

Prostatitis

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1. Introduction

The prostate is subject to various inflammatory disorders, both acute and chronic. Acute bacterial prostatitis is an acute infection of the prostate, usually caused by gram-negative bacteria, while chronic bacterial prostatitis indicates recurrent or longstanding urogenital symptoms caused by bacteria. Other associated prostatitis and chronic pelvic pain syndromes are characterized by urogenital symptoms based on presence or absence of inflammation.

Key Words

Prostate, Prostatitis, Perineum, Pain, Infection, Bacteria, Inflammation, Urine

2. Epidemiology

Prostatitis is the most common urologic diagnosis in men less than 50 years of age, and the third most common urologic diagnosis in men greater than 50 years of age, with the most common diagnosis in this age group being benign prostatic hyperplasia (BPH), and the second most common diagnosis being prostate cancer.^{1,2} Based on a physician survey study in Dane County, Wisconsin and a survey of younger men from a Wisconsin National Guard Unit, it has been estimated that **5% of men aged 20-50 years have a history of prostatitis.**³ Various worldwide population-based studies employing the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI), show widely varying results for the prevalence of prostatitis, including **12.2% in Nigeria, 8% in Malaysia, 6.6% in Canada, and 2.7% in Singapore.** Chronic prostatitis is also associated with significant costs, totaling \$84 million in 2000. This estimate excluded pharmaceutical spending, so actual costs are therefore significantly higher.^{4,5}

3. Definition and Classification

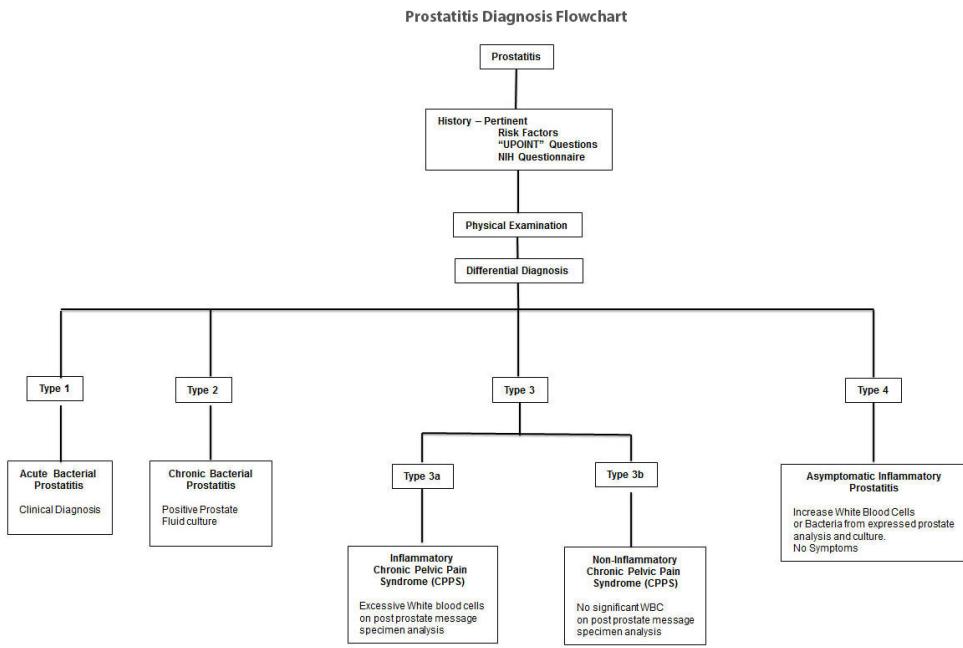


Figure 1

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3.1 Traditional Classification

The definition of prostatitis, infection or inflammation of the prostate gland, has evolved over time. However, the classification system that became known as the “Traditional” classification is based on a landmark paper by Meares and Stamey in 1968, which utilizes the “four-glass test”.⁶

This system divided prostatitis into four categories (Figure 1). The first category was known as **acute bacterial prostatitis** and was defined as purulent prostatic fluid (leukocytosis in the prostatic fluid), systemic signs of infection such as fever, chills, sepsis, etc., and positive bacterial cultures. The second category was **chronic bacterial prostatitis**. Purulent prostatic fluid was again observed, there were no systemic signs of infection or infection of the urinary tract, and bacterial cultures were positive. **Non-bacterial prostatitis was the third category**. Purulent prostatic fluid was still present, but bacterial cultures were negative. Finally, **prostatodynia** (prostatic pain) was the last category and was defined as pain and voiding symptoms, no purulent prostatic fluid, and negative bacterial cultures.

