Tuberculosis of the Genitourinary System

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Once considered a disease of the past, tuberculosis (TB), also known as “the great imitator,” remains one of the most deadly infectious diseases in the world today. Worldwide, 15 to 20 million people have TB of whom 8 to 10 million are infectious (Dirks, Remuzzi, Horton, Schieppati, & Rizvi, 2006). With one-third of the world’s population currently harboring latent mycobacterium tuberculosis infection, the World Health Organization (WHO, 2005) reports that the global epidemic is growing by 3% to 4% in Africa each year. TB accounts for 3 million deaths each year; the highest number of deaths related to an infectious disease (Centers for Disease Control and Prevention [CDC], 2005). Although, TB is most prevalent in developing countries, the incidence is highest in persons emigrating from Mexico or from Asian, Middle Eastern, and African countries (Soliman, Lessnau, & Hashmat, 2006). With international travel and the number of foreign-born persons living within the United States, the estimates are burgeoning near 15 million infected individuals in the United States alone (Gibson, Puckett, & Shelly, 2004).

Genitourinary TB is commonly a late manifestation of an earlier symptomatic or asymptomatic pulmonary TB infection (Pasternak & Rubin, 2001). A latency period ranging from 5 to 40 years between the time of the initial infection and the expression of genitourinary TB frequently occurs (Gibson et al., 2004). As one of the most common sites of involvement of extrapulmonary TB, genitourinary TB accounts for 15% to 20% of the infections outside of the lungs (Anwar & Azher, 2002). Overall, worldwide 20% to 73% of extrapulmonary TB is genitourinary and found in the urine of 15% to 20% of the individuals infected with TB (Soliman et al., 2006). While the development of effective interventions has decreased the incidence of pulmonary TB, the number of extrapulmonary cases has shown little change (CDC, 2005). In 1975, the CDC added extrapulmonary TB to their reportable data collection forms; up until that time, the reportable TB information was limited to the total number of TB cases (Leder & Low, 1979). Now with a rise in extrapulmonary cases, exploring the factors that account for this increase is a necessity to combat global TB (CDC, 2005).

For the health care professional, an awareness of atypical acute and chronic urologic disease should warrant the active inclusion of TB. Utilizing evidence-based decision making to identify the occult and insidious form of genitourinary TB may prevent the progressive destruction of the kidney (Peces, de la Torre, Alcázar, Tejada, & Gago, 1998). The question remains: For the health care professional, what clinical features of a client with a history of TB exposure, infection, or disease are most significant for suspecting genitourinary TB, and what diagnosis and best practices are used to prevent long-term sequelae? Evidence-based practice guidelines necessary to understand genitourinary TB and its treatment will be presented.

Causative Agent

In the United States, TB of the renal system is not unlike other forms of tuberculosis disease in that the most common causative agent is Mycobacterium tuberculosis, also referred to as the tubercle bacillus. The M. tuberculosis complex, comprised of closely related mycobacterial species (M. tuberculosis),
Predisposition to genitourinary TB disease is increased by medical conditions such as: vesicoureteral reflex, urinary obstruction, urinary calculi, diabetes mellitus, congenital anomalies of the urinary tract, analgesic abuse, gout, urinary diversion, neurogenic bladder, and kidney transplants. One of the greatest predisposing factors for genitourinary TB is a generalized compromised immune status, specifically HIV or AIDS (Kenney, 1990).

Pathology

Pulmonary TB is spread from person to person through the air by inhalation of the tubercle bacillus. In the genitourinary system, the tubercle bacillus lodges in the glomerular and peritubular capillary bed from hematogenous seeding of M. tuberculosis from the primary site of inhalation, the lungs (Gibson et al., 2004). Hematogenous seeding of both kidneys occurs, but clinically significant disease is usually limited to one side. Genitourinary TB is commonly reported as a disseminaton of the TB infection but the practitioner must also be aware that it may be a localized genitourinary disease (Eastwood, Corbischley, & Grange, 2001). Occasionally, lymphatic spread or secondary spread may occur from TB of the genitourinary tract or bone (Khan, Chandramohan, & MacDonald, 2004). The kidneys are the most commonly involved organ after the lung but the seminal vesicles, prostate, and testes although rare, may be primarily involved as well.

