

Diagnosis and Management of Epididymitis

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A variety of inflammatory conditions target the epididymis, including bacterial, viral, and fungal infections as well as idiopathic inflammation. Acute epididymitis is characterized by inflammation of the epididymis presenting as pain and swelling, generally occurring on one side and developing over several days. Multiple objective findings of epididymitis have been identified and, in variable degrees, may include positive urine cultures, fever, erythema of the scrotal skin, leukocytosis, urethritis, hydrocele, and involvement of the adjacent testis.

The true prevalence of epididymitis is unknown. Although epididymitis has been reported at any time from infancy up to 90 years of age, it is the fifth most common urologic diagnosis in men between the ages of 18 and 50 [1], with a mean patient age at presentation of 41 years [2]. The majority of patients are 20 to 39 years old (43%), followed by those 40 to 59 years old (29%) [2]. Of men presenting to Canadian outpatient urologists, 1% are diagnosed with epididymitis, with 80% of these patients having chronic epididymitis (>3 months) [3]. Although the financial impact of epididymitis on the health system is unknown, the morbidity of epididymitis is significant, with epididymitis accounting for a greater loss of man-hours in the United States military than any other urologic diagnosis [4].

The pathophysiology of acute epididymitis remains unclear, although it is postulated to occur

secondary to retrograde flow of infected urine into the ejaculatory duct. This hypothesis is strengthened by the finding that 56% of men older than 60 with epididymitis exhibit lower urinary tract obstruction, including benign prostatic hyperplasia, prostate cancer, and urethral stricture at the time of diagnosis [5]. In addition, multiple animal models have shown that injection of *Escherichia coli* or *Chlamydia trachomatis* into the vas deferens results in epididymitis that mimics clinical and microbiological findings of human epididymitis [6–8]. Control populations in these animal trials failed to develop epididymitis with injection of transport medium, though no studies have attempted injection of sterile urine into the vas deferens.

Infectious epididymitis

Evidence supporting retrograde inoculation of the epididymis from infected urine is supported by the increased risk of epididymitis following instrumentation of the urethra or bladder. In particular, patients who have infected urine during instrumentation are at highest risk for infectious epididymitis. Patients with complicated urinary tract infections, such as those requiring clean intermittent catheterization, account for 50% of all patients with infectious epididymitis [2,8,9]. Up to 80% of all cases of epididymitis may be bacterial in origin [10–13], though large epidemiologic studies have identified a clear bacterial etiology in fewer than 25% of subjects with clinical signs of epididymitis [2,9]. Transmission of *C trachomatis* is felt to be responsible for infectious epididymitis in patients 35 years old or younger, though the majority of men in this age range with epididymitis (up to 90%) have no objective

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laboratory evidence of *C trachomatis* on urethral swab polymerase chain reaction [10,14–16]. In patients older than 35, coliform bacteria are the most common pathogens isolated in infectious epididymitis, with *E coli* accounting for the majority of cases. Other reports have sporadically implicated other bacteria that may be found in epididymitis, including *Ureaplasma urealyticum*, *Corynebacterium sp*, *Mycoplasma sp*, and *Mima polymorph* [17].

Clinical epididymitis in children identified through ultrasonography or surgical exploration has often been attributed to viral infections. A prospective study by Somekh and colleagues [18], using viral cultures of throat, urine, and stool specimens and serologic tests for common viruses, revealed significantly elevated titers to certain pathogens in patients with epididymitis compared with controls, including *M pneumoniae* (53% versus 20%), enteroviruses (62.5% versus 10%), and adenoviruses (20% versus 0%). Mumps infection, which was a frequent cause of viral epididymo-orchitis in the past, has been virtually eliminated since the introduction of mumps vaccine in the United States in 1985. Because the majority of pediatric epididymitis is thought to be due to a viral etiology, management of nonbacterial epididymitis in children, defined by absence of pyuria, is often treated conservatively with ice and analgesics [19], which is in stark contrast to treatment of the adult population [2].

