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Prostate Gland Infections and Inflammation

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Dedication

Aos meus pais e à minha irmã, por me motivarem a seguir os meus sonhos e me ajudarem sempre a concretizá-los, pela única preocupação deles ser a minha felicidade, pela educação e valores que me transmitiram.

"The path from dreams to success does exist. May you have the vision to find it, the courage to get on to it, and the perseverance to follow it."

Kalpana Chawla

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Resumo

A prostatite é a terceira doença do trato urinário mais comum no sexo masculino depois do cancro da próstata e da hipertrofia benigna da próstata e representa 25% de todas as intercorrências urológicas. A alta incidência entre a população masculina torna a prostatite num problema de saúde sério que todos os médicos devem ter em atenção. Pacientes com prostatite normalmente queixam-se de disúria, incontinência ou hesitação e urgência miccional. Os sintomas urinários costumam estar associados a urina turva ou com sangue e dor (hipogastro, região inguinal e períneo). Em alguns casos, os pacientes apresentam síndrome gripal. O espectro de apresentação é dividido em quatro categorias distintas (prostatite bacteriana aguda, prostatite bacteriana crónica, síndrome de dor pélvica crónica e prostatite assintomática) que combinam sintomas e etiologia. Apesar da sua elevada incidência clínica, não há tratamento padrão para uma abordagem empírica. Infelizmente, o prognóstico é reservado e a abordagem futura ambiciona caracterizar fenotipicamente esta doença de maneira a fornecer o melhor tratamento ao paciente.

É necessário alertar para um correto diagnóstico de prostatite e subsequente investigação de maneira a identificar novas estratégias de tratamento e eventual prevenção em grupos de alto risco. Deste modo, nesta revisão, pretende-se fazer uma integração de conhecimentos atualizados sobre o diagnóstico e abordagem terapêutica.

Palavras-chave

Prostatitis; prostate gland infections; prostate gland inflammation; prostatitis treatment; prostatitis classification

Resumo Alargado

A prostatite é a terceira doença do trato urinário mais comum no sexo masculino depois do cancro da próstata e da hipertrofia benigna da próstata. Esta condição inflamatória afeta todas as idades, tendo maior prevalência nos países nórdicos. Enquanto a prostatite aguda é mais comum em jovens, a prostatite crónica está associada a idades mais avançadas.

De acordo com o *National Institutes of Health*, a prostatite é classificada em quarto categorias como bacteriana aguda (I), bacteriana crónica (II), crónica ou síndrome de dor pélvica crónica (IIIa) ou não inflamatória (IIIb) e inflamação assintomática (IV).

A bacteriana aguda é responsável por 10 % de todos os casos de prostatite e a bacteriana crónica varia entre 5-10 %. Esta última é diagnosticada quando há culturas positivas nas secreções prostáticas durante mais de 3 meses. Os sintomas desta patologia são semelhantes aos sintomas do trato urinário baixo tais como frequência e urgência miccionais e disúria. Podem ser acompanhados por sintomas de gripe. A síndrome de dor pélvica crónica é a categoria mais frequente e a que mais afeta a qualidade de vida e tem uma duração mínima de 3 meses documentada nos últimos 6 meses. Tem sintomas semelhantes à prostatite bacteriana crónica e pode estar incluída dor da região suprapúbica. A inflamação assintomática é a presença de células inflamatórias em avaliação oportunista em pacientes sem sintomas.

A etiologia da prostatite bacteriana aguda e bacteriana crónica é muito semelhante sendo causadas maioritariamente por *Escherichia coli*. Quanto à síndrome de dor pélvica crónica, a etiologia não é clara. Na inflamação assintomática, alguns estilos de vida podem ser fatores de risco.

A maior parte das prostatites bacterianas agudas são causadas por infeções uretrais ascendentes e resultam provavelmente de refluxo de urina infetada nos ductos ejaculatórios e prostáticos (refluxo urinário intraprostático). Isto pode acontecer após relações sexuais, biópsia prostática transretal ou manipulações transuretrais. A infeção é provocada pela entrada direta do microorganismo e libertação de endotoxinas na próstata criando assim uma resposta inflamatória. Se esta resposta não for controlada a imunidade pode ficar reduzida. A patogénese da síndrome de dor pélvica crónica apresenta várias hipóteses como defeito da integridade e função do urotélio, infeções das criptas, autoimunidade, desregulação endócrina, espasmo do músculo do assoalho pélvico ou sensibilidade, disfunção miccional, sensibilização periférica e central e neuroplasticidade, assim como condições psicossociais.

Pela semelhança de sintomas nas diversas patologias urológicas, é necessário diferenciar a prostatite da hipertrofia benigna da próstata, cistite, diverticulite, epididimite, orquite, proctite e carcinoma da próstata de maneira a fornecer o tratamento correto ao paciente.

O diagnóstico da síndrome de dor pélvica crónica é feito com base no Índex dos Sintomas de Prostatite Crónica desenvolvido pelo *National Institutes of Health* (NIH-CPSI) e pelo UPOINT. Também se pode recorrer a testes laboratórios como análises à urina e sémen e testes imagiológicos como a tomografia computorizada sem contraste e a ressonância magnética pélvica.

É importante alertar para um correto diagnóstico de prostatite e subsequente investigação de maneira a identificar novas estratégias de tratamento e eventual prevenção a grupos de alto risco.

Quanto ao tratamento pode optar-se por antibioterapia e medidas de suporte para a prostatite bacteriana aguda e crónica. Os bloqueadores-alfa também parecem ter um papel importante no alívio dos sintomas. A terapêutica para a síndrome de dor pélvica crónica tem sido alvo de investigação exaustiva sendo utilizadas terapias que parecem ter alguns benefícios na sintomatologia, nomeadamente produtos naturais (*Calendula officinalis* Linn., *Curcuma longa* e extrato de pólen), antidepressivos, bloqueadores-alfa, toxina botulínica, ultra-som pulsátil de baixa intensidade e prostatectomia.

Deste modo, nesta revisão, pretende-se fazer uma integração de conhecimentos atualizados sobre o diagnóstico e abordagem terapêutica.

Abstract

Prostatitis is the third most common urinary tract disease in men after prostate cancer and benign prostatic hypertrophy (BPH) and represents 25% of all urological office visits. The high frequency amongst male population makes prostatitis a serious health problem that physicians in general should be aware of. Prostatitis patients usually complain of dysuria, dribbling or hesitancy and urgency. Urinary symptoms are usually combined with cloudy or even bloody urine and pain (lower abdomen, groin and perineum). In some cases patients present with flu-like symptoms and signs. The different spectrum of presentation is currently grouped in four distinct categories (acute bacterial prostatitis, chronic bacterial prostatitis, chronic pelvic pain syndrome and asymptomatic) that combine symptoms and etiology. Despite the current knowledge about this highly frequent clinical entity there's no gold standard therapy which often leads to an empiric approach. Unfortunately, the clinical outcomes are poor and future treatments aim to phenotypically characterize this entity and provide patients with best treatment possible.

There is a clear need for awareness to properly diagnose prostatitis patients and further research is required to identify potential new strategies for treatment and eventual chemoprevention in high-risk subgroup of patients. This review aims to incorporate updated knowledge about diagnostics and therapy.

