fig. 4).[57,58] The prostate is involved in 40% to 50% of cases of GUTB.[59]

Clinical Manifestations: Clinical presentation can be varied and reflect the affected organ system and its function. **General symptoms of GUTB include flank pain, suprapubic pain and irritative voiding symptoms. The classic finding is sterile pyuria with a negative urine culture with or without hematuria.**

Renal TB can present with asymptomatic, slow renal destruction leading to papillary necrosis and infundibular stenosis, and ultimately loss of renal function. Ureteral TB presents with strictures (often multiple) and hydroureteronephrosis, most commonly in the distal ureter and ureterovesical junction. Bladder TB presents with symptoms of a fibrotic, contracted bladder with reduced bladder capacity and compliance, and distortion of the ureteral orifices and ureteral reflux on the unaffected (non-stenosed) side.[59] Genital TB, which is rare but sometimes associated with renal or pulmonary TB in males, can present with epididymitis and, less commonly, infertility.

Diagnosis: Urinary TB diagnosis is confirmed by 3 to 6 early morning urine samples for acid-fast staining and mycobacterial culture. Acid-fast staining is 97% specific, but the gold standard of culture requires multiple samples and at least 6 to 8 weeks to find a positive result.[59] Polymerase chain reaction for *M. tuberculosis* identification in the urine may offer a higher quality diagnostic tool due to its results within 24 to 48 hours and high sensitivity and specificity.[60]

Radiological imaging, particularly CT, can reveal findings suggestive of GUTB, including infundibular stenosis with calyceal dilatation, renal scarring or cavitation, ureteral stenosis or hydroureter, contracted or thickened bladder, and solid lesions in the kidney or bladder (fig. 5, *A*). **Specifically, CT urogram findings of pelvo-infundibular strictures, papillary necrosis, cortical low attenuation masses, scarring and calcification are diagnostic for GUTB (fig. 5, *B*).**[61] Renal ultrasound can reveal findings consistent with GUTB, such as renal collecting system ectasia, hydonephrosis, atrophy and calcification.[62] Epididymal TB can also be identified on ultrasound as a hypoechoic lesion with simultaneous testicular involvement in 40% of cases.[63]

Intradermal injection of tuberculin takes advantage of the late hypersensitivity-like local inflammatory reaction to form a positive induration 48 to 72 hours later, indicative of prior TB exposure. There are several caveats to the test, such as variable measurement of induration, presence of false-positives in patients who previously received the bacillus Calmette-Guérin vaccine and presence of false-negatives in patients with impaired T-cell function.[64]

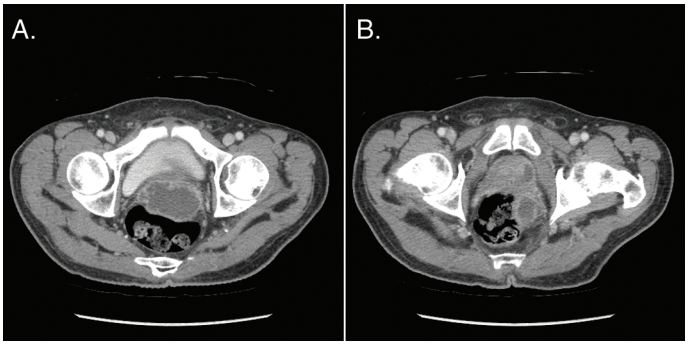

Figure 4. CT reveals genitourinary tuberculosis involving prostate (A) and left seminal vesicle (B). Normal tissues have been replaced with non-enhancing fluid density collections consistent with necrosis.

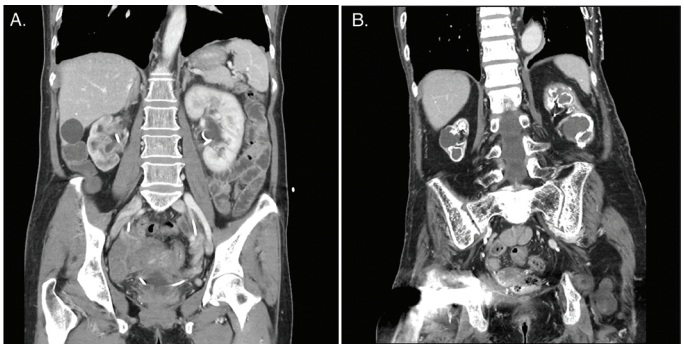

Figure 5. (A) CT of GUTB in right kidney shows infundibular stenosis with calyceal dilatation, renal scarring and cavitation, and solid lesions in parenchyma. (B) Over time, disease can progress to worsening infundibular strictures with papillary necrosis and significant scarring and calcification in both kidneys.