Chronic infectious epididymitis is most frequently seen in conditions associated with granulomatous reaction [20], with *Mycobacterium tuberculosis* (TB) being the most common granulomatous disease affecting the epididymis. Although renal involvement is often seen with epididymal TB, seeding of the epididymis is thought to occur from hematogenous spread of *M tuberculosis* rather than seeding of the urinary system via the kidneys [21]. Up to 25% of patients may have bilateral disease, with ultrasound demonstrating an enlarged hyperemic epididymis with multiple cysts and calcifications. Tuberculous epididymitis should be suspected in all patients with a known history of or recent exposure to TB, or in patients whose clinical status worsens despite appropriate antibiotic treatment. In addition, urologists must be cognizant of epididymo-orchitis related to Bacille Calmette-Guérin, which may occur following treatment of superficial bladder cancer [22].

Genito-urinary TB is often difficult to diagnose as organisms are identified in the urine in less than

half of the cases [23] and tuberculin skin testing is not specific for epididymal involvement. When present, cultures of a draining scrotal sinus may be used to identify epididymal TB. If a patient without a history of TB is confirmed to have tuberculous epididymitis, he should undergo the appropriate evaluation for systemic TB, including chest X ray, renal function tests, and CT or excretory urography if indicated.

Brucella is a gram-negative facultative coccobacillus that causes epididymitis in up to 10% of patients with brucellosis [24]. Infection with *Brucella* typically occurs from direct contact with infected animals or ingestion of their nonpasteurized milk, and primarily occurs in endemic areas [25]. In the United States brucellosis occurs primarily in California and Texas owing to their proximity to the Mexican border [25]. Patients with *Brucella* epididymitis are clinically similar to those with other causes of infectious epididymitis, although they are more likely to have complex septated hydroceles on ultrasound examination [26]. The diagnosis of brucellosis can be confirmed based on patient history and serologic testing that demonstrates a single titer of above 1:160 or a greater than fourfold increase in agglutinating antibodies during a 4- to 12-week period.

Although rare in the United States, funiculoe-epididymitis may occur from filarial invasion of the lymphatic system, leading to scarring and formation of cord masses, large hydroceles, and lymphedema [27]. More than 90% of human lymphatic filariasis are caused by *Wucheria bancrofti*, with *Brugia timori* and *B malayi* accounting for the remainder of cases. Infection typically centers in the epididymis and lower spermatic cord, and then spreads centrifugally. Death of the microfilaria leads to development of fever, localized lymphangitis, edema, and hydrocele. In addition, patients may present with chyluria owing to lymphatic obstruction. Ultrasound typically reveals enlarged lymphatic channels, and real-time imaging may demonstrate random movements of viable microfilaria (“dance sign”). Definitive diagnosis relies on identification of filaria on peripheral blood smear.

Noninfectious epididymitis

Although it is recognized that a large number of patients with epididymal inflammation have no evidence of genitourinary infection, little direct

evidence is available regarding the mechanism of noninfectious epididymitis. One proposed mechanism is the retrograde reflux of sterile urine into the vas deferens from contraction of a full bladder against a closed external urethral sphincter. However, multiple reviews attempting to confirm this concept have identified fewer than 10% of patients with a documented history of straining to void [2,9,10]. Although the reflux of sterile urine into the vas deferens may occur when men with nonobstructed bladder outlets or urethras strain to void, little evidence is available to support this mechanism as having a primary role in noninfectious epididymitis. In addition, the present authors' own experience reveals that men who have undergone vasectomy can present years later with noninfectious clinical testis or epididymal swelling and pain, possibly arguing against retrograde inoculation of the epididymis as the sole contributor to epididymitis. Postvasectomy epididymal enlargement or pain has been attributed to congestion and inflammation owing to obstruction or sperm granuloma formation, which causes local reaction surrounding nerves and vasculature [28].