Initially a small tubercle forms in the glandular and cortical arterioles of the kidney (Khan et al., 2004). Cortical granulomas form in the renal cortex bilaterally, adjacent to the glomeruli. A high rate of perfusion and favorable oxygen tension increases the likelihood of bacilli proliferating within this location (Pasternak & Rubin, 2001). Three to six weeks later cell-mediated immunity may inhibit the M. tuberculosis by containing the bacterial duplication and arresting the disease in the kidney cortex (Springhouse, 2005).

The cortical granulomas may remain dormant, asymptomatic, and stable as a sequelae of a primary pulmonary infection from as long ago as 10 to 15 years (Khan et al., 2004). Renal tuberculosis may occur as a result of reactivation after this period of dormancy, even when there is no evidence of active pulmonary tuberculosis, or it may be due to reactivation from active tuberculosis (Ahmed & Murty, 2003). A study by Kenney (1990) concluded that only 30% of the clients presented with active TB along with an abnormal chest x-ray, while 10% showed signs of active pulmonary TB. Christensen (1974) reported that active pulmonary TB does not usually accompany renal TB: the majority of the clients diagnosed with renal TB did not exhibit any respiratory symptoms.

Factors known to increase the risk of infection reactivation include gastrectomy, uncontrolled diabetes mellitus, Hodgkin’s disease, leukemia, silicosis, acquired immunodeficiency syndrome, treatment with corticosteroids or immunosuppressants, and advanced age (CDC, 2005). However, many times it is unknown why the host defense mechanism breaks down and M. tuberculosis activates.

When the infection reacti- vates within the cortical granulomas, the body’s response leads to caseation; converting the necrotic tissue to cheese-like material. As the granulomas enlarge, coalescence occurs with capillary rupture releasing organisms which spread to the medulla, causing papillitis that extends into the proximal loop of Henle (Khan et al., 2004). Eventually, the granulomas enlarge and undergo caseation and papillary necrosis develops (Pasternak & Rubin, 2001). As in the primary site, granuloma formation, caseous necrosis, and cavitation within the renal parenchyma are the hallmark stages of progressive infection. The host’s response induces fibrotic parenchyma which may lead to renal pelvic traction, calcium deposition with stone formation within the urinary collection system, and stricture formation contributing to obstruction and progressive renal dysfunction. The end-stage result of diffuse disease is destruction, loss of function, fibrosis, and calcification in a lobular distribution of the entire kidney producing autonephrectomy (Engin, Acunas, Acunas, & Tunaci, 2000). If granulomas spread to the collection system, regional spread by either ascension or descension of the bacilli to the renal pelvis, ureters, urinary bladder, and accessory genital organs is possible.

Diagnosis

Many modern day texts on nephrology do not discuss genitourinary TB as a serious cause of urological infections and advanced renal disease. Classic TB symptoms are rarely observed in these clients, compounding the difficulty of a diagnosis. Many times treatment of renal TB is delayed due to the vagueness of chronic, intermittent, and nonspecific urinary symptoms (Bennani, Hafiani, Debbagh, el Mrini, & Benjelloun, 1995). Clinicians must also be aware that the course of renal involvement may be indolent yet insidious which is not indicative of the severity of the stage of the TB disease and further complicates a correct diagnosis (Eastwood et al., 2001).

It is imperative for clinicians to complete a comprehensive client history and physical with questioning inclusive of country
of birth, residency (especially if the client has resided or is currently residing in areas where TB is endemic), international travel, history of Bacille Calmette-Guérin vaccination, a history of a TB exposure, infection or disease, TB skin test results and anergic TB test result, history of renal transplantation or renal dialysis, corticosteroid use, and a history of recurrent urinary tract infections that are non-responsive to common antibiotics.

Male clients may present with tender testicular swelling, beading of the spermatic cord, epididymitis, cystitis, epididymorchitis, scrotal wall thickening, tunica albuginea, and a moderate hydrocele (Soliman et al., 2006). Females may present with bladder pain, dysuria, back pain, infertility, and menstrual irregularities. Pregnancy is rare in the presence of genital TB and may be complicated by ectopic pregnancy and spontaneous abortion (Khan et al., 2004). A history of recurrent Escherichia coli infection should also serve as a warning sign.

**Laboratory Findings**

Samples of fluid or tissue must be obtained from the suspected site of infection and acid-fast bacillus (AFB) smears, nucleic acid amplification (if necessary), and culture should be performed for positive diagnosis of TB (Potter, Rindfleisch, & Kraus, 2005). Three to five first morning urines should be collected for urinalysis, acid-fast staining, and mycobacterial cultures. First morning specimens are preferred over 24-hour specimens because mycobacterial viability decreases with prolonged exposure to acid urine (Pasternak & Rubin, 2001). At least three serial urine cultures are considered the standard for evidence of active disease.