Keywords

Prostatitis; prostate gland infections; prostate gland inflammation; prostatitis treatment; prostatitis classification

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List of Abbreviations

ABP	Acute bacterial prostatitis
BoNT-A	Botulinum neurotoxin type A
BPH	Benign prostatic hypertrophy
CBP	Chronic bacterial prostatitis
CPPS	Chronic pelvic pain syndrome
CT	Computer tomography
EPS	Expressed prostate secretions
GP	Granulomatous prostatitis
ICC	Interstitial cells of Cajal
MRI	Magnetic resonance imaging
NB	Nanobacteria
NIH-CPSI	National Institutes of Health Chronic Prostatitis Symptom Index
NSAIDs	Nonsteroidal anti-inflammatory drugs
PCa	Prostate Cancer
PCR	Polymerase chain reaction
QoL	Quality of life
US	Ultrasound

Introduction

Prostatitis is the third most common urinary tract disease in men after prostate cancer (PCa) and benign prostatic hypertrophy (BPH) and represents 25% of all urological office visits. The high frequency amongst male population makes prostatitis a serious health problem that physicians in general should be aware of. Prostatitis patients usually complain with dysuria, dribbling or hesitancy and urgency. Urinary symptoms are usually combined with cloudy or even bloody urine and pain (lower abdomen, groin and perineum). In some cases, patients present with flu-like symptoms and signs. The different spectrum of presentation is currently grouped in four distinct categories (acute bacterial prostatitis, chronic bacterial prostatitis, chronic pelvic pain syndrome and asymptomatic) that combine symptoms and etiology. (1)

Methodology

For this dissertation, I searched for scientific articles based on PubMed's data using "prostatitis"; "prostate gland infections"; "prostate gland inflammation"; "prostatitis treatment"; "prostatitis classification" as keywords. The relevant references present in the selected articles were also used. There was a preference in the most recent articles about this theme and with similar goals as this monograph. The research was concluded in November, 2017.

The articles were organized by this dissertation's structure according to its content: definition and epidemiology, prostatitis classification, etiology and pathogenesis, clinical presentation, diagnosis and treatment.

Chapter 1: Definition and Epidemiology

Prostatitis is an inflammatory condition of the prostate (Figure 1) that affects men of all ages with an estimated prevalence of 2-16%, whereas in Nordic areas the prevalence is higher. Various studies found no racial differences in prevalence. It's estimated that prostatitis is one of the most common illnesses in men aged over 50 years and may affect up to 50% of men in their lifetime. Prevalence estimates of symptomatic prostatitis range between 9 and 12% in men between 20 and 79 years of age. The symptoms are related to lower urinary tract such as frequency, being the most common with a prevalence of 80%, dysuria with 45% and pain in 46-54%. Acute prostatitis makes up to <1% of all prostatitis cases and the most common type of prostatitis — asymptomatic (NIH Type IV) — is not fully studied in prevalence surveys. Acute prostatitis (Type I) is more common in younger men, whereas chronic prostatitis (Types II, III and IV) is associated with increasing age, Type III being the most common presentation in men under 50 years. (1–5)

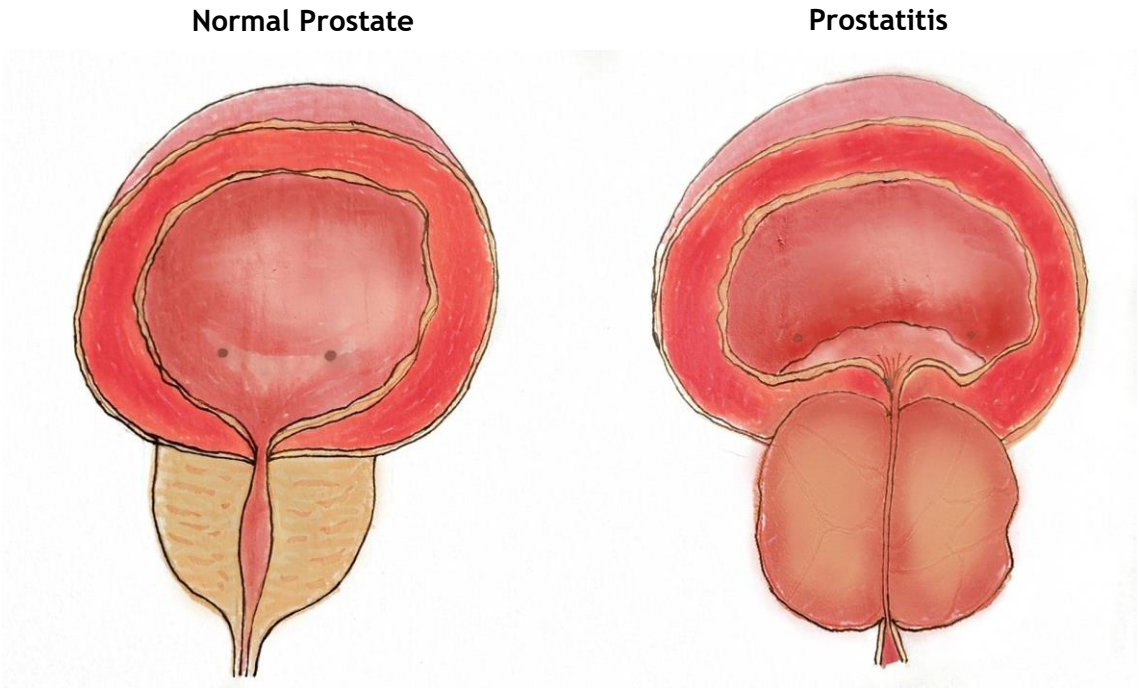

Figure 1. Ilustration of a normal prostate and prostatitis

Chapter 2: Prostatitis Classification

Prostatitis is classified into four categories by the National Institutes of Health: acute (I) or chronic (II) bacterial prostatitis, chronic prostatitis (CP)/chronic pelvic pain syndrome (CPPS) (III), inflammatory (IIIa) or noninflammatory (IIIb), and asymptomatic inflammation of the prostate gland (IV). Acute and chronic bacterial prostatitis are characterized by uropathogenic infections whose causative pathogens can be detected in semen [in expressed prostate secretions (EPS)], or urine (after prostatic massage) and by responding well to antibiotic therapy. CP/CPPS or NIH type III prostatitis is a complex disease, with symptoms that are difficult to assess as well as to treat effectively. (6,7)

Section 2.1: Acute bacterial prostatitis

ABP (NIH type I) comprises up to 10% of all prostatitis diagnoses, and its incidence peaks in individuals 20 to 40 years of age and older than 70 years. It's an acute inflammation of the prostate gland accompanied by the presence of pelvic pain and urinary tract symptoms. Patients with acute bacterial prostatitis can be diagnosed by a thorough anamnesis and physical examination. (8–10)

Section 2.2: Chronic bacterial prostatitis

CBP (NIH type II) accounts for 5 to 10% of all prostatitis cases. It's characterized by recurrent infections with positive cultures of EPS in a period longer than 3 months. CBP is frequently asymptomatic until the patient has a urinary tract infection accompanied with suprapubic, lower back or perineal pain. These patients usually present mild urgency, increased frequency and dysuria. Characteristically, patients with CBP are asymptomatic between acute infective episodes. (11,12)

