

Prostatitis

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Background

Almost 9% of Canadian men experience some prostatitis symptoms over the course of a year, in about 6%, the symptoms are a bother,¹ with approximately a third experiencing a remission of symptoms over a year during follow-up.² Men with clinically significant prostatitis symptoms account for about 3% of Canadian male outpatient visits³ and causes significant morbidity⁴ and cost.⁵ Less than 10% of the patients suffer from acute or chronic bacterial prostatitis, conditions which are well-defined by clinical and microbiologic parameters and usually amenable to antimicrobial therapy. Acute prostatitis is characterized by a severe urinary tract infection (UTI), irritative and obstructive voiding symptoms with generalized urosepsis. Acute prostatitis responds promptly to antimicrobial therapy, and is usually self-limiting. Chronic bacterial prostatitis is usually associated with mild to moderate pelvic pain symptoms and intermittent episodes of acute UTIs. Long-term antimicrobial therapy is curative in about 60% to 80% of patients.

Most men with "chronic prostatitis" have chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), characterized by pelvic pain (i.e., perineal, suprapubic, testicular, penile) variable urinary symptoms and sexual dysfunction (primarily pain associated with ejaculation).⁶ The National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) is a reliable means of capturing the symptoms and impact of CP/CPPS.⁷ The etiology of this syndrome is not fully known, the evaluation has been controversial and treatment is, unfortunately, frequently unsuccessful. Focused multimodal therapy appears to be more successful than empiric monotherapy.

The recommendations presented in these guidelines were developed from North American NIH consensus meetings,⁸ International Consultation on Urologic Disease (ICUD)/

World Health Organization (WHO) consensus meeting,⁹ European Guideline Committee recommendations,¹⁰ a recent comprehensive literature search performed by one of the authors¹¹ and expert Canadian panel discussion. Medline and EMBASE databases were used to identify relevant studies published in English from 1949 (for Medline) or 1974 (for EMBASE) until January 31, 2011. We used search terms and strategies for each database.¹¹ The levels of evidence and grades of recommendations were based on the ICUD/WHO modified Oxford Center for Evidence-Based Medicine Grading System. These recommendations are summarized at the end of this guideline document. Within the document, the level of evidence and recommendation grade are included where appropriate and denoted as 3:A which means Level 3 evidence and Grade A recommendation.

Definition

Prostatitis describes a combination of infectious diseases (acute and chronic bacterial prostatitis), CPPS or asymptomatic prostatitis. The NIH classification of prostatitis syndromes¹² includes:

Category I: Acute bacterial prostatitis (ABP) which is associated with severe prostatitis symptoms, systemic infection and acute bacterial UTI.

Category II: Chronic bacterial prostatitis (CBP) which is caused by chronic bacterial infection of the prostate with or without prostatitis symptoms and usually with recurrent UTIs caused by the same bacterial strain.

Category III: Chronic prostatitis/chronic pelvic pain syndrome which is characterized by chronic pelvic pain symptoms and possibly voiding symptoms in the absence of UTI.

Category IV: Asymptomatic inflammatory prostatitis (AIP) which is characterized by prostate inflammation in the absence of genitourinary tract symptoms.

Evaluation

A mandatory history is required for all patients at time of evaluation (4:C). The following presenting symptoms should be elicited: pain location (severity, frequency, and duration), lower urinary tract symptoms (obstructive/voiding and irritative/storage), associated symptoms (fever, other pain syndromes) and impact on activities/quality life. A comprehensive systems review should document past medical and surgical (particularly urologic) history, history of trauma, medications and allergies.

1. Acute bacterial prostatitis (NIH category I)

a. Physical examination

Mandatory (4:C): The abdomen, external genitalia, perineum and prostate must be examined. Prostate massage during a digital rectal examination (DRE) is not recommended.

b. Urine analysis and culture

Mandatory (2:A)

c. Imaging

Optional (2:A): A transrectal prostatic ultrasonography (TRUS) or computed tomography scan is indicated in ABP patients refractory to initial therapy to rule out prostate abscess/pathology. Pelvic ultrasound (or bladder scan) is indicated in ABP patients with severe obstructive symptoms, poor bladder emptying or physical examination findings of possible urinary retention. Initial imaging of the prostate is not recommended (3:B).

d. Serum PSA

Not recommended (3:C): Elevated prostate-specific antigen (PSA) associated with ABP usually leads to confusion and worry.