Sarcoidosis, a noninfectious, noncaseating, chronic granulomatous disease that is more common in black patients, affects the genitourinary system in up to 5% of cases [20,29]. Genitourinary manifestations include nephrocalcinosis; uremia; and granulomas of the epididymis, testis, and vas deferens, as well as cutaneous genital lesions. The typical presentation involves progressive enlargement of the epididymis in patients with a known history of sarcoidosis, occurring bilaterally in up to 30% of patients [29]. Ultrasound findings are variable, but often reveal an enlarged heterogeneous epididymis that may contain distinct nodules [30–32]. Treatment with corticosteroids relieves pain and swelling in the majority of cases and should be used before consideration of scrotal exploration. In the rare patient requiring exploration, frozen sectioning should be performed to prevent needless epididymectomy or orchietomy [29]. In addition, patients should be counseled preoperatively on the risks of testicular damage with epididymal exploration.

Sarcoid involvement of the epididymis can lead to azoospermia owing to extrinsic compression of epididymal ducts, so semen analysis should be obtained at disease diagnosis in all patients interested in paternity and those undergoing scrotal exploration [33]. If oligospermia is noted, the patient should be offered the use of sperm banking for possible future assisted reproductive

techniques. Steroid therapy may assist with transient restoration of genital tract patency and use; serial semen analysis may be useful for detecting rare sperm that may be banked in patients with azoospermia [34].

Several cases of noninfectious epididymitis have been linked to Behçet's disease—an idiopathic, multiorgan vasculitic disease displaying a large number of signs and symptoms, including recurrent aphthous ulcers, genital ulcers, uveitis, and epididymitis. Genital ulcers, which are tender to touch, are most common on the scrotum, although they may occur on the prepuce, glans, or penile shaft. To date, there have been no reports of patients with Behçet's presenting with objective evidence of urethritis or infection on urinalysis, urethral swab, or urine culture. Patients with epididymal involvement are more likely to have genital ulcers, cutaneous involvement, and arthritis than those without epididymal involvement [35]. Medical therapy for Behçet's disease is limited, with treatment primarily revolving around symptomatic relief and empiric treatment with topical or systemic corticosteroids.

Epididymitis can also be caused by medications, most notably the anti-arrhythmic amiodarone HCl [36]. High levels of this drug are achieved in the epididymis relative to serum (300 ×), leading to development of anti-amiodarone HCl antibodies that then attack the epididymis lining, resulting in pain and swelling. The incidence of epididymitis appears to be dose related, with clinical epididymitis developing in up to 11% of patients on high-dose amiodarone HCl [37]. Temporary discontinuation of the drug or a decrease in dosage is recommended for treatment of noninfectious epididymitis in patients on amiodarone therapy.

In children, Henoch-Schönlein Purpura, a small vessel vasculitis characterized by immunoglobulin A complex deposition, may also present with acute scrotum and vasculitic epididymitis. The disease typically occurs in children between 2 and 11 years old, presenting with palpable purpura, abdominal pain, hematuria, and joint pain. Scrotal swelling occurs in 2% to 38% of patients [38]. Ultrasound findings demonstrate findings consistent with epididymal inflammation, including epididymal enlargement, increased Doppler flow, scrotal skin thickening, and hydrocele. The disease is self-limiting and generally responsive to corticosteroid treatment. Once testicular torsion has been ruled out, awareness of the association of Henoch-Schönlein Purpura and scrotal pain should limit unnecessary surgical intervention in this population.

Chronic epididymitis

Chronic epididymitis, characterized by pain of at least 3 months in duration in the scrotum, testicle, or epididymis and localized to one or both epididymides on clinical examination, may account for up to 80% of patients presenting to the urology clinic with scrotal pain [3]. The average age at diagnosis of chronic epididymitis is 49 years, with the average patient having symptoms present for 5 years at the time of diagnosis [39]. Pain tends to be mild to moderate and typically does not affect daily activity, though chronic epididymal pain has a significant effect on quality of life, with 84% of patients describing quality of life as unsatisfying or terrible. Affected patients tend to have an increased number of sexual partners and a higher incidence of erectile dysfunction, musculoskeletal complaints, and neurologic disease compared with normal controls. Evaluation of patients with chronic epididymal pain should include assessment for chronic prostatitis and male pelvic pain syndrome, including prostatic fluid examination and careful evaluation for occult voiding dysfunction; however, patients with chronic epididymitis frequently have no history of documented infection or inciting event.

