Chapter from the book *Urinary Tract Infections*

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1. Introduction

Urinary tract infections (UTIs) are a significant source of morbidity and mortality, despite the widespread use of antibiotics. Prostatitis is a prevalent and debilitating disease, representing the most common urological diagnosis in men under the age of 50 years. Despite its prevalence and its drain on health care resources, our understanding of the etiology, diagnosis and treatment of prostatitis has not advanced to a widely accepted level. Recently, a consensus has been reached on the definition and classification of prostatitis. Traditionally, prostatitis has been classified into the four clinical entities: i) Acute bacterial prostatitis (ABP), ii) Chronic bacterial prostatitis (CBP) iii) Non or abacterial prostatitis (NBP), iv) Prostatodynia. To improve the definition and understanding of prostatitis a new classification system has been proposed by the National Institute of Health (NIH). It includes: i) ABP, ii) CBP, represents the traditional forms of acute and chronic bacterial prostatitis, defined by the presence of both prostatic inflammation and uro-pathogenic bacteria in prostatic culture, iii) Chronic pelvic pain syndrome (CPPS) with the inflammatory and non-inflammatory type, which is characterized by prostatitis like symptoms in the absence of bacterial localization to the prostate iv) asymptomatic inflammatory prostatitis, which is characterized by pathogenic evidence of prostatic inflammation in patients without symptoms (includes patients who have prostatic inflammation diagnosed after prostatic biopsy) (Magri et al., 2010).

Risk factors that allow bacterial colonization and/or infection of the prostate with potentially pathogenic bacteria include intraprostatic ductal reflux; phimosis; specific blood groups; unprotected anal intercourse; UTI; acute epididymitis; indwelling urethral or condom catheters; and transurethral operations (especially in men who have infected urine) (Westesson & Shoskes, 2010).

In a study, nearly 9.7% of male respondents (aged 20 to 74 years) reported pain or discomfort in the perineum or with ejaculation or both, plus a total pain score (possible 0 to 21) of 4 or greater (Vaidyanathan & Mishra, 2008). This location and level of pain would be sufficient to lead most physicians to make a diagnosis of chronic prostatitis (CP). In this age group, 6.6% of men reported similar symptoms over the previous week with a pain score of 8 or greater, which would place them in the moderate or severe category (Vaidyanathan & Mishra, 2008).

The modern era of prostatitis management began in the 1960s with Meares and Stamey’s description of the four-glass lower urinary tract segmented localization study. With this...
insight, prostatic massage as the mainstay of prostatitis therapy was abandoned, and antimicrobial therapy was rationalized for the percentage of patients with bacteria. Unfortunately, the vast majority of patients who were diagnosed with a nonbacterial cause continued to suffer the indignities of dismal urologic management (Wagenlehner & Naber, 2009).

2. Acute bacterial prostatitis (ABP)

2.1 Etiology & pathogenesis
ABP is a generalized infection of the prostate gland and is associated with both lower UTI and generalized sepsis. The most common cause of bacterial prostatitis is the Enterobacteriaceae family of gram-negative bacteria, which originate from the gastrointestinal flora. Aerobic gram-negative organisms principally cause ABP. The incidence of infection by various species and their antibiotic susceptibilities follow those of organisms that regularly infect the urine (Bruyere, 2010).

E. coli is implicated in 80% of infections. Pseudomonada aeroginosa, Serratia, Klebsiella and Proteas species account for 10-15% of the cases and enterococci for 10-15%. Bacteria reside deep in the ducts of the prostate gland and tend to form aggregates (also called bio-films); this appears to be a protective mechanism that allows bacteria to persist in the prostate gland even when the concomitant cystitis is treated with antibiotics (Bruyere, 2010). The gram-positive bacteria become pathogenic only under special circumstances. Anaerobes infections are usually polymicrobial. Most infections occur in the peripheral zone, where the ducts drain horizontally into the urethra, facilitating reflux of urine as well as intraductal stasis. Glands of the central zone empty obliquely and completely into the prostatic urethra, preventing easy reflux and stagnation. Invasion by rectal bacteria, either directly or via lymphogenous spread, has also been suggested to cause prostatitis (Maglakelidze, 2009). Investigators have demonstrated that urine and its metabolites (i.e. urate) are present in the prostatic secretion of patients with CP. Prostatic inflammation and subsequent symptoms may be simply due to a chemically induced inflammation secondary to the noxious substances in the urine that have refluxed into the prostatic duct (Bruyere, 2010).