Section 2.3: Chronic pelvic pain syndrome

CPPS (NIH type III) is the most frequent category that significantly worsens the quality of life (QoL). CPPS etiology is heterogeneous and generally unknown. It's characterized by pelvic or perineal pain in the absence of pathogenic bacteria (in EPS) lasting at least 3 months in the last 6 month period. It's often associated with irritative symptoms such as urgency, frequency, nocturia and urge incontinence and obstructive or voiding symptoms such as hesitancy, poor interrupted flow, straining to urinate and overflow incontinence. Symptoms can also include pain in the suprapubic region, lower back, penis, testes, or scrotum and painful ejaculation. CPPS may be inflammatory (IIIa) (leukocytes seen in semen, prostatic fluid, or urine after prostatic massage) or non-inflammatory (IIIb) (no leukocytes seen). (7,12)

Section 2.4: Asymptomatic prostatitis

AP (NIH type IV) is responsible for approximately 10% of all prostatitis cases. Its diagnosis is based in the identification of inflammatory cells in a prostate biopsy or noted in semen during opportunistic urological evaluation in a male with no symptoms of prostate inflammation. (11)

Chapter 3: Etiology

Section 3.1: Acute bacterial prostatitis

This type of prostatitis is caused by a multiplicity of different pathogens and also depends on the host's clinical morbidities. ABP is frequently caused by *Escherichia coli*, followed by *Pseudomonas aeruginosa*, and *Klebsiella*, *Enterococcus*, *Enterobacter*, *Proteus*, and *Serratia* species. In sexually active men, *Neisseria gonorrhoeae* and *Chlamydia trachomatis* should also be considered. However, immunocompromised men are more likely to have uncommon causes for prostatitis, such as *Salmonella*, *Candida*, and *Cryptococcus* species. Transurethral manipulations (catheters, transurethral resection) are more likely to be associated with *Pseudomonas* species, which have higher rates of resistance to cephalosporins and carbapenems. Transrectal prostate biopsies can cause infections which have been reduced to between 0.67% and 2.10% by prophylactic antibiotics. However, the incidence of prostatitis has increased mainly due to fluoroquinolone-resistant bacteria and extended spectrum beta-lactamase – producing *E. coli*. (13)

Section 3.2: Chronic bacterial prostatitis

Organisms commonly implicated in bacterial prostatitis include *Escherichia coli*, other gram-negative enterobacteriaceae, occasionally *Pseudomonas* species, and, rarely, gram-positive enterococci. CBP might be associated with *H. pylori* infection, therefore, treatment of *H. pylori* infection could be effective for chronic prostatitis treatment. As for ABP, factors for CBP include urethral catheterization or instrumentation, dysfunctional voiding and unprotected anal intercourse. (12,14)

Section 3.3: Chronic pelvic pain syndrome

The cause of CPPS is unclear, although it has been suggested that it may be caused by undocumented infections with *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Trichomonas vaginalis*, viruses, *Candida* (in immunocompromised patients) and parasites have also been implicated, albeit rarely. Non-infectious factors might also be involved, including inflammation, autoimmunity, hormonal imbalances, pelvic floor tension myalgia, intraprostatic urinary reflux, and psychological disturbances. In susceptible men, infectious urethritis or prostatitis could be the initial stimulus for chronic inflammation, although chronic inflammation and pain may persist after the infection has been cleared possibly by an autoimmune (in the presence of seminal plasma antigens), and/or neurogenic mechanism. Infection could be the triggering factor instead of the cause of the pathology. An unresolved chronic inflammation may potentiate tissue injury leading to pelvic floor

dysfunction (pelvic floor muscles spasms or tenderness) and central sensitization resulting in chronic pelvic pain. (6,12,15)

Section 3.4: Asymptomatic prostatitis

Age, smoking, alcohol consumption, and lower levels of education have been reported as possible risk factors for NIH-IV prostatitis. (15)

Chapter 4: Pathogenesis

Most cases of acute bacterial prostatitis are caused by ascending urethral infections, and probably results from the reflux of infected urine into the ejaculatory and prostatic ducts that empty into the posterior urethra (intraprostatic urinary reflux). Ascending urethral infection may follow sexual intercourse or inoculation after transrectal prostate biopsy and transurethral manipulations (e.g., catheterization and cystoscopy). This is facilitated by numerous risk factors. Occasionally, direct or lymphatic spread from the rectum or hematogenous spread via bacterial sepsis can cause acute bacterial prostatitis. Overall, community-acquired infections are three times more common than nosocomial infections. In community-acquired infections an organism may cause prostatitis by entering the prostate directly or penetrating the organs and release endotoxins (the lipopolysaccharide components of the outer membrane of Gram-negative bacteria) which are the primary initiator of Gram-negative bacteria infection. The local release of endotoxins stimulates the inflammatory response. If the infection is not brought under control, endotoxins increase secretion of cytokines and interleukins that will circulate in the bloodstream into the prostate causing inflammation or reduced body's immunity during the infection, affecting the prostate. (13,14,16,17)

Several hypotheses have been proposed to explain CP/CPPS pathogenesis including defective urothelial integrity and function, cryptic infections, autoimmunity, endocrine imbalances, pelvic floor muscle spasm or tenderness, voiding dysfunction, peripheral and central sensitization and neuroplasticity, and psychosocial conditions. (6)

Chronic pain may start after chronic peripheral inflammation or nerve injury and remain subsequent to tissue healing, becoming harmful. This results in the release of neurotransmitters, fragments of the complement system, neuropathic factors, cytokines, and chemokines in central and peripheral nervous system. Inflammatory and neuropathic pain can cause peripheral and central sensitization that can lead to allodynia, hyperalgesia, and spontaneous pain which play a central role in CP/CPPS. Chronic pelvic pain includes a combination of visceral and referred somatic pain and also the involvement of central sensitization in the spinal cord and brain, especially on the dorsal horn of the spinal cord. These changes support an ongoing reorganization of brain circuitry comparable to other chronic pain morbidities such as musculoskeletal and neuropathic pain, chronic low back pain and knee osteoarthritis. These findings suggest that the chronic presence of pelvic pain leaves specific brain neural imprints that persist for years. Alternatively, some of these neural abnormalities may predispose for CP/CPPS. (6)

Central sensitization is caused by chemical and anatomical changes leading to hyperexcitability in the dorsal horn cells from persistent afferent C fiber bombardment by

painful stimuli. Chronic pain is induced and maintained by mediators released by immune cells (macrophages, lymphocytes, and mast cells), neurons and glial cells that trigger peripheral and central sensitization, that, when activated, secrete cytokines that recruit more leukocytes augmenting tissue cell infiltration and enhancing prostate inflammation and chronic pelvic pain development. It has been proposed that neurogenic processes, autoimmune injury and mast cells may contribute to inflammation and trigger pain development in CP/CPPS in males. (6)