Laboratory abnormalities commonly found on routine urinalysis are pyuria, proteinuria, and hematuria (Gibson et al., 2000). Simon, Weinstein, Pasternak, Swartz, and Kunz (1977) isolated *M. tuberculosis* from the urine culture in 80% to 90% of clients with genitourinary TB. The polymerase chain reaction is a relatively new technique useful for amplifying extremely small amounts of specific genomic sequence rapidly. For detecting urinary TB, an extremely small amount of bacteria can be detected within 24 to 48 hours (Arisan, Sönmez, Cakir & Ergenekon, 2003). This is a promising new tool for rapid detection of urinary tract tuberculosis in urine samples.

**Radiographic Tests and Findings**

Kenney (1990) reported that multiple radiographic imaging findings can be attributed to genitourinary TB. Renal calcifications, a common manifestation of TB, may be amorphous, granular, or curvilinear, typically within the renal parenchyma (Engin et al., 2000; Harisinghani et al., 2000). Focal globular calcification may be associated with a granulomatous mass involving an entire renal lobe. End-stage TB is characterized by extensive parenchymal calcification in a nonfunctioning, autonephrectomized kidney (also known as a putty kidney) (Engin et al., 2000). Within the collecting system characteristic triangular ring-like calcifications are associated with papillary necrosis (Davidsson, Hartman, Choyke, & Wagner, 1999). Extrapulmonary findings of *M. tuberculosis* disease on conventional radiographs may manifest as mesenteric lymph node and adrenal calcifications, in addition to spinal abnormalities (Gibson et al., 2000).

Intravenous urography is beneficial for identifying the extensiveness and severity of genitourinary TB manifestations (Gibson et al., 2004). One of the earliest urographic abnormalities is a “moth-eaten” calyx due to necrotizing papillitis which can progress to medullary cavi-

ties that dilate and eventually communicate with the collection system (Kollins, Hartman, Carr, Segura, & Hattery, 1974). The progression of papillary cavitation spreads the infection to the urothelium and submucosa of the draining calyx which may be demonstrated by irregular pools of contrast on urographic findings (Harisinghani et al., 2000). Stenosis and strictures of the caliceal infundibula develops from a fibrotic reaction which can lead to localized caliciatosis or incomplete opacification of the calyx (Pasternak & Rubin 2001). Persistent infection can cause scarring resulting in a sharp angulation of the renal pelvis (Leder & Low, 1995). The ureters become involved due to the passage of infected urine manifesting in dilatation and mucosal irregularity which can progress with advanced disease to the formation of strictures and ureteral shortening (Engin et al., 2000). In tuberculous cystitis, the bladder may become diminutive and irregular with diminished bladder capacity (Harisinghani et al., 2000). A small contracted bladder is suggestive of extensive disease (Soliman et al., 2006).

Clients may present with a generalized hydrenephrosis and computed tomography (CT) is beneficial to identify the patterns of hydrenephrosis (Roylance, Penry, Davies, & Roberts, 1970). Parenchymal scarring and lesions as well as extension of genitourinary TB disease into the extrarenal space are other findings that can be identified with CT (Harisinghani et al., 2000).

Buchholz, Salahuddin, & Haque (2000) reported that ultrasound was very beneficial in the diagnosis of testicular TB. According to Kenney (1990), the key to proper diagnosis is the presence of multiple radiographic abnormalities such as calcifications and strictures which are rather characteristic and strongly suggest genitourinary TB.
Signs and Symptoms

Gokce et al. (2002) reviewed 174 cases of genitourinary TB diagnosed in a clinic, identifying the most common findings as flank pain, dysuria (nonspecific vesical symptoms), hematuria (microscopic or macroscopic), urinary frequency, nocturia, malaïses/fatigue, stomach pain, urgency and incontinence, night sweats, scrotal mass, abdominal mass, leakage of urine, and cough with or without bloody sputum. Gibson et al. (2004) reported that constitutional symptoms of weight loss, fatigue, and anorexia were less common.

The most common physical findings include tenderness over the costovertebral angle, and a low-grade fever. Less-common physical findings are a palpable kidney, hypertension, tenderness in the suprapubic region, a thickened epididymis, urethral stricture, scrotal fistula, and vesicovaginal fistula. While it is important to understand that local urinary symptoms may be predominant, the client may be completely asymptomatic until large granulomas have formed within the kidney.