The Traditional classification system was used until the late 1990’s, when it was abandoned for the newer National Institutes of Health Classification.⁷ This was due to a variety of limitations. One of the most important was the impracticality of the “four-glass test,” which was expensive and time-consuming. Additionally, patients seemed to respond to therapy, particularly antibiotics, independent of their classification. Providers also realized that many patients with prostatitis were not easily classified into the system. This led to the development of the NIH classification system in use since 1998. Since that time a “two-glass” method has been proposed that may be equivalent to the traditional four-glass test.⁸

3.2 NIH Classification

Table 1. NIH Classification for Prostatitis Syndromes

Category I—Identical to acute bacterial prostatitis

Category II—Identical to chronic bacterial prostatitis

Category III Chronic Pelvic Pain Syndrome (CPPS)—Presence of GU pain in absence of uropathogenic bacteria

Category IIIA (Inflammatory CPPS)—Excessive WBC in EPS or post-prostatic massage urine or semen

Category IIIB (Non-inflammatory CPPS)—No significant WBC

Category IV (Asymptomatic Inflammatory Prostatitis)—Significant WBC or bacteria in prostate specimens with no symptoms

The National Institutes of Health Classification was developed in 1998.⁷ The major difference is the acknowledgement of pain as the main symptom in “abacterial chronic prostatitis,” with variable voiding and sexual dysfunction. Similar to the Traditional Classification system, there are four Categories. **Category I is identical to acute bacterial prostatitis and is an acute infection of the prostate gland. Category II is identical to chronic bacterial prostatitis and is a chronic infection of the prostate. Category III differs from the traditional classification and is defined as the presence of genitourinary pain in the absence of uropathogenic bacteria . It is further subdivided into Category IIIA, also known as Inflammatory Chronic Pelvic Pain Syndrome, which is characterized by excessive white blood cells in expressed prostatic secretions or post-prostatic massage urine or semen. Category IIIB, or Non-Inflammatory Chronic Pelvic Pain Syndrome, demonstrates no significant white blood cells in fluid samples.** These two sub-categories equate to the traditional classifications of non-bacterial prostatitis and prostatodynia, respectively. A new category, **Category IV, or Asymptomatic Inflammatory Prostatitis, is defined as significant white blood cells or bacteria in prostate specimens with no symptoms.**

4. Etiology

The etiology of prostatitis is thought to be multifactorial. Theories are numerous and varied, particularly when attempting to explain Category IIIA and IIIB disease. The primary causes are listed in **Table 2.**

4.1 Microbiology

Given that gram-negative organisms, particularly *Escherichia coli*, are the dominant cause of urinary tract infections, we would expect that these organisms play a significant role in prostatitis. **E. coli is the most commonly identified bacteria in prostate infections, accounting for 65-80% of documented infections.** Additional gram negatives include *Pseudomonas aeruginosa*, *Serratia*, *Klebsiella*, and *Enterobacter*, which combined account for 10-15%. These bacteria may have different patterns of virulence and resistance than those regularly associated with the remaining urinary tract, particularly in regards to the prevalence of Type 1 (mannose-sensitive) fimbria and bacterial P-fimbriae. Gram-positive cocci, specifically Enterococci, account for only 5-10% of documented prostate infections. Anaerobic and Chlamydial infections are controversial as to whether they are a cause of prostatitis or are incidentally found, with multiple studies for and against. It is important to note that **bacteria form aggregates deep in the prostate, making treatment difficult and contributing to recurrent urinary tract infections and the development of Category II prostatitis.** Although tuberculosis is less common in the US, international exposure from various settings may be a rare etiology and should be considered in difficult to treat patients or those with risk factors.