Bartoletti and colleagues found biofilm-producing bacteria were commonly isolated and had a significant negative effect on clinical response to antibiotic treatment. The presence of bacterial biofilm could be the *primum movens* of the flogosis process in the prostatic tissue. Interstitial cells of Cajal (ICC) continue this process. CP can also occur without any evidence of bacterial prostatic infection. Many investigators have proposed neuromuscular etiology in inflammatory and non-inflammatory prostatitis. Chronic pain associated with these syndromes is definitively of neuropathic type. According to one hypothesis, non-inflammatory prostatitis can emerge as a form of reflex sympathetic dystrophy. Symptoms of all patients with non-inflammatory prostatitis closely resemble to those with cases of reflex sympathetic dystrophy. This spontaneous contractile activity enhances with entry of calcium and that these short-acting spontaneous depolarizations trigger one or more nifedipine sensitive calcium voltage increments. These slow-waves have myogenic origins and they are not affected by blockers of conduction of action potential, sympathetic, parasympathetic, sensorial and synaptic nerve impulse transmission or prostaglandin synthetase inhibitors. In the human prostate, conduction networks of c-kit positive cells have been located between glandular and stromal muscle layers of prostate acini and in the stromal smooth muscle layer so it may be responsible for the transport of glandular secretion into urethra. In patients with diseases that progress with decreased intestinal motility including diabetes, chronic or inflammatory bowel diseases, and in those with defective interstitial cell network, there is higher probability of development of BPH due to ICC-like cell dysfunction. Absence of ICCs has been associated with relative obstruction and mechanism of reflux of the microbial material from its reservoir back into prostate gland. This can happen also because mast cells increase the regeneration capacity of ICC which is perceived as a tumoral activity by immune system which leads the related cells to death via cytokine release and autophagy. These events justify the prostatic ductal contractility disorder that occurs. Therefore, the medical treatment of prostatitis with mast cell degranulation inhibitors (such as pentosan polysulfate) before total ICC apoptosis occurs could achieve permanent treatment response. (6,18,19)

The inflammatory/immune factors such as IgE, C3, C4, CRP, ASO, and RF were mainly associated with NIH-IIIb prostatitis, rather than NIH-IIIa and NIH-IV and contribute to the pain experienced in CP/CPPS. Also, hormonal elements (osteocalcin, testosterone, FSH, and

insulin), tumor-related proteins (CEA and PSA), and nutrition markers (FERR) might participate in the systematic low-grade inflammation recruiting the leukocytes to EPS. (15)

Osteocalcin may stimulate testosterone biosynthesis in Leydig cells of the testis, and therefore affect male fertility. Although there is no direct evidence of an association of osteocalcin with CP/CPPS and type IV prostatitis, Woodworth and colleagues identified unique microstructural changes in the brain of a patient with CPPS. This suggests that osteocalcin might be a protective factor, especially in the psychological aspect. It is possible that osteocalcin functions as a neuropeptide in the brain of CP/CPPS (NIH-III prostatitis) patients. On the other hand, NIH-IV prostatitis is usually asymptomatic accompanied by persistent leukocytosis. Unlike NIH-III prostatitis, recent studies suggested that the inflammatory process may play a role in the pathogenesis. Moreover, previous studies identified osteocalcin as a protective factor against low-grade inflammation. Therefore, it seems plausible that osteocalcin could influence the inflammatory process of NIH-IV prostatitis. (15)

Chapter 5: Clinical Presentation

Section 5.1: Acute bacterial prostatitis

Acute bacterial prostatitis often presents with acute onset of irritative (e.g., dysuria, urinary frequency, urinary urgency) or obstructive (e.g., hesitancy, incomplete voiding, straining to urinate, weak stream) voiding symptoms. Painful ejaculation, hematospermia, and painful defecation may be present as well. Systemic symptoms, such as fever, nausea, emesis, and malaise, commonly occur, and their presence should determine if patients meet clinical criteria for sepsis. The physical examination should include an abdominal examination to detect a distended bladder and costovertebral angle tenderness, a genital examination and a digital rectal examination. In digital rectal examination, a vigorous prostatic massage can induce bacteremia, and subsequently, sepsis. The prostate will often be tender, enlarged, or boggy. If there is concern for obstructed voiding, postvoid residual urine volumes should be measured using ultrasonography (US). Several conditions present with similar symptoms and must be differentiated from acute bacterial prostatitis (Table 1). (13)

Table 1. Differential diagnosis of acute bacterial prostatitis. (13)

Diagnosis	Distinguishing characteristics
Benign prostatic hypertrophy	Obstructive voiding symptoms; enlarged, nontender prostate; negative urine culture
Chronic bacterial prostatitis	Recurring prostatitis symptoms for at least three months; positive urine culture with each episode
Chronic pelvic pain syndrome	Pain attributed to the prostate with no demonstrable evidence of infection
Cystitis	Irritative voiding symptoms; normal prostate examination
Diverticulitis	Left lower-quadrant abdominal pain; acute change in bowel habits; history of diverticulitis; tenderness to palpation localized to the left lower abdominal quadrant
Epididymitis	Irritative voiding symptoms; tenderness to palpation on affected epididymis
Orchitis	Swelling, pain, and/or tenderness to palpation in one or both testicles
Proctitis	Tenesmus; rectal bleeding; feeling of rectal fullness; passage of mucus through the rectum
Prostate cancer	Presence of constitutional symptoms; presence of nodules on prostate examination

Section 5.2: Chronic bacterial prostatitis

Symptoms such as suprapubic, lower back, or perineal pain, with or without mild urgency and increased frequency of urination and dysuria may be intermittent during a period of weeks and months. This makes it hard to detect the bacteria responsible for the inflammation. Some bacteria cannot be identified because of difficult growth when cultured. There is a possibility that bacteria may still survive in the prostate and symptoms may often recur, even with treatment. Clinical relapses were mainly caused by microorganisms other than those causing the initial infection. Pathogens most commonly associated with clinical relapses were *Enterococcus faecalis* and *E. coli*. The mean time interval between CBP relapses was 13.9 months (range, 2 – 56 months). (1,12,20)

Section 5.3: Chronic pelvic pain syndrome

Chronic pelvic pain syndrome (CPPS) is characterized by pelvic or perineal pain without evidence of urinary tract infection, with accompanying symptoms such as dysuria, arthralgia, depression, and hysteria. Recent studies suggest that CP/CPPS is associated with many systemic syndromes, including diabetes, prospermia, fibromyalgia, cardiovascular disease, stress, depression, anxiety, irritable bowel syndrome, and male reproductive dysfunction. All these complaints lead to patient frustration, diminished QoL as well as impairment of intimate relationships. In terms of pain and diminished QoL, CP/CPPS patients may be compared with patients who have suffered myocardial infarction or bear Crohn disease. (6,15)

Section 5.4: Asymptomatic prostatitis

Asymptomatic prostatitis has no clinical features, and is only evident with the presence of inflammatory cells in EPS, or histological prostate biopsy specimens. (6,15)

Chapter 6: Diagnosis

To structure the assessment of CP/CPPS patients, the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) was developed in 1999. The NIH-CPSI is a formally developed and psychometrically validated instrument for the evaluation of CP/CPPS symptoms. It contains 13 items that are scored in three discrete domains: pain [total of items 1–4], urinary symptoms [total of items 5 and 6], and the impact on QoL [total of items 7–9]. This assessment is a reliable, convenient, self-administered index that is widely used across scientific research and clinical studies. It is a comprehensive and brief measure that quantifies the qualitative experience of men with this condition. It can be take in less than 5 minutes and is well understood by patients (Figure 2). (21,22)