Diagnostic considerations

Although most diseases of the epididymis are benign, a thorough history and physical exam should always be performed to differentiate amongst epididymal pathology [17]. Patients presenting with a clinical diagnosis of epididymitis should undergo testing for the appropriate bacteria according to the Centers for Disease Control (CDC) guidelines (Box 1) [40]. Children and adolescents who are not sexually active should have urine obtained from a midstream urine collection, as should adults over the age of 35. Urine should be examined by urinary dipstick as well as microscopy. Patients with a positive dipstick or microscopy should have urine sent for definitive culture. In addition, patients with risk factors for complicated urinary tract infections such as those with recent urinary tract instrumentation, indwelling ureteral stents, or recent anal intercourse should also undergo urine culture for coliform bacteria. (Owing to increasing rates of antibiotic resistance, antibiotic sensitivities are routinely obtained at the authors' institution.)

Sexually active patients younger than 35 years old, as well as those over 35 with a new sexual

Box 1. Centers for Disease Control's 2006 guidelines for the diagnosis and management of epididymitis

Younger than 35

- Gram stain of urethral exudate for urethritis (>5 white blood cells/high power field) *or* leukocyte esterase test *or* microscopic examination of first-void urine sediment demonstrating at or above 10 WBC/hpf
- Culture or nucleic acid amplification test of urethral swab (or urine)
- Empiric antibiotics to cover *N gonorrhoeae* and *C trachomatis*
 - *Ceftriaxone 250 mg intramuscularly × 1

and

- *Doxycycline 100 mg po bid × 10 days

Older than 35

- Leukocyte esterase test *or* microscopic examination of first-void urine sediment demonstrating at or above 10 WBC/hpf
 - Culture and gram stain of voided urine
 - Empiric antibiotics to cover coliform bacteria
 - Levofloxacin 500 mg qd × 10 days
- or*
- Ofloxacin 300 mg bid × 10 days

* Patients younger than 35 with allergies to penicillins or tetracyclines should be treated with levofloxacin or ofloxacin.

* If *N gonorrhoeae* is suspected, patients may need to be desensitized to penicillin on account of the high rate of fluoroquinolone resistance evolving in *N gonorrhoeae*.

partner, should undergo testing for *C trachomatis*. In these instances, a gram-stained smear of urethral exudate or intraurethral swab specimen is indicated for diagnosis of urethritis (ie, ≥ 5 polymorphonuclear leukocytes per oil immersion field) and for presumptive diagnosis of gonococcal infection. If the urethral gram stain is negative, first-void uncentrifuged urine should be examined for leukocytes. Definitive diagnosis should be obtained on the basis of nucleic acid amplification tests such as polymerase chain reaction if available, as these tests have a greatly increased

sensitivity for detection of *C trachomatis* over routine cultures [41]. Direct fluorescent antibody testing and optical immunoassay testing, although less sensitive than polymerase chain reaction, allow for rapid results that improve patient counseling and treatment. Patients with positive results for *C trachomatis* or *N gonorrhoea* should be referred for further testing for other sexually transmitted diseases, including HIV, owing to an increased prevalence in this population.

Despite clear guidelines that have been in place for decades, epidemiologic studies of practice patterns reveal that both American and European physicians often do not follow established guidelines. In fact, for patients between the ages of 18 and 35, fewer than one third receive the appropriate diagnostic evaluation and fewer than half receive appropriate treatment according to established guidelines [42]. The explanation for why physicians do not follow guidelines is unknown, but may be the result of poor penetration of CDC guidelines into practice or a discordance between empiric experience and current guidelines.