Renal Transplantation

The incidence of infection with *M. tuberculosis* is estimated to occur in 0.5% to 1.3% of clients that have undergone renal transplant recipients in North America (Dowdy et al., 2001). While *M. tuberculosis* infection is rare in renal transplant recipients, the presentation is atypical. The diagnosis can be inherently delayed but is frequently associated with graft rejection and should be considered with unexplained fever and systemic symptoms (Dowdy et al., 2001).

Treatment

The decision for treatment should be based on the client's history and clinical findings. Health care providers may choose not to wait for pending laboratory results before beginning treatment (Potter et al., 2005). As a general rule, evidenced-based regimens that are adequate for treating pulmonary TB are also effective for treating extrapulmonary disease (CDC, 2005). When active TB is suspected, a four-drug regimen is recommended provided the client does not have a drug-resistant TB. Initially, a combination chemotherapy is employed using first-line and second-line antitubercular drugs. A continuation chemotherapy phase will follow for 6 to 12 months depending upon client response. Four recommended regimens are presented in Table 1, along with the level of evidence. The clinician must be aware that the duration of the therapy depends on the drugs used, the drug susceptibility (culture and sensitivity of the tissue or body fluid) results, and above all the patient’s response to treatment (CDC, 2005). In a client whose cultures have not become negative or whose symptoms do not resolve, despite 3 months of chemotherapy, the clinician should suspect drug-resistant disease or failure of the client to adhere to the medical regimen. Over the past several years, antibiotic resistant strains of *M. tuberculosis* are emerging which may require an intensive or longer duration of the antibiotic regimen.

The clinician must be aware that early diagnosis and appropriate drug therapy could lead to cure, and salvage of the kidney (Khan et al., 2004). Continued radiologic monitoring is extremely important because strictures can develop or worsen, and a stent should be placed if this is detected (Kenney, 1990).

Follow-Up

Clients should be seen at 3, 6, and 12 months after completion of chemotherapy for follow-up urinalysis and urine cultures for AFB. Clients can be discharged following a year of disease-free follow-up. However, the status of calcyceal deformities and renal calcifications should be followed with kidney, ureter, and bladder KUB x-rays and intravenous urography.

Surgical Interventions

Surgical interventions are not uncommon as part of the first-line treatment plan for genitourinary TB. In cases of sepsis or perinephric abscesses, nonfunctioning renal tissue, ureteral strictures, and severely restricted contracted bladders related to genitourinary TB, surgery is necessary. In developing countries, clients often present with advanced disease and complete destruction of a renal unit necessitates immediate surgical intervention. Management of a severely diseased TB kidney or nonfunctioning kidney with secondary hypertension due to *M. tuberculosis* indisputably requires a nephrectomy. One advantage of a nephrectomy is that it facilitates the removal of a large amount of the *M. tuberculosis*, facilitating the effectiveness of anti-tubercular drugs to attack the residual mycobacteria (Nagraj, Kishore, & Nagalakshmi, 2006).

Conclusion

Many challenges exist before TB can be controlled successfully in the United States. With 11% of the population made up of foreign-born persons residing in the United States permanently or temporarily, the incidence of TB in this population is now comparable to the U.S. born citizen (CDC, 2005). Five challenging areas in the United States for progressing towards controlling TB are:

- The prevalence of TB among foreign-born persons residing in the United States.
- Delays in detecting and reporting cases of pulmonary TB.
- Deficiencies in protecting contacts of persons with infectious cases of TB and in preventing and responding to TB outbreaks.
Table 1. Regimen Options for Treatment of TB