4.2 Host Defense Alterations

Table 2: Etiology of Prostatitis

The etiology of prostatitis is thought to be multifactorial. Theories are numerous and varied, particularly when attempting to explain Category IIIA and IIIB disease. The primary causes may be due to any individual or mixture of:

Microbial

Altered host defense mechanisms

Dysfunctional voiding

Ductal reflux

Immunological

Chemically induced inflammation from toxic substances in the urine

Pelvic floor muscle abnormalities

Neuroendocrine mechanisms

Psychological factors

Interstitial cystitis/painful bladder syndrome

A second proposed cause of prostatitis is alterations in the prostatic host defense. Risk factors that may cause these alterations include **intraprostatic ductal reflux of urine into the prostate, phimosis, which allows bacterial colonization near the urethral meatus, unprotected anal intercourse, indwelling catheters including condom catheters, and transurethral surgery**, particularly in patients who have untreated urinary tract infections. Alterations in prostate secretions are hypothesized to be caused by each of these and include decreases in fructose, citric acid, acid phosphatase, zinc, magnesium, calcium, and prostatic antibacterial factor. Markers of inflammation are increased in the prostatic fluid, including pH, LDH, ceruloplasmin, and complement C3. These alterations are thought to adversely affect the normal anti-bacterial nature of the prostatic secretions. Caution is advised, as it remains unclear whether these alterations are the result of inflammation or its underlying cause.

4.3 Dysfunctional Voiding

Dysfunctional voiding has also been implicated in men with chronic prostatitis, particularly **high-pressure dysfunctional flow. 60% of treatment refractory chronic prostatitis patients in one study demonstrated bladder neck hypertrophy**. Dyssynergic, high pressure voiding is thought to lead to an autonomic overstimulation of the perineal-pelvic neural system with attendant development of a chronic neuropathic pain state. It can also lead to intraprostatic ductal reflux.

4.4 Pelvic Floor Muscle Abnormalities (Myofascial Pelvic Pain)

It is imperative that clinicians perform a thorough exam of the pelvic floor muscles to assess for myofascial tenderness, especially in patients with Category IIIb. Pelvic pain may arise from chronic muscular guarding of the pelvic floor, leading to pelvic floor hypertonicity. Anxiety may further perpetuate this cycle of tension and pain. **Myofascial physical therapy of the pelvic floor muscles has been shown to provide clinical relief in pain**. In addition to physical therapy, perineal extracorporeal shock wave (ESW), percutaneous tibial nerve stimulation (PTNS), and acupuncture are other forms of treatment available for this etiology.

4.5 Intra-prostatic Reflux

Intraprostatic ductal reflux, which causes retrograde propagation of urine and bacteria into the prostate, is thought to be one of the most important mechanisms in the pathogenesis of chronic bacterial and non-bacterial prostatitis. Kirby et al, demonstrated the presence of this reflux by instilling a carbon particle solution into the bladders of men diagnosed with non-bacterial prostatitis.⁹ Carbon particles were subsequently found in the expressed prostatic secretion macrophages and prostatic acini and ductal system of the patients. It has also been noted that prostatic calculi are composed of substances found exclusively in urine, not in prostatic secretions. Pathogenic bacteria are also known to reside in calculi and are felt to provide a source for chronic infections, both urinary and prostatic. As previously stated, increased intra-prostatic pressures can result from inflammation and further contribute to the presence of chronic prostatitis.

4.6 Immunology

The immune system may also bear some responsibility. The prostatic immune system is activated during prostatitis. **Increased IgG and IgA levels are immediately detected following an acute infection. The slow return to normal over 6-12 months after treatment indicates that the prostate remains in an activated state.** PSA levels are also markedly elevated during infection. There is also some evidence for an autoimmune role in chronic prostatitis. The antigen responsible for the activation of the immune system remains unclear, but it may be PSA itself. Interleukin-10 has been demonstrated to be present in high levels in patients with chronic prostatitis. Interleukin-8 is the most common cytokine localized to the semen of men with chronic prostatitis and may also play a role. The exact role of these cytokines is unclear, but they serve as markers that the immune system is activated and remains activated in this disease process.

4.7 Prostate Biopsy and Urethral Instrumentation

Prostatitis is a potential complication after common urologic procedures, such as prostate needle biopsy and cystoscopy. Prostate needle biopsy is more commonly approached via the transrectal approach under ultrasound guidance. The AUA Best Practice Policy Statement on **Urologic Surgery Antimicrobial Prophylaxis** and the AUA White Paper on **The Prevention and Treatment of the More Common Complications Related to Prostate Biopsy Update** recommends prophylactic antibiotics for prostate biopsy (1st line: fluoroquinolone or cephalosporin). The AUA panel concluded that **antimicrobial prophylaxis** is justified for simple cystourethroscopy and urodynamic studies in patients with risk factors (1st line: TMP-SMX or a fluoroquinolone). **Despite prophylaxis to prevent infection, infections from transrectal prostate needle biopsies are on the rise from fluoroquinolone resistance.** If a patient presents with a febrile UTI after prostate biopsy, one should presume fluoroquinolone resistance exists and broad-spectrum intravenous antimicrobial treatment should be commenced.