2. Chronic bacterial prostatitis (NIH category II)

a. Physical examination

Mandatory (4:C): This must include examination of the abdomen, external genitalia, perineum, prostate and pelvic floor.

b. Microbiological localization cultures of the lower urinary tract (4-Glass Test or 2-Glass Pre- and Post-Massage Test [PPMT])

Recommended (3:A): The 4-glass test is the criterion standard for the diagnosis of CBP. The 2- glass pre- and post-

massage test (PPMT) is a simple and reasonably accurate screen for bacteria. Microscopy is optional. Rationale and description can be found in reference.⁶

c. Semen cultures

Not recommended (3:D): Based on limited evidence, semen cultures have not been shown to be significantly helpful in identifying men with CBP, unless the same organism causing recurrent UTIs is cultured.

d. Transrectal prostatic ultrasonography

Not recommended (3:B): A TRUS cannot be relied upon for differential diagnosis of categories of prostatitis. A TRUS can be considered optional (4:D) if there is a specific indication.

e. Urodynamics

Optional (4:D): Uroflow may be helpful to confirm obstruction. Urodynamics cannot be relied upon for differential diagnosis of categories of prostatitis, but may help document obstruction and/or bladder problems.

3. Chronic prostatitis/chronic pelvic pain syndrome (NIH category IIIA, IIIB)

a. Symptom scoring questionnaire

Recommended (3:A)- the NIH-CPSI (Fig. 1) has become the established international standard for symptom evaluation (not for diagnosis) of prostatitis. The index has been shown to be reliable and can evaluate the severity of current symptoms and be used as an outcome measure to evaluate the longitudinal course of symptoms with time or treatment.

b. Physical examinations

Mandatory (4:C): Examination of abdomen, external genitalia, perineum and prostate is mandatory. Exacerbation of typical pelvic pain with normal DRE pressure is helpful in determining prostate centricity, while evaluating myofascial trigger points and/or possible musculoskeletal dysfunction of the pelvis and pelvic floor during DRE is believed to be helpful in treatment decisions.

c. 4-Glass test and 2-glass pre- and post-massage test (PPMT)

Recommended (3:A): Culture of the lower urinary tract urine specimens is recommended. The 4-glass test is the criterion standard to rule out CBP. The 2-glass PMT is a simple and reasonably accurate screen for bacteria. A rationale and description for this recommendation are available.⁶ At this