Biomarkers that would allow us to classify patients in a way that could guide therapy for chronic pelvic pain (CPPS and interstitial cystitis) haven't been validated. However, currently is being investigated if chemokines MCP-1 and MIP-1alpha and mast cell tryptase could be used as biomarkers for CPPS in humans and correlate their levels with NIH-CPSI. In response to this situation, it was proposed a 6-point clinical phenotyping system to classify patients and to choose the appropriate therapy. The clinical parameters comprise urinary symptoms, psychosocial dysfunction, organ-specific findings, infection, neurologic/systemic, and muscle tenderness (UPOINT - Table 2). Each parameter has been clinically defined, linked to specific mechanisms of symptom production or propagation, and associated with specific therapy. (23,24)

Using UPOINT or a different approach will require a look beyond the urinary system to the whole patient. It might require multidisciplinary approach, with the urologist orchestrating this process. The urologist will need to consider the patient in a holistic way and try to find aspects of the syndrome that are amenable to treatment. Musculoskeletal tenderness might require exercise and physical therapy, depression or catastrophizing might require or psychotropic medications, and chronic pain might require long-term management. The treatment of one condition might benefit one another. (24)

NIH-Chronic Prostatitis Symptom Index (NIH-CPSI)

Pain or Discomfort

1. In the last week, have you experienced any pain or discomfort in the following areas?

	Yes	No
a. Area between rectum and testicles (perineum)	❑1	❑0
b. Testicles	❑1	❑0
c. Tip of the penis (not related to urination)	❑1	❑0
d. Below your waist, in your pubic or bladder area	❑1	❑0

2. In the last week, have you experienced:

	Yes	No
a. Pain or burning during urination?	❑1	❑0
b. Pain or discomfort during or after sexual climax (ejaculation)?	❑1	❑0

3. How often have you had pain or discomfort in any of these areas over the last week?

- ❑0 Never
- ❑1 Rarely
- ❑2 Sometimes
- ❑3 Often
- ❑4 Usually
- ❑5 Always

4. Which number best describes your AVERAGE pain or discomfort on the days that you had it, over the last week?

❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
0	1	2	3	4	5	6	7	8	9	10
NO PAIN										PAIN AS BAD AS YOU CAN IMAGINE

Urination

5. How often have you had a sensation of not emptying your bladder completely after you finished urinating. over the last week?

- ❑0 Not at all
- ❑1 Less than 1 time in 5
- ❑2 Less than half the time
- ❑3 About half the time
- ❑4 More than half the time
- ❑5 Almost always

6. How often have you had to urinate again less than two hours after you finished urinating, over the last week?

- ❑0 Not at all
- ❑1 Less than 1 time in 5
- ❑2 Less than half the time
- ❑3 About half the time
- ❑4 More than half the time
- ❑5 Almost always

Impact of Symptoms

7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?

- ❑0 None
- ❑1 Only a little
- ❑2 Some
- ❑3 A lot

8. How much did you think about your symptoms, over the last week?

- ❑0 None
- ❑1 Only a little
- ❑2 Some
- ❑3 A lot

Quality of Life

9. If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?

- ❑0 Delighted
- ❑1 Pleased
- ❑2 Mostly satisfied
- ❑3 Mixed (about equally satisfied and dissatisfied)
- ❑4 Mostly dissatisfied
- ❑5 Unhappy
- ❑6 Terrible

Scoring the NIH-Chronic Prostatitis Symptom Index Domains

Pain: Total of items 1a, 1b, 1c, 1d, 2a, 2b, 3, and 4 = _____

Urinary Symptoms: Total of items 5 and 6 = _____

Quality of Life Impact: Total of items 7, 8, and 9 = _____

Figure 2. NIH-CPSI

Table 2. Domains of UPOINT classification and typical inclusion criteria for each. (24)

Urinary
Chronic Prostatitis Symptom Index urinary score >4
Patient complaint of bothersome urgency, frequency, or nocturia
Postvoid residual urine volume >100 mL
Psychosocial
Clinical depression
Evidence of catastrophizing (helplessness, hopelessness)
Organ specific
Specific prostate tenderness
Leukocytosis in prostatic fluid
Hematospermia
Extensive prostatic calcification
Infection
Excluding patients with clinical category I or II prostatitis
Gram-negative bacilli or Enterococcus localized to prostatic fluid
Neurologic/ systemic conditions
Pain beyond abdomen and pelvis
Irritable bowel syndrome Fibromyalgia
Fibromyalgia
Chronic fatigue syndrome
Tenderness of skeletal muscles
Palpable muscle spasm or trigger points in abdomen and pelvic floor

Section 6.1: Diagnostic tests in suspected prostatitis

Clinical presentation and laboratory tests are used to differentiate and categorize the four types of prostatitis. When acute bacterial prostatitis is suspected, midstream urine is examined for bacterial culture before administering antibiotics. Same for blood cultures in patients with a body temperature greater than 101.1°F (38.4°C), a possible hematogenous source of infection (e.g., endocarditis with *Staphylococcus aureus*), complicated infections (e.g., sepsis), or immunocompromised. Although blood and urine cultures can aid in diagnosis and management, up to 35% of urine cultures in patients with acute prostatitis will fail to grow an organism. In addition, C-reactive protein, procalcitonin, and prostate-specific antigen (PSA) should be evaluated. (11)

Several studies have indicated that pro-inflammatory cytokines (IL-8, IL-6) are associated with seminal leukocytes (Eggert-Kruse et al., 2001; Kopa et al., 2005) and may serve as additional inflammatory markers in the diagnostic workup. IL-6 is a cytokine that plays a key role in acute inflammation but also dictates the transition from acute to chronic inflammation (Gabay, 2006). (4)

Prostate massage could be harmful and should not be performed. In the diagnosis of chronic prostatitis or chronic pelvic pain syndrome, several special diagnostic tests should be performed. (11,13)

A study by Kim and colleagues has reported isolation of nanobacteria DNA (NB - cytotoxic, sterile-filterable, gram-negative, atypical bacteria) in EPS of patients with type-III prostatitis and the therapy designed to eliminate NB resulted in significant improvement in the symptoms of type-III prostatitis in most men. It is difficult to detect NB by ordinary methods, but these bacteria can be observed by immunologic testing or transmission electron microscopy (TEM). However, TEM and immunologic methods are often expensive or time consuming. Polymerase chain reaction (PCR) analysis has a higher sensitivity than indirect immunofluorescence staining (IIFS) for NB detection in type-III prostatitis. PCR can detect nanobacterial infection equally well as culture and subsequent IIFS and offers significant advantages for the rapid, simple, and economical detection of NB in EPSs from patients with type-III prostatitis. (25–27)

Section 6.2: Urine and semen examination

A first-void urine sample and semen are examined with microscopy and quantitative culture. Budía and colleagues showed that the sensitivity of semen samples was higher than EPS samples for the diagnostic of chronic bacterial prostatitis. For Gram-negative organisms, the

sensitivity of semen cultures was 97% versus 82.4% for EPS cultures, and for Gram-positive organisms the sensitivity of semen samples was 100% versus 16.1% for EPS. (11)