2.2 Clinical features
ABP is marked by fever and chills; rectal, low back, and perineal pain; urinary urgency, frequency and dysouria. Prostatic swelling may result in acute urinary retention. Malaise, arthralgia, and myalgia are also common. Digital rectal examination reveals an exquisitely tender, enlarged gland that is irregularly firm and warm. The urine may be cloudy and malodorous because of concomitant UTI. Gross hematuria may be observed occasionally. Physical examination is an important part of the evaluation of a patient with prostatitis, but it is usually not helpful in making a definitive diagnosis or further classifying prostatitis. It assists in ruling out other perineal, anal, neurologic, pelvic, or prostate pathologies and is an integral part of the lower urinary tract evaluation.

In ABP, the patient may be systemically toxic: flushed, febrile, tachycardic, tachynoic, and even hypotensive. The patient usually has suprapubic discomfort due to a degree of urinary retention. Perineal pain and anal sphincter spasm may complicate the digital rectal examination. The prostate itself is usually described as warm, buggly, and exquisitely tender. In cases of ABP, prostatic massage is believed to be unnecessary and even harmful (Erlikh et al., 2009).
2.3 Diagnosis
ABP is often diagnosed on the basis of symptoms and physical examination. A complete blood count typically shows leukocytosis with a shift toward immature forms. Transurethral catheterization as well as prostatic massage should be avoided. Acute urinary retention requiring bladder drainage should be managed with a suprapubic tube. The voided urine usually shows pyuria and microscopic hematuria due to a UTI (Bruyere, 2010).

2.4 Management
Empiric treatment should not be delayed, and should be directed primarily against gram-negative rods and enterococci. Patients will often respond dramatically to agents that would otherwise diffuse poorly into prostatic tissue. The choice of antibiotic is ultimately guided by in vitro susceptibility tests. The fluoroquinolones work very well as initial therapy, as does TMP-SMX. The recommended duration of antibiotic treatment is 4-6 weeks in order to prevent the development of complications such as prostatic abscess and chronic prostatitis. Supportive measures include antipyretics, analgesics, stool softeners, hydration and bed rest. Patients with significant comorbidities, sepsis, immunodeficiency and acute urinary retention need hospital admission. Any transurethral catheterization or instrumentation is contraindicated during the phase of acute infection. Acute urinary retention should be managed with suprapubic drainage until the patient is able to void spontaneously (Weidner et al., 2008).

2.5 Complications
Some patients may progress to chronic bacterial prostatitis, especially if attention is not focused on bacterial eradication. Prostatic abscess can develop in the setting of acute prostatitis. Immunocompromised patients, diabetics, those with indwelling urethral catheters, or those on chronic dialysis are at higher risk for this complication (Weidner et al., 2008).