In summary, prostatitis is a significant worldwide health issue in men and is associated with increasing health spending. **Prostatitis is likely caused by an interrelated cascade of inflammatory, immunologic, neuroendocrine, neuropathic mechanisms that begin with a bacterial initiator.** Apart from bacterial mechanisms for Category I and II acute and chronic bacterial prostatitis, the exact etiology of other chronic prostatitis and pelvic pain syndromes appears multifactorial.

5. Clinical Presentation

5.1 Symptoms

The symptoms of prostatitis are varied but are dominated by **pain, including suprapubic pain, testicular pain, penile and/or urethral pain, difficulty urinating, dysuria, painful ejaculation, perineal pain.** Prostatitis is also associated with other symptoms of infection including fever, nausea, and vomiting. Acute prostatitis typically presents with pain and symptoms of infection, whereas

chronic prostatitis presents primarily with pain. NIH has also developed a Chronic Prostatitis Symptom Index (NIH-CPSI) as an instrument to measure the symptoms and quality of life of patients with chronic prostatitis for research and clinical use.⁴

The NIH-CPSI consists of nine questions that address three domains of chronic prostatitis. **Four questions cover pain focusing on its location, severity, and frequency. Urinary function is covered by two questions, one addressing irritative and the other obstructive symptoms. Quality of life is covered by three questions and assesses the impact of symptoms on daily activities.** The scores are added at the end to provide three domain scores. A sample of the questionnaire can be found in Appendix 2 of the Dr. Litwin article entitled: The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure (**Figure 2**). Chronic Prostatitis Collaborative Research Network.⁴

5.2 Patient Evaluation

NIH-Chronic Prostatitis Symptom Index (NIH-CPSI)

Figure 2: NIH Chronic Prostatitis Symptom Index (NIH-CPSI)

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A detailed history and physical is required. In the history it is important to address the **location of the pain, urinary symptoms, STI history, and any recent instrumentation**. Many men also have sexual dysfunction and new research indicates this may have significant implications regarding quality of life and outcomes of therapy.¹⁰ Associated lower urinary tract symptoms can be evaluated with the **American Urologic Association Symptom Score** and a post void residual if retention is suspected. Once prostatitis is suspected, using the NIH-CPSI form may offer additional information and allow follow up surveys to gage symptom improvement. A growing concept is to use the phenotypic classification of the patient based on primary symptoms from the Urinary, Psychosocial, Organ specific, Infection, Neurologic/systemic, and Tenderness of skeletal muscles (UPOINT)

classification. While the concept continues to be investigational, it has promise to allow categorization for future trials and allow a guided approach to therapeutics.¹¹

A history of tuberculosis exposure or BCG therapy for bladder cancer should be assessed in the medical history, as these can cause a nodular prostate on exam due to granulomatous prostatitis.^{12,13} The physical includes a digital rectal exam, which will often demonstrate a tender, boggy, warm prostate in acute prostatitis and a tender prostate in chronic prostatitis. Examinations should also evaluate the abdomen, external genitalia, and perineum, with attention to evaluating myofascial trigger points or possible musculoskeletal dysfunction of the pelvis and pelvic floor, which may be helpful in determining treatment options. There is no need for expression of prostatic fluid to obtain cultures in acute bacterial prostatitis, as **there is a risk that an aggressive prostate exam may cause sepsis.**

In the evaluation of chronic prostatitis, expression of prostatic fluid is required to accurately define the Category of disease. A genital exam should be included to assess for STI. A careful pelvic exam should be performed to inspect for pelvic floor muscle tenderness and spasm, which can help identify trigger point tenderness. This should be distinguished from prostatic tenderness by palpating the muscles lateral, anterior, and inferior to the gland. **In acute prostatitis, urinalysis and urine culture is all that is required. PSA is not necessary as it will be elevated. In chronic prostatitis, additional tests are necessary.**

5.3 Lower Urinary Tract Evaluation and Culture

The Meares-Stamey “four-glass test” is the gold standard of diagnosis. As its name suggests, it consists of four samples of fluid, which are sent for analysis, primarily to assess for leukocytes and for culture. These four samples help distinguish between urethral, bladder, and prostate infections.

