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Prostatitis: US perspective

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Abstract

The diagnosis and management of prostatitis syndromes is a challenge to the clinician. Careful history and examination of the prostate fluid and quantitative segmented bacteriologic cultures will lead to proper categorization into the recognized forms of the prostatitis syndrome. Antimicrobial therapy is effective in the majority of men with acute and chronic bacterial prostatitis (CBP). Fluoroquinolone agents appear to have an increasingly important role in this regard, although a randomized, prospective, double-blind study is still lacking. Alpha-1-selective blocking agents may relieve symptomatology of chronic pelvis pain syndrome (CPPS). Other non-prostatic sources of voiding symptoms should be sought and ruled out, especially malignancy or inflammatory disorders. © 1998 Elsevier Science B.V./International Society of Chemotherapy. All rights reserved.

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The prostatitis syndrome is one of the most common entities encountered in urologic practice. It has been estimated that annually prostatitis syndrome constitutes over 25% of male office visits for genitourinary complaints [1,2]. The symptoms may mimic the symptoms of bladder outlet obstruction from benign prostatic hyperplasia, irritating symptoms associated with interstitial cystitis or other bladder inflammatory malignant conditions, or a variety of pelvic disorders, including myofascitis, etc. which may further confuse the patient and clinician. The diagnosis requires careful attention to details and a thoughtful systematic evaluation. Treatment with antimicrobials should be directed at patients with known bacterial infection and empiric therapy should be monitored for relief of symptoms and improvement of quality of life.

1. Classification of prostatitis syndromes

Classification of the prostatitis syndrome is based on the clinical presentation of patients, the presence or absence of white blood cells (wbc) in the expressed prostatic secretion, and the presence or absence of bacteria in the expressed prostatic secretions.

Evaluation of seminal fluid for inflammation is difficult because wbc are frequently indistinguishable from immature sperm, controlled studies of a seminal fluid from patients with chronic pelvis pain syndrome (CPPS) and healthy individuals have not been performed and urethral inflammation which can contaminate the seminal fluid can only be assessed by examination of the first voided urine prior to ejaculation.

On December 7, 1995 the National Institute of Diabetes Digestive and Kidney Diseases (NIDDK) of the National Institute of Health convened a workshop to 'develop a plan which would enable clinicians and research investigators to effectively diagnose, treat, and eventually prevent the prostatitis syndrome' [3]. Over 70 participants representing various clinical research and patient concerns participated. At the conclusion of the workshop, uniform classification and definition of the categories of the prostatitis syndrome was determined. The following classification system was approved by the workshop committee and will be the NIDDK reference standard for research studies on these diseases and disorders:

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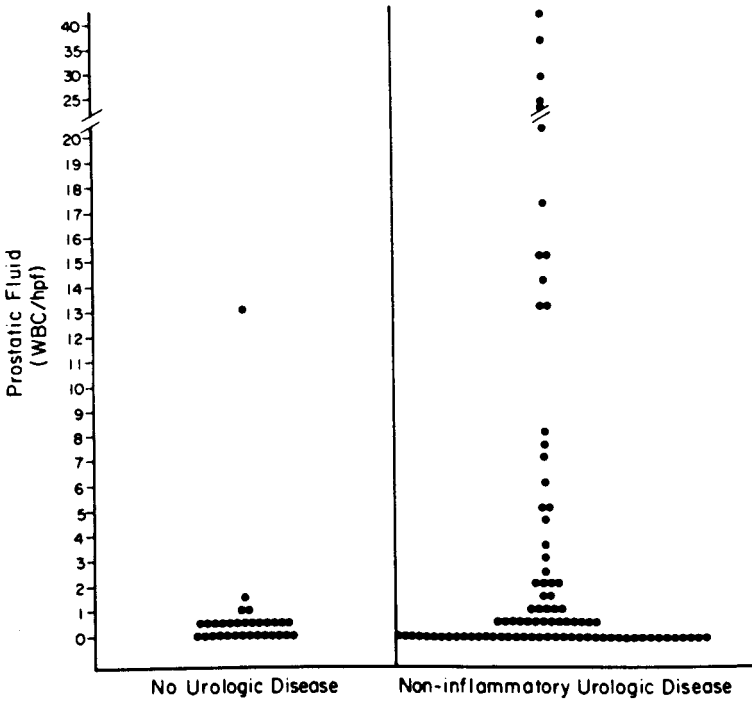

Fig. 1. Number of wbc/hpf in prostatic fluid from patients with no urologic disease or non-inflammatory urologic disease [45].