3. Chronic bacterial prostatitis (CBP)

3.1 Etiology & pathogenesis
Chronic bacterial prostatitis is associated with recurrent lower UTIs secondary to focal uropathogenic bacteria residing in the prostate gland. Gram-negative bacteria and enterococci are usually the causative microorganisms in CBP. Mycoplasms, ureoplasms and chlamydial species are appreciable pathogens in BCP and most of them are also implicated in the chronic pelvic pain syndromes. Intraprostatic reflux, ductal anatomy, secretory dysfunction and alkaline prostatic secretions contribute to CBP. Reflux of urine and possibly bacteria into the prostatic ducts has been postulated as one of the most important etiologic mechanisms involved in the pathogenesis of chronic bacterial and nonbacterial prostatic inflammation. Anatomically, the ductal drainage of the peripheral zone is more susceptible than other prostatic zones to intraprostatic ductal reflux (Wagenlehner et al., 2008). Investigators have measured high levels of urate and creatinine in EPS, which they postulated was caused by urine reflux into the prostatic ducts (Touma & Nickel, 2010). Furthermore, carbon particles have been found in the EPS macrophages and prostatic acini and ductal system after surgery in men with nonbacterial prostatitis. Bacterial microcolonies may adhere to ductal and acinar walls and become impervious to antibiotics. Prostatic calculi also provide sanctuary for pathogens. A large proportion of men...
with CBP have multiple prostatic calculi demonstrated on transrectal ultrasound. Prostatic calculi can serve as a source for bacterial persistence and recurrent UTIs. It is believed that the source of the pain is located at the pelvic area of the sacrum, coccyx, ischial tuberosity, pubic rami, and endopelvic fascia (Saini et al., 2008). These areas are immediately adjacent to the prostate and bladder and can be recognized by the demonstration of a hyperirritatable spot (myofascial trigger point) that is painful on compression. It is hypothesized that the formation of myofascial trigger points in this area may be correlated with mechanical abnormalities in the hip and lower extremities, toilet straining, sexual abuse, repetitive trauma, constipation, heavy sports, trauma or unusual sexual activity, recurrent infections, and surgery (Sandhu, 2008).

### 3.2 Clinical features

The physical examination of a patient with category II CBP and category III CPPS is usually unremarkable. Careful examination and palpation of external genitalia, groin, perineum, coccyx, external anal sphincter, and internal pelvic side walls may pinpoint prominent areas of pain or discomfort (Magri et al., 2010). The digital rectal examination should be performed after the patient has produced pre-prostatic massage urine specimens. The prostate may be normal in size and consistency, and it has also been described as enlarged and boggy. The degree of elicited pain during prostatic palpation is variable and is unhelpful in differentiating a prostatitis syndrome. The prostate should be carefully checked for prostatic nodules before a vigorous prostatic massage is performed (Westesson and Shoskes, 2010).

Most patients report dysuria as well as urgency, frequency, and nocturia. Low back and perineal pain or discomfort may be present. The natural history is marked by disease relapse with occasional acute exacerbations, at which time fever, chills and malaise might manifest. Sometimes, the diagnosis is made in an asymptomatic patient in whom bacteriuria is found incidentally. There are no characteristic findings on digital rectal examination. The prostate frequently feels normal although tenderness, swelling, and firmness may be present. Secondary epididymitis is sometimes present. Hematuria, hematospermia and urethral discharge are usually rare (Jonsson & Hedelin, 2008).

### 3.3 Diagnosis

The 4-glass test is the standard in prostatitis diagnosis. This technique allows localization of bacteria by examining specimens from the urethra, midstream urine, and prostatic secretions. The examiner obtains the first voided 10 mL of urine (urethral specimen), a late midstream sample (bladder specimen), a specimen of prostatic secretions following prostatic massage, and the first voided 10 mL of urine following the massage. The specimens are labeled VB1, VB2, EPS, and VB3, respectively, and they are sent for bacterial identification and quantification using standard microbiologic methods. Two or more bacterial localization tests may then be required to identify the pathogenic bacteria. If no organisms can be cultured, and the prostatic fluid has increased leukocyte count (> 10 per HPF), a diagnosis of chronic pelvic pain syndrome (inflammatory type) can be made (Westesson & Shoskes, 2010). Despite sterilization in the urine, the pathogen often remains sheltered in the prostate because most antibiotics diffuse poorly into prostatic fluid. The prostate-specific antigen may be elevated.
3.4 Management
At least 3-4 months of treatment is generally recommended, although some studies have reported success with a 4-week course of a fluoroquinolone. Factors that promote antibiotic diffusion into the prostate include lipid solubility, weak binding to plasma proteins, and an uncharged state. Suppressive antibiotic therapy aimed at eliminating bacterial growth in the urine is often instituted. Most antibiotics are concentrated in the urine, allowing for reduced dosing while maintaining bactericidal efficacy. The most common daily suppressive regimens are nitrofurantoin (100 mg daily), TMP-SMX (200 mg daily), and ciprofloxacin (250 mg daily). Suppressive therapy can provide relief from symptoms for most men.