Section 6.3: Imaging

Imaging studies are usually unnecessary during the initial evaluation but may help when the diagnosis remains unclear or when patients do not respond to antibiotic therapy. Patients who remain febrile after 36 hours or whose symptoms do not improve with antibiotics should undergo transrectal US for evaluation of a prostatic abscess. Early diagnosis is beneficial because prostatic abscesses require prolonged treatment protocols or surgical drainage. Alternatively, noncontrast computed tomography (CT) or magnetic resonance imaging (MRI) of the pelvis should be considered. Prostate biopsy should not be performed to avoid septicemia. (13,28)

Granulomatous prostatitis (GP) foci have been characterized on multiparametric magnetic resonance imaging (MP-MRI) as a lesion pathologically proven to higher-grade PCa lesions without evidence of clinically significant malignancy on targeted biopsies. This may not be extrapolated to lower-grade PCa lesions which may occasionally be occult on MP-MRI and likely harbor different imaging characteristics when visible. Similarly, cases of acute prostatitis and other inflammatory processes are better described in the literature than GP which can disguise PCa on MP-MRI. (29)

Section 6.4: Four-glass test

A sample of first-void urethral urine is collected (from the distal urethra). Then, the patient passes a further 100 to 200 ml of urine and then collects mid-stream bladder urine. By digital rectal examination, massage of the prostate gland is performed and any EPS are collected in a sterile container. Immediately after the massage, urine is collected (Figure 3). No antibiotics should be taken for 1 month before the test, the patient should not have ejaculated for 2 days, and a full bladder is required. The three urine samples are examined with microscopy and quantitative culture. (11)

Such testing should not be performed in patients with suspected acute bacterial prostatitis because prostatic massage increases the risk of bacteremia, and subsequently, sepsis. (11,13)

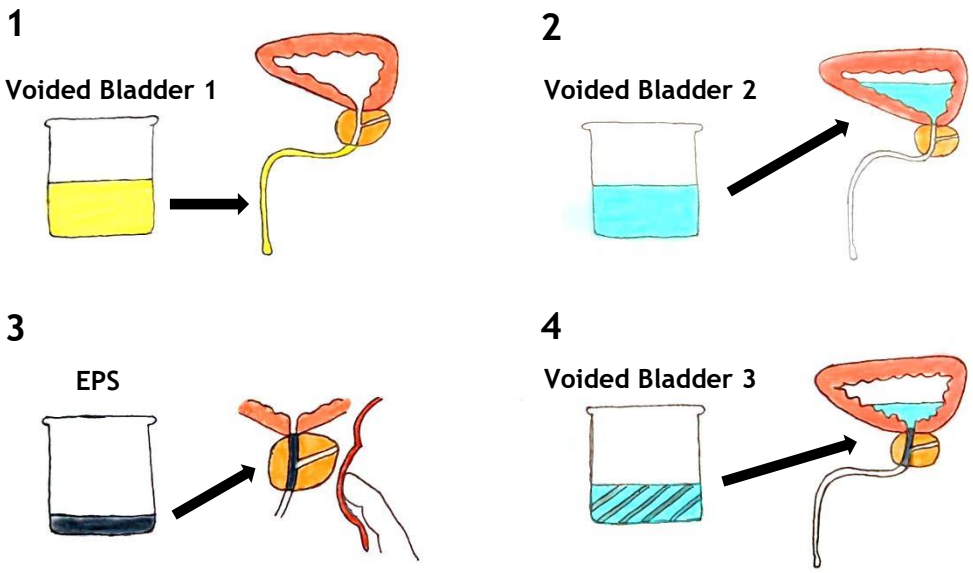

Figure 3. Ilustration of the Four-glass Test

Section 6.5: Two-glass test

The four-glass test is seldom used in regular clinical practice because it is difficult to perform, time-consuming, and unpleasant for the patient. The sensitivity of the two-glass test is similar to the four-glass test. (11)

Section 6.6: Additional tests

Prostatitis caused by *C. trachomatis*, *U. urealyticum*, or *T. vaginalis* can be diagnosed using molecular assays or with isolation of the causative organism in the samples of EPS, semen, or urine after prostate massage with the absence of the organisms in the urethral swab before ejaculation or prostate massage. When a sexually transmitted disease is suspected, screening for these infections should be performed: *Treponema pallidum*, *N. gonorrhoeae*, hepatitis B virus, and HIV virus. (11)

Intermediate-resolution genotyping for HLA-A, B, and DRB alleles (which are related to GP) and high-resolution genotyping for select HLA DRB1 and DRB 3/4/5 alleles performed by PCR amplification using group-specific probes and subsequent hybridizations of the amplicons with sequence specific oligonucleotide probe because there is an evidence of a possible autoimmune etiology can also be done. (30)

Only 60% of patients with acute prostatitis and 20% of patients with chronic prostatitis have elevated PSA level. A decrease after successful antibiotic treatment correlates with clinical and microbiological improvement. Prostate biopsy culture is neither sensitive nor specific (because inflammation in the gland is not uniformly distributed). When a prostatic abscess is suspected, transrectal US or a computer tomography scan of the gland should be performed. (11,13)

Section 6.7: Prognostic Factors

These outcomes included septic shock, positive blood culture, and prostatic abscess. In patients with any of these factors, the physician should order a complete blood count and a basic metabolic panel. Inflammatory markers, such as C-reactive protein and erythrocyte sedimentation rate, will likely be elevated, but with minimal clinical or diagnostic utility. (13,15)

Prostate-specific antigen (PSA) is not indicated in the workup of acute bacterial prostatitis. Approximately 70% of men will have a spurious PSA elevation due to disruption of prostatic architecture caused by inflammation. Elevated PSA levels can persist for one to two months after treatment. If PSA levels remain elevated for more than two months, PCa should be considered as 20% of persistent elevations are associated with malignancy. It is estimated that 5 to 10% of cases acute inflammation can evolve to chronic prostatitis. (11,13)

Chapter 7: Treatment

There are several differences in treatment recommendations for acute and chronic bacterial prostatitis. In case of an acute bacterial prostatitis, empirical antibiotic treatment should be started immediately after urine and possible blood cultures are obtained and adjusted to the isolated organisms later on. Treatment of chronic bacterial prostatitis should be delayed until culture and susceptibility results are available. When infection with *N. gonorrhoeae* is diagnosed, a patient has to be treated for a possible coinfection with *C. trachomatis* or *M. genitalium*. When a sexually transmitted organism is diagnosed, sexual partners should be examined and treated simultaneously. (11)

Fluoroquinolones have the best pharmacological properties for treating bacterial prostatitis, allowing concentrations in the prostate from 10 to 50% of that in the serum. Antibiotics with high penetration into the prostate tissue also include trimethoprim-sulfamethoxazole, clindamycin, doxycycline, and azithromycin. Cephalosporins, carbapenems, piperacillin and some of the aminoglycosides also attain therapeutic levels in prostate tissue. A major threat is the growing resistance of microorganisms, especially to fluoroquinolones. (11)