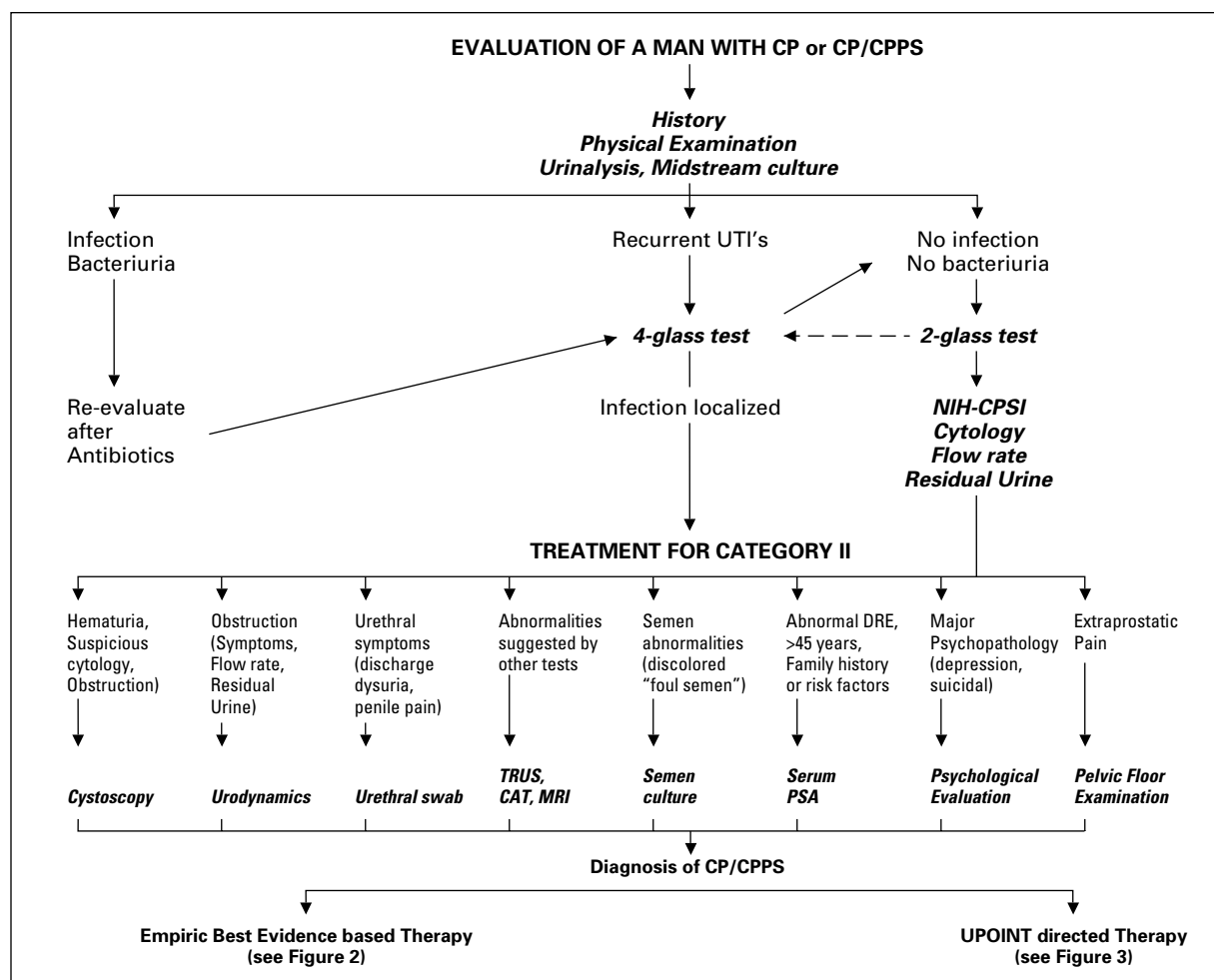


Fig. 2. Diagnostic algorithm for a patient presenting with a chronic prostatitis syndrome.

f. Transrectal ultrasound

Not recommended (3:B) in routine practice, unless there is a specific indication.

g. CT scan and/or magnetic resonance imaging (MRI)

Not recommended (3:B): At present, value is unknown.

h. Urodynamics

Optional (3:C): In selected men with obstructive voiding symptoms, it is reasonable to consider urodynamic evaluation (e.g., flow rates, post-void residual, pressure flow studies).

i. Serum PSA Levels

Not recommended (3:B): There is no evidence that serum PSA levels in patients with CP/PPS will help diagnosis and direct therapy. Indications for serum PSA determinations should be the same as for men without CP/PPS.

j. Psychological Assessment

Optional (3:B): There is accumulating evidence that psychosocial parameters, such as depression, maladaptive coping mechanisms (catastrophizing, resting as a coping mechanism) and poor social support impact symptoms and results of therapy. The physician should screen for these psychological problems.

There is a practical algorithm to assess a man presenting with presumed CP/PPS (Fig. 3).

4. Asymptomatic prostatitis (NIH category IV)

Investigations

Not recommended (3:C): While some evidence suggests that this category may have biological relevance, at this time there is no evidence that determination of asymptomatic prostatitis has any clinical relevance.