Treatment: Mainstay of treatment consists of early diagnosis and anti-TB medical therapy. **For patients with a history of pulmonary TB, annual urinalysis is recommended to assess for microscopic hematuria and pyuria.** The average latent period between pulmonary infection and symptomatic urogenital TB is 22 years, with reactivation most commonly occurring in one kidney and potentially descending to cause symptoms in the ureter and bladder.[59] Bacterial and bacteriostatic drugs are used, with recommended first line therapy being isoniazid, rifampin, pyrazinamide and ethambutol (Appendix 3). The 4-drug regimen has the lowest risk of relapse (up to 6.7%), and a move to shorter durations of 8 weeks is preferred due to high urinary concentration of the medications, lower toxicity, low bacillary load in the urine (no bacilli can be identified after 2 weeks of treatment) and comparable efficacy to longer duration regimens.[59]

More than half of patients with GUTB undergo surgical treatment, which can take the form of an ablative (removal of destroyed kidney), palliative (nephrostomy tube or stent placement for ureteral obstruction) or reconstructive (remove a stricture or augment a contracted bladder) procedure. The general consensus is to operate after at least 4 to 6 weeks of medical therapy. Nephrectomy should be considered for a poorly functioning kidney with or without hypertension or other complicating factors, to avoid relapse and/or abscess formation.[59]

Fungal infections. **Description, Epidemiology and Pathophysiology:** Urinary fungal infections may affect the entire length of the urinary tract. These infections may range from simple cystitis to intrarenal fungal balls or bezoars. Indwelling lines, uncontrolled diabetes, instrumentation, female gender and host immunosuppression are all contributing risk factors for developing fungal urinary tract infections.[65,66] Patients who have undergone renal transplant appear to be at particular risk for upper tract fungal infections, with up to 8% of positive urine cultures in renal transplant patients being fungal infections.[67] While the overwhelming majority of fungal infections are due to *Candida*, there are reports of cryptococcal infections in patients with HIV/AIDS.[68]

Clinical Manifestations: As with other urinary tract infections, differentiation between colonization and infection is key in management. This is especially the case in those with chronic indwelling devices. The feared sequela of funguria is progression to fungemia and sepsis. Historically, candidemia has been reported to have mortality rates over 50%. However, it is important to note that this is quite rare. The contemporary literature has reported progression from candiduria to candidemia at a rate of <3%.[66,69] This risk is increased in patients who suffer from concurrent obstructive uropathy.

The majority of patients with funguria are asymptomatic. Commonly, patients present with irritative voiding systems in cases of cystitis. Upper tract infection will result in typical symptoms of upper tract inflammation (fever, flank pain, nausea/vomiting).

Development of fungal bezoars has been reported to occur throughout the urinary tract. These are thought to be due to sloughing of renal papillae and necrosis. When viewed on imaging, this rare entity can be mistaken for more common conditions, such as urothelial carcinoma, low density calculus and blood clot.[70] Suspicion for fungal ball should be raised when pneumaturia or passage of sediment is present.[69] Accumulation of fungus and formation of bezoars are often difficult to eradicate.

Diagnosis: As with other urinary tract infections, urinalysis with culture should be the initial step in diagnosis. If the patient has a urinary catheter, replacement of the device should be considered. If subsequent tests are negative, no further workup is necessary.

In cases of positive culture, it is important to note that counts as low as 10^4 cfu/ml can be considered for treatment. When upper tract involvement is suspected, imaging may be acquired. Ultrasound is cost-effective and can be performed portably, which is especially valuable in cases of critically ill patients who cannot be transported. Lesions may appear similar to abscess or as hypoechoic lesions. CT demonstrates multiple small abscesses, or a conglomeration forming a large abscess. If a bezoar is present, it can be mistaken for urothelial carcinoma due to its appearance as a filling defect when located in the collecting system.[71]

Treatment: For the overwhelming majority of fungal infections, antifungal therapy is the mainstay of treatment. In those with indwelling devices, exchanging the device at the earliest time is recommended. For symptomatic funguria, fluconazole may be used, with treatment reserved for high risk or critically ill patients.[72] Meta-analysis of 9 studies (377 patients) demonstrated that continuous bladder irrigation with amphotericin B for at least 5 days was also an effective measure to eliminate funguria. However, it is important to note that bladder irrigation does not treat systemic infection.[73] Instillation of antifungal agents such as amphotericin B has also been shown to be an effective measure.