Management of acute bacterial prostatitis should be based on symptoms, risk factors, and local antibiotic resistance patterns. Initial empiric antibiotic therapy should be based on the mode of infection and the possible infecting organisms. Sexually active men younger than 35 years and men older than 35 years who engage in high-risk sexual behavior should be treated with regimens that cover *N. gonorrhoeae* and *C. trachomatis*. Patients with risk factors for antibiotic resistance require intravenous therapy with broad-spectrum regimens justified by the high risk of complications. (13)

The duration of antibiotic therapy in acute bacterial prostatitis goes from 10 to 14 days in mild infections (with a two-week extension if the patient remains symptomatic), to four weeks in severe infections. Febrile patients should generally become afebrile within 36 hours. When severe infections start to resolve and the patient is afebrile, antibiotics should be changed to oral form and continued for another two to four weeks. Repeat urine cultures one week after cessation of antibiotics to ensure bacterial clearance. The supportive measures include antipyretics, hydrating fluids, and pain control. (13)

When acute urinary retention develops as a complication of acute bacterial prostatitis, a urethral catheterization is contraindicated as it may worsen the infection by hindering the outflow of the secretion through the urethra and intensifies the existing ailments. The preferred treatment is to create a temporary urine outflow from the bladder towards the outside directly through the skin (cystostomy). This procedure is performed under local anesthesia guided by US control with a well filled bladder. (11,31)

Prostatic abscesses larger than 1 cm in diameter should be surgically drained. (11)

In chronic bacterial prostatitis clinical success rates (defined as complete resolution of symptoms, improvement in symptoms, or clear improvement without need for additional antimicrobial drugs) at 6 months, comparing oral antimicrobial drugs, lomefloxacin or levofloxacin seem as effective as ciprofloxacin. The bacteriological eradication rates at 6 months of lomefloxacin or levofloxacin seem as effective as ciprofloxacin and prulifloxacin – levofloxacin combination seems equally effective at increasing microbiological eradication rates at 6 months. Combination of *serenoa repens*, selenium, lycopene and bromelain, methylsulfonylmethane extracts is even able to improve the clinical efficacy of levofloxacin in patients affected by chronic bacterial prostatitis, without any adverse drug reactions. The efficacy of bromelain and methylsulfonylmethane on prostatic symptoms is probably due to its anti-inflammatory effect by increasing the production of anti-inflammatory cytokines such as TNF-alfa or interleukin (IL)-6. Curcumin has been also combined with other compounds like quercetin and prulifloxacin for the treatment of chronic bacterial prostatitis. (32–34)

Alpha-blockers may alleviate symptoms and reduce recurrence of chronic prostatitis when added to antimicrobial treatment. (32)

Available therapeutic options for CP/CPPS are far from satisfactory (Table 3). The main reason for the lack of effective and uniform therapies is that the etiology of CP/CPPS still remains unknown. For instance, antimicrobial treatment proved unsuccessful in most cases because usually there is no obvious symptomatic benefit from infection control or cultures that support an infectious cause. Adding an alpha-blocker improve symptomatic outcomes, but mainly in patients that were alpha-blocker naive. (6,7,11)

This phenotype of prostatitis is associated with anxiety, depression, and other psychological symptoms, and cognitive behavior therapy is not useful. Many antidepressant drugs have been used in the treatment of chronic pain to exert the analgesic effect. The mechanism of antidepressant drugs on chronic pain is direct action on neurons for pain and indirect improvement of depression, anxiety, and other emotional disorders, thereby improving the experience of pain and the ability to cope with pain. Duloxetine hydrochloride is a new selective 5-serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressant drug with high efficacy and tolerability in treating a variety of types of chronic pain and is recommended as a first-line drug by the International Association for the Study of Pain for chronic pain syndromes such as post herpetic neuralgia, and fibromyalgia. Duloxetine hydrochloride combined with the alpha-blocker doxazosin was safe and effective in the treatment of pain disorder in CP/CPPS. (35)

A study confirmed that zinc supplements may be effective in the management of chronic prostatitis. That can be attributed to anti-bacterial and immunomodulatory role of organic zinc. Zinc reduces total NIH-CPSI and pain scores in chronic prostatitis patients. (36)

The effect of phytotherapy is mainly based on the reduction of pain and in improving QoL, in addition to a mild anti-inflammatory effect. In this context, *Calendula officinalis* Linn. (Asteraceae) has been the subject of chemical and pharmacological studies and it has been used for multiple pharmacological uses including anti-inflammatory and antioedematous, antioxidant, immunostimulant, wound healing, hepatoprotective, antibacterial and antifungal and antiviral. Also, numerous lines of evidence support *Curcuma longa* (turmeric) ability to modulate multiple cell signaling molecules such as pro-inflammatory cytokines. (34)

Several studies have shown that flower pollen extract preparations may contribute to a lasting and marked symptom reduction in patients with inflammatory prostatitis/chronic pelvic pain syndrome (CP/CPPS) without any severe adverse effects, with a significant decrease in the NIH-CPSI score. Its clinical efficacy was demonstrated in association with vitamins for managing patients affected by CP/CPPS, and the results revealed a correlation between the reduction of IL-8 and clinical efficacy. It was also revealed that the reduction of IL-8 (65%) could be considered a marker in the response to treatment for CP/CPPS and improvement of patient QoL. (5,37)

It's unclear how effective alpha-blockers are in people with abacterial prostatitis and whether 5-alpha-reductase inhibitors, NSAIDs, pentosan polysulfate, allopurinol, transurethral microwave thermotherapy, prostatic massage, sitz baths, biofeedback, mepartricin or quercetin reduces symptoms in men with CP/CPPS. (32)

Commonly CP/CPPS requires a long treatment with anti-inflammatory drugs like corticosteroid or nonsteroidal anti-inflammatory drugs (NSAIDs) in combination with antibiotics that can lead to gastrolesive and nephrotoxic side effects. Regarding that aspect, of the utmost importance for clinicians who face this pathology, phytotherapeutics are valuable options of treatment due to their generally minimal side effects. (38)

Botulinum neurotoxin type A (BoNT-A) has been used to treat neurogenic detrusor over-activity, detrusor-sphincter dyssynergia, motor and sensory urgency urinary incontinency and, more recently, BPH and CP/CPPS. Relevant local or systemic side effects of BoNT-A are uncommon. Its anti-cholinergic effect on neuroglandular junctions, when intraprostatically administered, leads to scattered apoptosis and atrophy of the prostate gland. In addition, the release of pain mediators such as calcitonin gene-related peptide, substance P, glutamate and adenosine triphosphate are inhibited, resulting in nociceptive pain relief. Given the importance of sensory function in symptoms of CP/CPPS, BoNT-A may be considered a

therapeutic option for this syndrome. There are several ways of injection into the prostate, including the transperineal, transurethral and transrectal routes. (39)

Physiotherapeutic approaches have been shown to provide moderate clinical relief in pain syndromes associated with skeletal muscle dysfunction. In regard to CP/CPPS, various modalities like myofascial physical therapy, percutaneous posterior tibial nerve stimulation, acupuncture or electro-acupuncture, perineal extracorporeal low instensity shock wave therapy (LiSWT), sono-electro-magnetic therapy, or aerobic exercise have been evaluated in randomized sham-controlled trials and showed a significant benefit in the reduction of pain. (40)