Improvements in ultrasound technology, including higher megahertz transducers, has led to increased sensitivity and specificity in the evaluation of scrotal pathology. Although ultrasound is primarily used for ruling out torsion of the spermatic cord in cases of acute scrotum, it will often demonstrate epididymal hyperemia and swelling in patients with epididymitis. However, differentiation between testicular torsion and epididymitis is based on clinical evaluation, as partial spermatic cord torsion may mimic epididymitis on scrotal ultrasound [17]. Ultrasound of patients with a clear history consistent with epididymitis offers no diagnostic advantage: only 69% of patients with clinical epididymitis have a positive ultrasound, and a negative ultrasound does not alter physician management of clinical epididymitis [43]. Ultrasound, therefore, should be reserved for patients who have scrotal pain and no definitive diagnosis by physical exam, history, or objective laboratory findings.

Although rarely used because of advances in color-Doppler ultrasound, scrotal radionuclide scintigraphy may be used with a relatively high degree of sensitivity and specificity in differentiating testicular torsion from epididymitis in patients with acute scrotum [44]. A single bolus of $\text{Na}^{99\text{TcO}_4}$ is injected intravenously and perfusion imaging is obtained at 2-second intervals for 2 minutes. A static image is performed after 10 minutes and compared with perfusion images.

In the nonpathologic scrotum, scrotal and testicular vessels are poorly visualized in the perfusion state, and the scrotum appears symmetric and homogeneous on static images. Patients with testicular torsion have an asymmetric decreased uptake in the affected testicle on perfusion imaging and decreased or absent uptake on static images. Conversely, patients with epididymitis have increased uptake of the radionuclide on perfusion and static images. Late torsion may elicit inflammatory changes that are confused with epididymitis.

Treatment

Treatment of epididymitis includes bed rest, scrotal elevation, analgesics, nonsteroidal anti-inflammatory drugs, and empiric antibiotics when infection is suspected. Although most patients can be treated on an outpatient basis, hospitalization may be considered if the patient appears toxic or has significant systemic findings (fever, leukocytosis, etc), or severe pain suggests other diagnoses (eg, torsion, testicular infarction, or necrotizing fasciitis). Additional consideration for admission should be given to patients with significant comorbidities, including severe immunosuppression or uncontrolled diabetes mellitus.

Antibiotics continue to be the primary treatment modality for epididymitis, despite evidence demonstrating that up to three quarters of patients do not have an identifiable bacterial infection [2,9]. Despite the fact that antibiotics do not alter the course of epididymitis in the absence of identifiable infection, the use of antibiotics has increased from 75% to 95% between 1965 and 2005 [2,9]. In 2007 the CDC published updated guidelines for the treatment of epididymitis, with the choice of antibiotics depending on patient age as well as history, including urinary tract instrumentation and sexual history (see Box 1). Patients who are younger than 35 or have a recent sexual risk factor are treated with a 10-day course of doxycycline as well as a single intramuscular injection of ceftriaxone to cover *N gonorrhoea*. If patients are penicillin allergic, *C trachomatis* infections may be treated with levofloxacin or ofloxacin, but older quinolones such as ciprofloxacin should not be used on account of their incomplete coverage of *C trachomatis*. As of April 2007, the CDC no longer recommends use of fluoroquinolones to treat *N gonorrhoea*, owing to an increasing prevalence of resistant organisms [40]. Therefore, patients with a suspected *N gonorrhoeal* infection

should be treated with a single intramuscular dose of ceftriaxone in addition to doxycycline to cover *C trachomatis*. Patients with a cephalosporin allergy and fluoroquinolone-resistant *N gonorrhoea* can be treated with spectinomycin (not available in United States) or undergo cephalosporin desensitization. Patients older than 35 and those with risk factors for enteric pathogens are treated with a quinolone antibiotic for 10 days [45]. Antibiotic sensitivities should be obtained in all patients with recent urinary tract instrumentation or risk factors for complicated urinary tract infections, as this population has higher rates of antibiotic resistance.