<table>
<thead>
<tr>
<th>Regimen 1 (Initial Phase)</th>
<th>Drugs: Isoniazid (INH); Rifampin (RIF); Pyrazinamide (PZA); Ethambutol (EMB)</th>
<th>Interval and doses(^1) (minimal duration): Seven days per week (wk) for 56 doses (8 wk) or 5 days/week (d/wk) for 40 doses (8 wk)(^3)</th>
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</thead>
<tbody>
<tr>
<td>Regimen 1a (Continuation Phase)</td>
<td>Drugs: INH/RIF</td>
<td>Interval and doses(^1) (minimal duration): Seven days per week for 126 doses (18 wk) or d/wk for 90 doses (18 wk)(^3) Ranges of total doses (minimal duration): 182-130 (26 wk)</td>
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<tr>
<td>Rating (evidence): HIV-: A (I); HIV+: A (II)</td>
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<tr>
<td>Regimen 1b (Continuation Phase)</td>
<td>Drugs: INH/RIF</td>
<td>Interval and doses(^1) (minimal duration): Twice weekly for 36 doses (18 wk)</td>
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<tr>
<td>Ranges of total doses (minimal duration): 92-76 (26 wk)</td>
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<tr>
<td>Rating (evidence): HIV-: A (I); HIV+: A (II)</td>
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<tr>
<td>Regimen 1c ** (Continuation Phase)</td>
<td>Drugs: INH/RPT</td>
<td>Interval and doses(^1) (minimal duration): Once weekly for 18 doses (18 wk)</td>
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<tr>
<td>Ranges of total doses (minimal duration): 74-58 (26 wk)</td>
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<tr>
<td>Rating (evidence): HIV-: B (I); HIV+: E (I)</td>
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<tr>
<td>Regimen 2 (Initial Phase)</td>
<td>Drugs: INH, RIF, PZA, EMB</td>
<td>Interval and doses(^1) (minimal duration): Seven days per week for 14 doses (2 wk), then twice weekly for 12 doses (6 wk) or 5 d/wk for 10 doses (2 wk)(^3); then twice weekly for 12 doses (6 wk)</td>
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<tr>
<td>Regimen 2a (Continuation Phase)</td>
<td>Drugs: INH/RIF</td>
<td>Interval and doses(^1) (minimal duration): Twice weekly for 36 doses (18 wk)</td>
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<tr>
<td>Ranges of total doses (minimal duration): 62-58 (26 wk)</td>
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<tr>
<td>Rating (evidence): HIV-: A (II); HIV+: B (II)(^4)</td>
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<tr>
<td>Regimen 2b** (Continuation Phase)</td>
<td>Drugs: INH/RPT</td>
<td>Interval and doses(^1) (minimal duration): Once weekly for 18 doses (18 wk)</td>
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<tr>
<td>Ranges of total doses (minimal duration): 44-40 (26 wk)</td>
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<tr>
<td>Rating (evidence): HIV-: B (I); HIV+: E (I)</td>
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<tr>
<td>Regimen 3 (Initial Phase)</td>
<td>Drugs: INH, RIF, PZA, EMB</td>
<td>Interval and doses(^1) (minimal duration): Three times weekly for 24 doses (8 wk)</td>
</tr>
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</table>

1 When direct observation of therapy (DOT) is used, drugs may be given 5 days/week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice.

2 Patients with cavitation on initial radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31 week; either 217 doses [daily] or 62 doses [twice weekly]) continuation phase.

3 Five-day-a-week administration is always given by DOT. Rating for 5 day/week regimens is Alll.

4 Not recommended for HIV-infected patients with CD4+ cell counts <100 cells/microliter

** Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on initial radiograph (see text). For patients started on this regimen and found to have a positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

Definitions of evidence ratings: A = preferred treatment; B = acceptable alternatives; C = offer when A and B cannot be given; E = should never be given; I = randomized controlled trial; II = data from clinical trials that were not randomized or were conducted in other populations; III = expert opinion.
• Presence of a substantial population of persons living in the United States with latent TB infection who are at risk for progression to TB disease.

In controlling genitourinary TB, the clinician must be cognizant of unusual or vague renal system findings. One negative result should never exclude a TB diagnosis (Cahill, Dhanji, Williams, Smith, & Montgomery, 2001). Genitourinary TB should be suspected in clinical situations of atypical and chronic urologic disorders (Tanagho, 1992). When the infection is caused by an antibiotic-susceptible strain of the M. tuberculosis organism, the chances improve for a better prognosis. Four recommended regimens adapted from the American Thoracic Society, CDC, and the Infectious Diseases Society of America (2003) are presented in Table 1. However, major consideration must be given to a treatment regimen that fosters client adherence. Public health departments should be assigned primary responsibility for managing specific clients and monitoring adherence to therapy as well as educating them regarding TB.

In closing, the health care clinician may benefit from the urologic expertise of Chang’s (1976) words of advice, “The kidney is an articulate organ; its vocal cords are the bladder,” which appropriately reflects valuable insight of fundamental urology. For the clinician, the bladder may be sending a clue, “Think TB” (WHO, 2002).

**References**