1. Acute bacterial prostatitis (ABP) acute infection of the prostate
2. Chronic bacterial prostatitis (CBP) recurrent infection of the prostate
3. CPPS no demonstrable infection.
   3.1. Inflammatory CPPS-chronic abacterial prostatitis white cells in expressed prostatic secretions/voided bladder urine-3, (VB-3)
   3.2. Non-inflammatory CPPS no white cells in EPS/VB-3
4. Asymptomatic inflammatory prostatitis (AIP) no subjective symptoms detected either by prostate biopsy or the presence of wbc in prostate secretions during evaluation for other disorders

The participants agreed that the most prevalent of the symptomatic diseases (i.e. 1–3) is CPPS. This might be the most prevalent of all the diseases of the prostate. It has not been scientifically demonstrated that CPPS is primarily either a disease of the prostate or that it is an inflammatory process.

The following diagnostic criteria for CPPS were approved as the criteria for NIDDK sponsored research studies on chronic prostatitis/CPPS.

Inclusion criteria:

male, 18 years of age or older

three month or greater duration of pain or discomfort somewhere in the pelvic area (e.g. penis, scrotum, perineum)

Exclusion criteria will include:

the presence of cancer of the genitourinary tract

active urinary tract stone disease

herpes of the genitourinary system

bacteriuria (100000 colonies per ml) in a midstream urine within the past 3 months

antibiotic therapy within the past 3 months

peri-rectal inflammatory disorders

inflammatory bowel disease

history of pelvic radiation or systemic chemotherapy

history of intravesical chemotherapy

documented gonorrhea, chlamydia, mycoplasma, or trichomonas infection of the urinary tract within the past 3 months

clinical epididymitis within the past 3 months

urethral stricture of 12 French or smaller

neurological disease or disorder affecting the bladder

prostate surgery (not including cystoscopy) within past 3 months

2. Diagnosis

To diagnose prostatitis, the degree of inflammatory changes that can be found in normal prostatic fluid must first be determined. This is done by microscopic examination of expressed prostatitic fluid and counting the number of white blood cells per high power field (wbc/hpf) [4]. Available data suggest that wbc are rarely present in normal prostatitic fluid and that ten or more wbc/hpf are diagnostic of prostatitis (Fig. 1).

Recent advances in technology have allowed the application of transrectal prostate ultrasound in the diagnosis of both benign and malignant prostate disease.

The sonographic features of prostatitis on transrectal prostatic ultrasound, however, are neither sensitive nor specific enough to allow identification of any one feature as being diagnostic of prostatitis [5]. In fact, granulomatous prostatitis, one of the potential sequels of ABP, is often confused with carcinoma of the prostate due to its hypoechogenic feature. Elucidation of this confusion requires histologic confirmation by biopsy [6].

2.1. Quantitative segmental bacteriologic localization cultures

Bacterial prostatitis can be differentiated from non-bacterial prostatitis only by sequential, quantitative bacteriologic cultures of the urethra, bladder urine, and prostatic secretions. The lower tract bacterial localization studies described by Meares and Stamey [7] remain the gold standard for the diagnosis and follow-up of prostatitis syndromes (Fig. 2). When the patient has cystitis, all specimens will show bacterial growth. In such cases the patient should be treated with an antimicrobial drug such as nitrofurantoin or penicillin derivatives. This will sterilize the bladder urine and clear the urethra of prostatic organisms without altering the prostatic microbial flora. Demonstration of bacteria in the post-prostatic-massage urine or expressed prostatic secretions when the urethra and midstream urine specimens show no growth is highly diagnostic of bacterial prostatitis. Alternatively, a significant increase of tenfold or more in the bacterial count in the prostatic specimens when compared with the urethral specimen is considered diagnostic of bacterial prostatitis [7].

A summary of the clinical, microscopic and microbiologic characteristics of prostatitis syndromes is provided in Table 1.

3. Acute bacterial prostatitis

ABP is usually dramatic in presentation and easy to diagnose on physical examination. The disease is associated with large numbers of typical uropathogenic bacteria in the prostatic secretions and/or bladder urine and is curable with antimicrobial therapy. It is characterized by malaise, fever/chills, low-back or perineal pain, and myalgia for several days prior to onset of symptoms of both irritative and obstructive voiding symptoms. Palpation of the prostate reveals a tender, warm, swollen, irregular gland that may be partially or totally indurated. However, patient discomfort and the risk of bacteremia generally make prostatic massage unwise. Since acute cystitis usually accompanies ABP, the pathogen can be identified by culture of the voided urine.