Transurethral prostatectomy (TURP) has been described as an alternative treatment. Surgical therapy often provides the only chance at cure in relapsing cases. Studies of patients undergoing TURP for chronic bacterial prostatitis followed by 6-8 weeks of antibiotic therapy report varying success rates (30%-100%).

3.5 Complications
Recurrent UTIs are a major complication of CBP that may even result to infertility. Reports of successful treatment of prostatitis leading to improvement in semen parameters and pregnancy rates have been made. Although more difficult to quantify, CBP has a negative impact on the patient’s quality of life.

4. Chronic pelvic pain syndrome (CPPS)
4.1 Etiology & pathogenesis
CPPS is the most common form of prostatitis and the most poorly understood. CPPS categories are divided into inflammatory (category IIIA) and noninflammatory (category IIIB) forms, based on the presence of leukocytes in the prostatic fluid. The inflammatory type was previously called “nonbacterial prostatitis” (associated with elevated prostatic immunoglobulin level); while the non-inflammatory type was called “prostatodynia” (not associated with increased immunoglobulins). Several studies have demonstrated chlamydial antigens in the prostatic fluid and anti-chlamydial antibodies in the serum of men with CPPS. In a study, transperineal prostate biopsy of men with CPPS failed to detect chlamydia by either immunofluorescence or culture (Wagenlehner et al., 2008). There seems to be an association between backflow of urine into the prostatic ducts and a subsequent chemically induced inflammatory prostatitis. Backflow of urine could lead to high concentrations of urinary urate and creatinine in the prostate fluid, resulting in a chemical prostatitis. Investigators have demonstrated a positive correlation between leukocyte count and urate concentration in the prostate fluid (Touma & Nickel, 2010).

Anatomic or neurophysiologic obstruction resulting in high-pressure dysfunctional flow patterns has been implicated in the pathogenesis of prostatitis. Urodynamic studies confirm that many patients, particularly those with prostatodynia, have obstructive flow rate patterns (e.g. decreased maximal flow rate). During video-urodynamic studies, many patients with prostatitis show incomplete funneling of the bladder neck as well as vesicourethral dysynergic patterns. Dysynergic voiding may lead to autonomic overstimulation of the perineal-pelvic neural system with subsequent development of a chronic neuropathic pain state. Alternatively, dysfunctional voiding may result in intraprostatic ductal reflux (Hedelin & Fall, 2008). Investigators have found an increased maximal urethral closure pressure and a decreased urinary flow rate in patients with CPPS.
compared with control patients (Strauss & Dimitrakov, 2010). They attributed the high maximal urethral closure pressure to increased adrenergic stimulation in the proximal urethra and bladder neck and proposed that this might cause intraprostatic reflux of urine. Based on these observations they suggested the use of the term "painful male urethral syndrome". Furthermore, spasm of the pelvic floor muscles alone or in combination with bladder neck dysfunction may contribute to chronic pelvic pain (Strauss & Dimitrakov, 2010).

4.2 Clinical features
Voiding dysfunction consisting of dysuria, slow stream, urgency, and frequency. Sexual dysfunction may also be reported. On digital rectal examination the prostate may be tender. During palpation patients may have tenderness of the pelvic floor muscles and a tight anal sphincter (Dellabella et al., 2009).

4.3 Diagnosis
The EPS in patients with inflammatory CPPS shows numerous leukocytes and lipid-laden macrophages. A 5-fold increase in leykocytes and an 8-fold increase in lipid-laden macrophages may be revealed in such patients in comparison control subjects. Urodynamic studies may disclose urethral hypertonia and diminished flow in the absence of striated sphincter dyssynergia (Vaidyanathan & Mishra, 2008).