Voided Bladder 1 (VB-1) consists of the first 10cc of voided urine and represents urethral bacteria. **VB-2** is a mid-stream urine collection and represents the bladder urine. A prostatic massage is then performed and **expressed prostatic secretions (EPS)** are collected during the massage (at least four drops should be collected). **VB-3** is the first 10cc of voided urine following prostatic massage and includes any EPS trapped in the urethra. Category II, chronic bacterial prostatitis, is diagnosed if there is a 10-fold increase in bacteria in the expressed prostatic secretions or VB-3 when compared to VB1 or VB2. Category IIIA prostatitis is diagnosed when there is greater than 5-10 WBC per HPF in the EPS or VB3. Category IIIB is diagnosed when there are no bacteria or white blood cells noted.

Although the 4-glass test remains the gold standard for diagnosis, it has been replaced in contemporary practice by a 2-glass test. This 2-glass test consists of a pre-massage mid-stream urine and a post-massage urine collection of at least 10cc.¹⁴ These samples are sent for urinalysis, microscopy, and culture. **Nickel et al. demonstrated that this test had a 91% sensitivity and specificity compared with the traditional Meares-Stamey test.⁸**

5.4 Other Evaluations

The addition of other clinical evaluations is unclear. A wide constellation of urinary symptoms is

associated with chronic prostatitis and chronic pelvic pain syndrome. Chronic lower urinary tract symptoms are often misdiagnosed as chronic prostatitis in young men and urodynamics may help clarify other sources of urinary dysfunction. Transrectal ultrasonography may also be useful in identifying and draining obstructed seminal vesicles, prostatic cysts, and prostate abscesses prostatitis-like symptoms.

Some patients may have had exposure to tuberculosis and this could be a cause of prostatitis as well.

6. Treatment

Treatment options include **antibiotics, alpha-blockers, anti-inflammatories, 5-alpha-reductase inhibitors, physical therapy, prostate massage, frequent ejaculation, and surgery**.

6.1 Antibiotics

Antibiotics are the most commonly prescribed treatment for prostatitis. In the patient with acute bacterial prostatitis, unless the patient has an anatomic abnormality of the urinary tract or develops an abscess, antibiotics are almost always successful. TMP-SMX was the most commonly used antibiotic in the 1970's thru the 1990's. In chronic prostatitis, TMP-SMX has had efficacy rates of 30-50% with treatment courses reaching up to 90 days. **Since the 1990's, fluoroquinolones have almost universally been used as initial and follow-on treatment.** They are more efficacious and require shorter durations of therapy, usually one month, and with 57-77% cure rates. **It has been suggested that antibiotic therapy should only be continued for 4-6 weeks if pretreatment cultures are positive and/or the patient reports positive improvement from treatment.** This is based on multiple studies that report no difference in the symptoms of patients with chronic prostatitis who were treated with additional courses of antibiotic therapy versus placebo. That being said, Magri et al in 2007 observed that 20% of patients who fail an initial course of antibiotic therapy can be salvaged with an additional course of a different antibiotic.¹⁵ This has led to the suggestion that clinicians should not re-use antibiotics if patients fail a therapeutic course. Additionally, antibiotics should be avoided in patients previously treated with antibiotics who have a long duration of symptoms (thought to be considered non-responsive). However, patients that initially presented with a bacterial infection and improved with antibiotics, may benefit from additional antibiotic courses with recurrent symptoms.¹⁶

6.2 Alpha-blockers

An additional therapeutic option is alpha-blockers. Given that the bladder neck and prostate are rich in alpha-adrenergic receptors, it is thought that relaxation via alpha-adrenergic blockade may improve outflow obstruction, thereby improving urinary flow and decreasing intra-prostatic ductal reflux. The results of multiple studies appear mixed as to whether alpha-blocker therapy is efficacious.¹⁷ They may be of most benefit for those men with recent onset disease, and for those not heavily pre-treated or who have been on therapy longer than 6 weeks.¹⁸ However, Nickel et al in 2008 tested this hypothesis and compared patients treated with alfuzosin versus placebo for 12 weeks.^{19,20} All

patients had been diagnosed with chronic prostatitis within 2 years and were alpha-blocker naïve. There was no significant difference in resolution rates. In a more recent study, 4 mg of silodosin relieved symptoms and improved quality of life in men with chronic prostatitis and chronic pelvic pain syndromes.²¹ Ultimately, however, more work needs to be done to further delineate the true role of alpha-blockers for management of acute and chronic prostatitis.