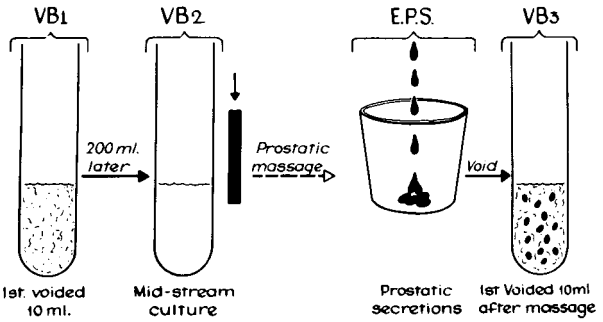

Fig. 2. Segmented culture technique for localizing urinary infections in the male to the urethra or the prostate [7].

Patients with ABP respond dramatically to antimicrobial drugs that do not normally achieve therapeutic levels in the prostatic fluid. If the patient is very toxic, he should be hospitalized and treated with parenteral antimicrobial drugs, typically an aminoglycoside–penicillin derivative combination. If the patient is compliant and can be monitored carefully and frequently at home he can be treated with an oral fluoroquinolone for 10 days. Supportive measures such as analgesics, stool softeners, hydration, and bed rest should be instituted. Urinary retention should be treated with suprapubic aspiration or catheter placement rather than urethral catheterization until the acute inflammation resolves.

Complications of ABP can include pyelonephritis and sepsis. Aggressive parenteral therapy based on bacterial susceptibility is indicated for patients with progressive symptoms despite initial empiric antimicrobial therapy.

Abscess is a potential but rare complication of ABP. An abscess can be suggested by a digital rectal examination revealing a fluctuant prostate and confirmed with the aid of transrectal ultrasonography or computed tomography. In addition to antimicrobial therapy, surgical or percutaneous drainage of the prostatic abscess is generally required, by either the transurethral or transperineal route, respectively. Prolonged oral antimicrobial therapy of at least 30 days is recommended to prevent the complication of CBP [8]. Granulomatous prostatitis is a histologic stage of a resolving ABP. It is usually detected as a local area of prostatic induration suspicious of carcinoma.

4. Chronic bacterial prostatitis

CBP is a relatively rare phenomenon characterized by asymptomatic periods between episodes of recurrent bacteriuria. However, it is one of the most common causes of relapsing urinary tract infections in men. In men with recurrent bacteriuria whose excretory urogram is normal, the possibility of CBP should be strongly suspected and pursued with appropriate localization cultures. Some men experience a preceding bout

Table 1
Classification of prostatitis syndromes

	Symptoms of cystitis	Pain in the prostate or perineum	Rectal examination (prostate)	Evidence of inflammation (EPS)	Culture positive (bladder)	Culture positive (EPS)	Common etiologic bacteria	Treatment (duration)
Bacterial prostatitis								
Acute	+	+	Abnormal	+	+[a]	+	Enterobacteriaceae	TMP/SMX or TMP or fluoroquinolone (14 days)
Chronic	±	±	Normal	+	+[b]	+	Enterobacteriaceae	TMP/SMX or TMP or fluoroquinolone (28+ days)
Chronic pelvic pain syndrome								
Inflammatory	0	±	Normal	+	0	+	?	Sitz-baths or α-blocker or ibuprofen
Non-inflammatory	0	±	Normal	0	0	0	0	Sitz-baths or α-blocker or ibuprofen
Asymptomatic inflammatory prostatitis	0	0	Normal	+	0	0	0	none

EPS = Expressed prostatic secretion.Modified from Stamey TA: Pathogenesis and Treatment of Urinary Tract Infections. Williams and Wilkins, Baltimore, 1980, p. 344.
[a] ABP is nearly always accompanied by bladder infection.
[b] Characterized by recurrent bacteriuria, at varying intervals up to several months, after stopping antimicrobial therapy.

of ABP, but many do not. Most patients with CBP, however, complain of mild to moderate irritative voiding symptoms and pain or discomfort involving various sites: the perineum, low back, scrotum and penis.