4.4 Management
Patients may experience symptomatic improvement with antibiotics. This has prompted the recommendation of a trial of antibiotic therapy. If chlamydia is suspected, then tetracycline, minocycline, doxycycline or erythromycin should be administered. Antibiotic therapy should continue for several weeks. Alpha blockers may improve urination and symptoms. By decreasing adrenergic tone in the proximal urethra, alpha blockers alleviate urethral hypertonia and may prevent intraprostatic reflux of urine. Intraprostatic ductal reflux of urine increases the concentration of metabolites containing purine and pyrimidine bases in the prostatic ducts, resulting in inflammation (Sandhu, 2008). High concentrations of urate in urine can be reduced with the use of allopurinol, a xanthine oxidase inhibitor. This may alleviate chemical irritation in the prostate caused by refluxed urine. Studies have demonstrated a significant effect of allopurinol on urate concentration in the prostatic fluid resulting in symptoms improvement (Maglakelidze 2009). Pelvic floor relaxation techniques, biofeedback, prostate massage, and muscle relaxants may reduce pelvic floor spasticity and chronic pelvic pain (Maglakelidze, 2009). Interestingly, a pollen extract (Cernilton) was recently assessed in a multicentre, prospective, randomised, double-blind, placebo-controlled phase 3 study (Wagenlehner, 2009). Participants were randomised to receive oral capsules of the pollen extract or placebo for 12 weeks. Compared to placebo, the pollen extract significantly improved total symptoms, pain, and QoL in patients with inflammatory CP/CPPS without severe side-effects.

Prostatic inflammation is associated with category III CPPS, while elevated cytokine levels are noted in the semen and EPS of patients with inflammatory CPPS. Non-steroidal anti-inflammatory drugs, steroids, and immunosuppressive medication theoretically may improve the symptoms. Surgical therapy with transurethral microwave thermotherapy or neodymium:YAG laser has also been suggested (Hedelin & Fall, 2008).
4.5 Complications
CPPS may have a negative effect in fertility. Lower sperm counts and abnormal morphologic and motility parameters have been described in affected patients. These parameters may worsen with time. As with chronic bacterial prostatitis, the quality of life is adversely affected (Jonsson & Hedelin, 2008).

5. Epilogue
ABP can be efficiently treated with antibiotics that will eventually eradicate the bacteria. CBP treatment is based on long-term antibiotic regimens. CP/CPPS management needs multimodal medication with antibiotics, alpha blockers, anti-inflammatory drugs and hormonal agents (Westesson & Shoskes, 2010).

Chronic nonbacterial prostatitis and prostatodynia (category III CPPS) constitute the vast majority of prostatitis cases and are difficult to manage. Performing a lower urinary tract evaluation (at least a two-glass premassage and postmassage screen) to rule out uropathogens, microscopy of postprostatic massage urine sediment (to differentiate inflammatory from non-inflammatory CPPS), and employment of the newly validated NIH-CPSI will allow optimal management (Strauss & Dimitrakov, 2010). Available treatments include: i) antibiotics that cover potential pathogens (including Chlamydia and Ureaplasma, at least in category IIIA); ii) alpha blockers (especially in patients with obstructive voiding symptoms); iii) anti-inflammatory agents; iv) muscle relaxants; v) pento-san polysulfate (in patients with bladder or interstitial cystitis-like symptoms); and vi) physical therapy (i.e. prostate, perineal, or pelvic floor massage, myofascial trigger point release, and biofeedback). For refractory symptoms, other treatment modalities include microwave hyperthermia or thermotherapy and TURP (Magri et al., 2010).

Asymptomatic inflammatory prostatitis (category IV) does not require symptomatic therapy. However, antibiotic medication may be indicated in patients who are scheduled to undergo endoscopic procedures, and in patients with concomitant inflammation and infertility (Murphy et al., 2009).

6. References


Urinary tract infections (UTIs) are among the most common bacterial infections worldwide, and they are also the leading cause of hospital-acquired infections. Therefore, the appropriate management of UTIs is a major medical and financial issue. This book covers different clinical manifestations of UTI, with special emphasis on some hard-to-treat diseases, and special conditions in respect of treatment; antibiotic resistance and the available alternative strategies for the prevention and treatment of UTIs and it deals with urinary tract infections in children. The aim of this book is to give a summary about the different aspects of the diagnosis, management and prevention of urinary tract infections for all medical disciplines.

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