With regard to coordination of care, clinical judgment should be used to consider when it is appropriate to exchange lines. Urologists should be consulted for management, especially in cases of upper tract involvement or in those with concurrent obstructive uropathy. Several case reports have described surgical management of fungal balls and bezoars involving the kidney. Nephrectomy should be the mainstay of therapy in these patients.

DID YOU KNOW?

- Acute lobar nephronia and renal or perinephric abscesses <3 cm can be effectively managed with antimicrobial therapy alone.
- Treatment of emphysematous pyelonephritis includes antibiotics and percutaneous drainage and/or ureteral stent, and may require radical nephrectomy for severe cases.
- The vast majority of emphysematous cystitis can be managed conservatively with urethral catheter placement and antibiotic therapy.
- The management of xanthogranulomatous pyelonephritis is nephrectomy ± treatment of concurrent abscess.
- Although often self-limiting and benign, malakoplakia can mimic cancer, especially in the bladder, thus making it important to recognize.
- Genitourinary tuberculosis is the second most common extrapulmonary tubercular infection and is associated with HIV or an immunosuppressed state. The classic finding is sterile pyuria with a negative urine culture with or without hematuria. Treatment consists of multiple anti-tubercular drugs and sometimes surgery for involved tissues.

Appendix 1. Classification systems of emphysematous pyelonephritis

	Michaeli (kidney, ureter and bladder x-ray; intravenous pyelogram)	Wan (CT findings)	Huang (CT findings)
Class I	Gas in renal parenchyma or perinephric tissue	Renal necrosis with gas but no fluid	Gas contained to only the collecting system
Class II	Gas in kidney and surroundings	Parenchymal gas with within the parenchyma, perinephric space, or collecting system	Gas within the parenchyma, but without extension into the perinephric space
Class III	Extension through fascia or bilateral disease		A: Extension of gas or abscess in to the perinephric space B: Extension of either gas or abscess into the pararenal space
Class IV			Bilateral infection or solitary kidney

Appendix 2. Differential diagnosis of malakoplakia in the urinary system[35]

Xanthogranulomatous cystitis
Chemotherapy induced cystitis
Inflammatory
Urothelial carcinoma
Squamous cell carcinoma
Lymphoma
Langerhans cell histiocytosis

Appendix 3. Suggested TB treatment regimens

Preferred Regimen	**Alternative Regimen**
Initial Phase Daily isoniazid, rifampin, pyrazinamide, ethambutol for 8 wks	*Initial Phase* Daily isoniazid, rifampin, pyrazinamide, ethambutol for 2 wks, then twice weekly for 6 wks
Continuation Phase Daily isoniazid, rifampin for 18 wks	*Continuation Phase* Twice weekly isoniazid, rifampin for 18 wks

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Study Questions Volume 40 Lesson 12

1. The most common presenting symptom or sign in a patient with a renal abscess is
   a. nausea/vomiting
   b. flank pain
   c. fever
   d. positive urinalysis

2. Xanthogranulomatous pyelonephritis, an infection of the renal parenchyma, is thought to be caused primarily by
   a. acute urinary tract infection
   b. bloodborne bacterial infection
   c. chronic urinary tract infection and obstruction
   d. poorly controlled diabetes mellitus

3. A 79-year-old woman with dysuria, frequency and urgency has a cystoscopy for intermittent gross hematuria. She has had recurrent infections with pan-sensitive *E. coli* but her most recent urine culture is negative. The bladder is inflamed throughout. There is a lesion at the posterior bladder wall that is biopsied and shows inflammatory cells and Michaelis-Gutmann bodies in the lamina propria. Random bladder biopsies show inflammatory changes. The next step is
   a. observation
   b. suppression with trimethoprim-sulfamethoxazole
   c. transurethral resection of bladder tumor
   d. cystectomy

4. The best radiological study to evaluate and diagnose renal TB is
   a. renal ultrasound
   b. CT urogram
   c. intravenous pyelogram
   d. cystoscopy and retrograde pyelogram

5. The mainstay of treatment for a systemic fungal infection involving the kidney is
   a. oral or intravenous antifungal therapy
   b. immediate exchange of indwelling ureteral stents
   c. continuous percutaneous irrigation of the kidney with amphotericin B
   d. nephrectomy