Trimethoprim–sulfamethoxazole (TMP–SMX), 160 mg/800 mg twice daily for 12 weeks, will cure ≈ 30–40% of patients [9].

One of the most exciting recent developments in the treatment of CBP is the use of fluoroquinolones. The fluoroquinolones have a broad spectrum of activity against aerobic Gram-negative and Gram-positive bacteria [10–12]. They act by inhibiting bacterial gyrases essential to deoxyribonucleic acid replication, transcription, and repair [13]. Spontaneous development of resistance is extremely rare [13]. These drugs have small molecular sizes, high lipid solubility, and low protein binding (14–30%), which may facilitate tissue penetration [14]. In addition, unlike trimethoprim, which is a base, fluoroquinolones are carboxylic acids and thus should undergo 'ion trapping' in the alkaline milieu of the prostatic secretions found in human CBP.

The pharmacokinetics of the fluoroquinolones have been described in many studies [15–21]. Intraprostatic concentration of norfloxacin and ciprofloxacin were 79–250% of simultaneous serum levels. Norfloxacin achieved prostatic levels of 0.78–1.63 μg/g; these are inhibitory to $\geq 90\%$ of commonly isolated Enterobacteriaceae, with the exception of some species of Serratia and Providencia [13]. The mean ciprofloxacin prostate levels of 1.28–3.49 μg/g are inhibitory to $\geq 90\%$ of Enterobacteriaceae as well as P. aeruginosa and enterococci [13].

Studies have shown that norfloxacin, ciprofloxacin and ofloxacin have achieved 60–92% cure rates in the treatment of CBP [16,22–26]. The high cure rates (74–92%) were achieved in patients followed-up for 1–2.5 months. Two studies, with minimum follow-up of 6 months, report cure rates of 53–64% [27,28].

Patients who are not cured by prolonged antimicrobial therapy can be managed with suppressive therapy to prevent recurrent urinary tract infection. The bacteria usually remain susceptible to many antimicrobial agents. Low dose TMP–SMX, nitrofurantoin, or tetracycline are appropriate choices for suppressive therapy. Even prolonged treatment, however, fails to clear the pathogen from the prostate, and discontinuation of the medication eventually leads to recurrent symptoms and bacteriuria.

Transurethral resection of the prostate is the only alternative, short of radical prostatectomy, for surgical management of bacterial prostatitis. About one third of patients with well documented bacterial prostatitis have been cured by this technique [29]. The morbidity of radical prostatectomy, including impotence, hardly justifies its use in the treatment of prostatitis, especially in sexually active patients. Transurethral prostatectomy is curative only if all the foci of infected tissue and calculi are removed. Since most inflammation of chronic prostatitis occurs in the peripheral zone of the gland [30] and all the ducts from the peripheral zone empty into the urethra distal to the verumontanum, radical transurethral resection beyond the verumontanum is required to remove the infected tissue [31]. Such an extensive resection carries a higher than usual risk of urinary incontinence. It is possible that some patients respond to extensive transurethral resection as a result of the incidental resolution of a bladder neck obstruction.

5. Chronic pelvic pain syndrome

5.1. Inflammatory CPPS

This condition, previously called abacterial prostatitis, is the most common form of the prostatitis syndromes, approximately eight times more common than bacterial prostatitis. Usually, the symptoms, physical findings, and the microscopic appearance of the prostatic expressates in abacterial prostatitis and CBP are indistinguishable. However, the patient with inflammatory CPPS typically has no history of documented urinary tract infection and has localization cultures that exclude an infectious etiology. The patient is characterized by pain localized to the pelvic, suprapubic perineal, scrotal, or low back area. Irritative or obstructive voiding symptoms are common. Since the etiology is unknown, the treatment is empiric and often unrewarding.

Controversy regarding the role of chlamydia, ureaplasma, and mycoplasma in the pathogenesis of prostatitis continues. Most investigators have found that mycoplasma and ureaplasma are not causative agents in abacterial prostatitis [32–35]. In 1983, however, Brunner et al. [36] found a ten-fold or greater increase in quantitative counts of *Ureaplasma urealyticum* in prostatic cultures compared with urethral culture in 82 (13.7%) of 597 patients who appeared to have abacterial prostatitis. Most of these patients were said to respond favorably to tetracycline. Until culture results are substantiated by demonstration of antigen-specific immune response in the prostatic secretions, however, *U. urealyticum* remains an unconfirmed pathogen in prostatitis. *Chlamydia trachomatis* remains the most controversial putative agent in prostatitis. Both Berger et al. [32] and Mardh et al. [33] studied 50 or more patients with abacterial prostatitis and found little or no evidence that *C. trachomatis* is an etiologic agent. In contrast, Poletti et al. [37] performed transrectal aspiration biopsies of the prostate in 30 men with abacterial prostatitis and reported isolating *C. trachomatis* in tissue cultures from ten (33%). Schachter, [38] however, in an accompanying editorial expressed concerns over the