In patients where *C trachomatis* is confirmed or highly likely, consideration should be given to treating sexual partners. *C trachomatis* infections are a major cause of pelvic inflammatory disease, ectopic pregnancy, infertility, and chronic abdominal pain in women. In addition, continued infection of a partner may lead to recurrent infections and recurrent epididymitis. Partners may be treated directly, referred to their primary care physician for testing, or receive patient-delivered partner therapy, whereby the treating physician prescribes a second course of antibiotics that the patient then gives to his partner [46].

Atypical infections of the epididymis require specific treatment for the offending organism. Treatment of tuberculous epididymitis involves a 6-month triple drug course with isoniazid, rifampin, and pyrazinamide. Ethambutol should be added to the antimicrobial regimen while bacterial sensitivities are pending if the patient comes from an area with high drug resistance [47,48]. In contrast to patients with community-acquired TB, patients with Bacille Calmette-Guérin epididymitis should be treated with isoniazid and rifampin only, as all strains are resistant to pyrazinamide. Patients with *Brucella* epididymitis should be treated with 100-mg doxycycline orally twice daily for 6 weeks and either 1-gm streptomycin intramuscularly daily for 14 days or 600- to 900-mg rifampin orally daily for 6 weeks [49]. Treatment of filarial funiculoepididymitis consists of testis/cord-preserving surgical excision and use of diethylcarbamazine or ivermectin to control microfilaremia.

Although there are no specific studies regarding medical management of chronic epididymitis, reports of patients with orchalgia reveal that the use of local therapy (heat), nerve blocks, analgesics, anti-inflammatories, or drugs such as tricyclics and anticonvulsants (gabapentin) are

rarely effective, largely empirical, and not supported by randomized placebo controlled trials [50]. Medical management, therefore, must rely on a combination of therapies with effectiveness often being patient specific.

Attempts at treatment of idiopathic epididymal pain should begin with use of a long-acting anti-inflammatory agent, such as naproxen sodium, given on a daily basis for at least 2 weeks. Anti-inflammatories should be given in conjunction with limiting patient activity as well as scrotal ice and elevation. If the patient fails to have relief from these measures, the use of a tricyclic antidepressant or a neuroleptic such as gabapentin should be considered, with selection based on any other comorbidities. Patients who do not respond to a several-month course of one of these centrally acting medications may be considered for spermatic cord block using a mixture of 6-mL 1% plain lidocaine along with 1 mL of methylprednisolone (40 mg/mL). Despite these multiple therapies, the vast majority of patients may continue to have substantial discomfort and may be considered for chronic pain management with narcotics and referral to a chronic pain specialist [39].

Epididymectomy has high failure rates (> 75%) in the treatment of chronic epididymitis owing to plasticity in circuits involved in central pain processing [51]. Transient relief following surgery is often followed by either recurrence of pain or transfer of symptoms to the contralateral epididymis. In addition, epididymectomy may be associated with infertility or testicular loss intra-operatively or from subsequent atrophy. Orchiectomy may be considered in patients with unrelenting epididymal pain that significantly affects their quality of life, though up to 50% of patients may continue to have scrotal pain [50]. Patients should undergo extensive conservative management as well as psychologic evaluation before consideration of orchiectomy for chronic orchalgia, and the surgeon should be aware of the medical legal aspects of this radical procedure, which may fail to achieve its goal in a significant number of patients.

Summary

Epididymitis affects a large cross section of the population. There are several causes of epididymal inflammation: infection, trauma, autoimmune disease, vasculitis, and idiopathic. Epididymitis should be further classified as acute (< 6 weeks) or chronic, with evaluation and treatment based

on duration of symptoms. Diagnosis is determined based on clinical history and studies for evaluation of urinary tract infection, with imaging modalities reserved for distinguishing torsion of the spermatic cord. Although classically thought of as an infectious process, the majority of men in large epidemiologic studies have no demonstrable infection. CDC guidelines outline the current approach to the evaluation and treatment of acute infectious epididymitis, though guidelines are often not followed. Treatment of chronic epididymitis is difficult, and treatment must be based on individual response to therapy following a stepwise treatment plan. Additional research into the etiology and treatment of this common urologic condition is warranted and may alter future treatment guidelines.

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