6.3 Anti-inflammatory Medications

Anti-inflammatory medications have also been used to treat chronic prostatitis symptoms. **These include non-steroidal anti-inflammatories, corticosteroids, and immunosuppressive drugs.**¹⁷ Multiple studies point to modest effects in the short term, but they do not appear to lead to resolution and lose their effects over time. A randomized study by Dimitrakov in 2004 showed that high dose methylprednisolone, followed by rapid tapering of the dose, may have more efficacy than placebo even after 12 months, but the side effect profile was deemed to be moderately severe and thus limits its use clinically.

6.4 Hormonal Agents

5-alpha-reductase inhibitors have also been addressed as a potential treatment for prostatitis. Multiple studies have shown reductions in prostatitis and BPH symptom scores. In a recent study, long-term dutasteride therapy resulted in improvement in prostatitis related symptoms in older men with an increased prostate specific antigen and enlarged prostates.²² In a clinical trial use of mepartircin, a compound that reduces estrogen levels in the prostate, resulted in a significant clinical improvement measured by the NIH-CPSI after a 2 month course (40 mg 4 times per day) vs. placebo. Currently hormonal agents cannot be recommended as first line treatment.

6.5 Physical Therapy, Prostate Massage, Phytotherapies, Combinations, and Alternative Medicine

For most of the 20th century the primary form of therapy for chronic prostatitis was repetitive prostate massage. Traditionally, treatment consisted of a 10-minute prostate exam 3 times per week.²³ This was supplanted by antibiotic therapy. It is thought that its benefits arise from draining occluded prostatic ducts and improving circulation and antibiotic penetration, however this explanation is controversial. Uncontrolled trials indicate there may be some improvement in one to two thirds of patients treated with prostatic massage, but additional trials have not shown any benefit. **Physical therapy** has been shown to provide clinical relief in patients with chronic prostatitis/chronic pelvic pain syndrome.^{24-25,26} The reason for myofascial pain can be multi-factorial and duration of therapy appears to predict treatment where longer duration has a better response.²⁷ Patients should be referred to specialists in pelvic floor physical therapy, as clinical experience in delivery of therapy methods correlates with better patient outcomes.²⁸ A recent meta-analysis showed a variety of treatments including physical therapy, myofascial trigger point release, biofeedback, and cognitive behavioral treatment can provide clinically meaningful improvement of CPSI score.²⁹ Recent studies reveal that (**PTNS, perineal ESW and acupuncture show clinical benefit.**³⁰ A single trial of PTNS

demonstrated at least a 6-point reduction in overall NIH-CPSI score.³¹ A randomized trial showed clinically meaningful and long-lasting benefits of acupuncture when compared to sham.²⁹ As data continues to emerge and show the effectiveness of physical therapy and acupuncture, these treatments should be considered prior to medications.³²

In a randomized trial the efficacy of quercetin, a bioflavanoid with antioxidant properties, was tested against a placebo and found to have significant symptom relief over the 4 week period. A single trial of PTNS demonstrated at least a 6-point reduction in overall NIH-CPSI score.³¹

Several combinations have also been evaluated. In particular alpha blockers have been combined with anti-inflammatories with clinical outcomes being superior to a placebo group. In another meta-analysis, Cohen et al identified that triple therapy comprised of doxazosin + ibuprofen + thiocolchicoside (DIT) resulted in a clinically and statistically significant reduction in NIH-CPSI total score.²⁴

Some refractory patients may be diagnosed with chronic prostatitis/pelvic pain syndrome. This clinical scenario may be frustrating for patients and physicians alike and will likely require a multi-modal approach. For example, stress may bring about flares where the patient has an increase in symptoms. In addition to repeating physical therapy and/or alternative medicine treatments, stress reduction management and potentially counseling may improve the patient's approach to stressful situations.²⁷

Videos

Prostatitis

Presentations

Prostatitis Presentation 1

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The difficulty in treating prostatitis is that patients may present with a variety of complaints. One symptom may be dominant and may or may not be related to infection. The UPOINT phenotypic classification system may be a way to help strategize treatment plans and further clinical trials based on the their phenotype of prostatitis. I found the diagrams in this review to be very helpful in the office.

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