authors' methods of identifying Chlamydia and over the observation that all 30 men had positive urethral cultures for Chlamydia, which raised questions about specimen contamination. He therefore concluded that *C. trachomatis* remains an unproved pathogen in prostatitis.

In 1988, Weidner et al. [39] found *C. trachomatis* in 43 patients out of 233 with signs and symptoms of chronic prostatitis. Their analysis of the micro-immunofluorescence test against the sera of patients with positive chlamydial cultures and high leukocyte counts in post-prostatic massage urine found titers of $\geq 1{:}8$ in 13 out of 15 patients. This was taken as evidence of the role of chlamydia in the pathogenesis of chronic prostatitis, although their data on urethral cultures in a relatively small number of patients were not presented.

Abdelatiff et al. [40] studied 23 transurethrally resected prostate specimens with 'histologic' evidence of chronic abacterial prostatitis by using colorimetric in situ hybridization technique for evidence of *C. trachomatis*. Intracellular chlamydia bodies were detected in seven of 23 cases (30.4%). However, this histopathologic finding was not correlated with preoperative clinical and bacteriologic results. Indeed their definition of abacterial prostatitis was different from the accepted definition of Meares and Stamey [7]. Lastly, Shortliffe et al. [41,42] detected insignificant antigen-specific antibody elevations against Chlamydia in the prostatic secretions of their patients with abacterial prostatitis. No unequivocal evidence exists to support the etiologic role of chlamydia for abacterial prostatitis thus far. Chlamydia therefore must be assumed to play an insignificant role in the etiology of prostatitis.

If Chlamydia or ureaplasma are a likely cause of urethritis associated with abacterial prostatitis, a trial of tetracycline derivatives or erythromycin for 7 days is reasonable. Continuation of antimicrobial therapy without clear effectiveness is futile and unwarranted. Management should include a frank discussion with the patient and reassurance about the nature of the entity. Some patients have responded to symptomatic therapy with hot sitz-baths, anti-inflammatory drugs, such as ibuprofen, or α-blocking agents as discussed below.

5.2. Non-inflammatory CPPS

The typical patient is young to middle-aged and experiences variable signs and symptoms of abnormal urinary flow, irritative voiding dysfunction, and pain in the perineum or lower back. Considerable evidence is accumulating that pelviperineal pain results from neuromuscular dysfunction of the bladder outlet and prostatic urethra. Urodynamic studies performed on patients with pelviperineal pain show spasm and narrowing of the urethra at the bladder neck and just proximal to external urethral sphincter, with resultant incomplete 'funneling' [43,44]. Urethral pressure profiles typically show a high maximum urethral closure pressure in the distal prostatic and membranous urethral segments, despite electrical silence of the external sphincter on electromyography. This region of the prostate is known to be rich in α-adrenergic receptors. This condition may be a form of detrusor internal sphincter dyssynergia. Treatment with α-blockers, especially the newer selective α-1-blockers such as prazosin and terazosin, may relieve symptomatology. The dosage must be titrated to individual tolerance to minimize side effect.

Stress is thought by some clinicians to play a primary role in the etiology of pelviperineal pain. Most men with pelviperineal pain do admit to stress and emotional tension. Whether the stress is the cause or the effect is not certain. However, those patients with pelviperineal pain who seem to have significant emotional disturbances should be referred to an interested psychiatrist or psychologist. Lastly, the irritative and obstructive voiding symptoms may be a reflection of other concomitant processes, such as benign prostatic hyperplasia, carcinoma-in-situ of bladder, or interstitial cystitis, and should be addressed appropriately.

6. Asymptomatic inflammatory prostatitis

This condition is detected either by identification of inflammatory cells in prostate biopsy or in expressed prostatic secretions obtained during evaluation of patients for other disorders such as subfertility or prostate cancer. Since the patients are asymptomatic, microbiologic evaluation and/or antimicrobial therapy should be used only if it is warranted by the underlying problem.

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