Recently, low-intensity pulsed US (<0.1 W/cm2) and a constant frequency (1–1.5 MHz), which reduces any significant thermal effect, has been widely utilized to promote tissue healing, inhibit inflammation and pain, treat CP/CPPS, activate stem cell and nerve and muscle regeneration, and enhance cardiac angiogenesis. (41)

The complete resolution of symptoms after prostatectomy indicates this procedure as a potential treatment for recurrent sepsis in severe cases refractory to intravenous antibiotic treatment. (42)

Table 3. Prostatitis treatment

ABP and CBP	CP/CPPS
Antibiotics	Alpha-blockers
	Antidepressants (duloxetine hydrochloride) + Alpha-blockers
Serenoa repens + Selenium + Lycopene + Bromelain	Zinc
	Calendula officinalis Linn.
Curcumin + Quercetin + Antibiotics	Curcuma longa
	Pollen extracts
Alpha-blockers	Botulinum neurotoxin type A
	Physiotherapy
Cystostomy (if urinary retention)	Low-Intensity Pulsed Ultrasound
	Prostatectomy

Chapter 8: Prevention

Although there are no known strategies for preventing community-acquired acute bacterial prostatitis, nosocomial infections can be reduced by avoiding unnecessary manipulation of the prostate, such as transrectal biopsy or urethral catheterization. Administering antibiotics before transrectal prostate biopsies reduces postoperative complications such as urinary tract infections, acute prostatitis, bacteriuria, and bacteremia. New preventive approaches are needed to reduce fluoroquinolone resistance and extended spectrum beta-lactamase –producing *E. coli* (ESBL-EC) infections. Preoperative enemas do not reduce infection rates. In patients who are at increased risk of harboring fluoroquinolone-resistant bacteria, preoperative stool cultures may allow antibiotics prescription at the time of the procedure. (13)

Conclusions

Prostatitis is an infection or an inflammation of the prostate gland that can decrease men's QoL and it's a serious health problem that physicians should be concerned about. This condition is widespread and affects all ages, especially above the 20's. While bacterial prostatitis (acute or chronic) are caused by microorganisms, CP/CPPS's causes are not fully understood but may be caused by undocumented infections or non-infectious factors including inflammation, autoimmunity, hormonal imbalances, pelvic floor tension, myalgia, intraprostatic urinary reflux, and psychological disturbances. To structure the assessment of CP/CPPS patients, physicians use the NIH-CPSI which is a questionnaire that quantifies the experience of men with this condition. In addition, UPOINT can also be used and it's a clinical phenotyping system based on patient symptoms in order to choose the appropriate therapy. This will require a look beyond the urinary system to the whole patient. Besides these indexes, laboratory tests are used to categorize the four types of prostatitis. The treatment is managed according to the etiology such as antibiotics and alfa-blockers for acute and chronic bacterial prostatitis (Figure 4). CP/CPPS treatment is more complex than the other types using alpha-blockers, antidepressants, pollen extracts, BoNT-A, physiotherapy, low-intensity shockwave therapy, low-intensity pulsed US and in extreme cases, prostatectomy.

Future analysis is needed to better understand diagnosis and treatment, in particular CP/CPPS. New studies have been proposed to found biomarkers in CPPS or treatment without side effects observed in some physiotherapeutic approaches such as acupuncture or low-intensity pulse US.

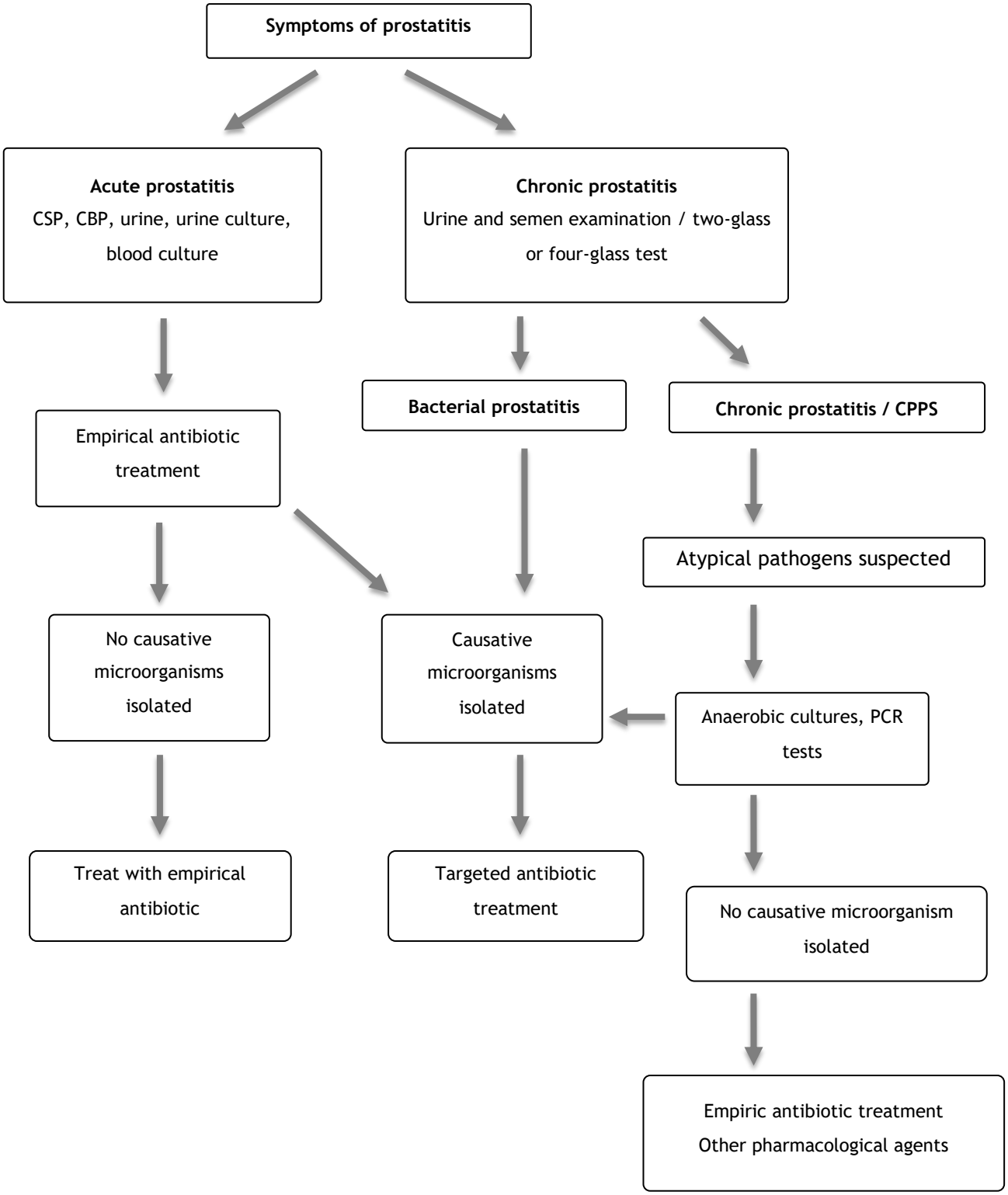

Figure 4. Diagnosis and treatment algorithm. (11)

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