Treatment

1. Acute bacterial prostatitis (NIH category I)

ABP can be a serious infection with fever, intense local pain and general symptoms. Septicemia and urosepsis are always a potential risk. The following factors must be taken in account when treating ABP: potential urosepsis, choice of antimicrobial agent, urinary drainage, risk factors justifying hospitalization and auxiliary measures intended to improve treatment outcomes.¹³

a. Antimicrobial Therapy (2:A)

The choice and duration of antimicrobial therapy for ABP are based on experience and expert opinion and are supported by many uncontrolled clinical studies.^{14,15} For initial treatment of severely ill patients, the following regimens are recommended: intravenous administration of high doses of bactericidal antimicrobials, such as aminoglycosides in combination with ampicillin, a broad spectrum penicillin in combination with a beta-lactamase inhibitor, a third-generation cephalosporin or a fluoroquinolone is required until defeverescence and normalization of associated urosepsis (this recommendation is based on treatment of complicated UTIs and urosepsis). Patients who are not severely ill or vomiting may be treated with an oral fluoroquinolone.^{14,15} Trimethoprim-sulfamethoxazole (TMP/SMX) is no longer recommended as first line empirical therapy in areas where TMP/SMX resistance for *E. coli*, the most frequent pathogen, is greater than 10% to 20%.¹⁵⁻¹⁹ Treatment should continue for 2 to 4 weeks.^{14,15}

b. Urinary drainage (3:B)

A single catheterization with trial of voiding or short-term small caliber urethral catheterization is recommended for patients with severe obstructive voiding symptoms or urinary retention. Suprapubic tube placement is optional for patients who cannot tolerate a urethral catheter.

c. Hospitalization (3:B)

Hospitalization is mandatory in cases of hyperpyrexia, prolonged vomiting, severe dehydration, tachycardia, tachypnea, hypotension and other symptoms related to urosepsis. Hospitalization is recommended in high-risk patients (diabetes, immunosuppressed patient, old age or prostatic abscess) and those with severe voiding disorders.¹³

d. Drainage of prostate abscess (4:A)

Incision and drainage of prostate abscess are required in selected treatment refractory patients. Transurethral route appears to be modality of choice but abscess may be drained via perineum, rectum or transperineal route.

d. Auxiliary measures

Nonsteroidal anti-inflammatory agents have been suggested for reducing symptoms including fever.¹³⁻¹⁵ Alpha-blockers may be considered, particularly in men with moderately severe obstructive voiding symptoms to reduce the risk of urinary retention and facilitate micturition.¹³⁻¹⁵

2. Chronic bacterial prostatitis (NIH category II)

a. Antimicrobial therapy (2:A)

Because of their unique and favourable pharmacokinetic properties, their broad antibacterial spectra and comparative clinical trial evidence, the fluoroquinolones are the recommended agents of choice for the antimicrobial treatment of CBP.^{14,15,17,18} Data from CBP fluoroquinolone treatment trials with a follow-up of at least 6 months support the use of fluoroquinolones as first-line therapy.²⁰⁻²⁸ The recommended 4- to 6-week duration of antimicrobial treatment is based on experience and expert opinion and is supported by many clinical studies.^{14,15,17,18} In general, therapeutic results (defined as bacterial eradication) are good in CBP due to *E. coli* and other members of the family *Enterobacteriaceae*. CBP due to *P. aeruginosa* and *Enterococci* shows poorer response to antimicrobial therapy.¹⁸

CBP associated with a confirmed uropathogen that is resistant to the fluoroquinolones can be considered for treatment with trimethoprim-sulfamethoxazole (or other antimicrobials), but the treatment duration should be 8 to 12 weeks.¹⁸

b. Alpha-Blockers (3:C)

The combination of antimicrobials and alpha-blockers has been suggested to reduce the high recurrence rate²⁸ and this combination of two therapeutic regimens is considered optional for in-patients with obstructive voiding symptoms.

c. Treatment refractory cases

For treatment refractory patients with confirmed uropathogen localized to the prostate, the following are optional treatment strategies:

- intermittent antimicrobial treatment of acute symptomatic episodes (cystitis) (3:A);

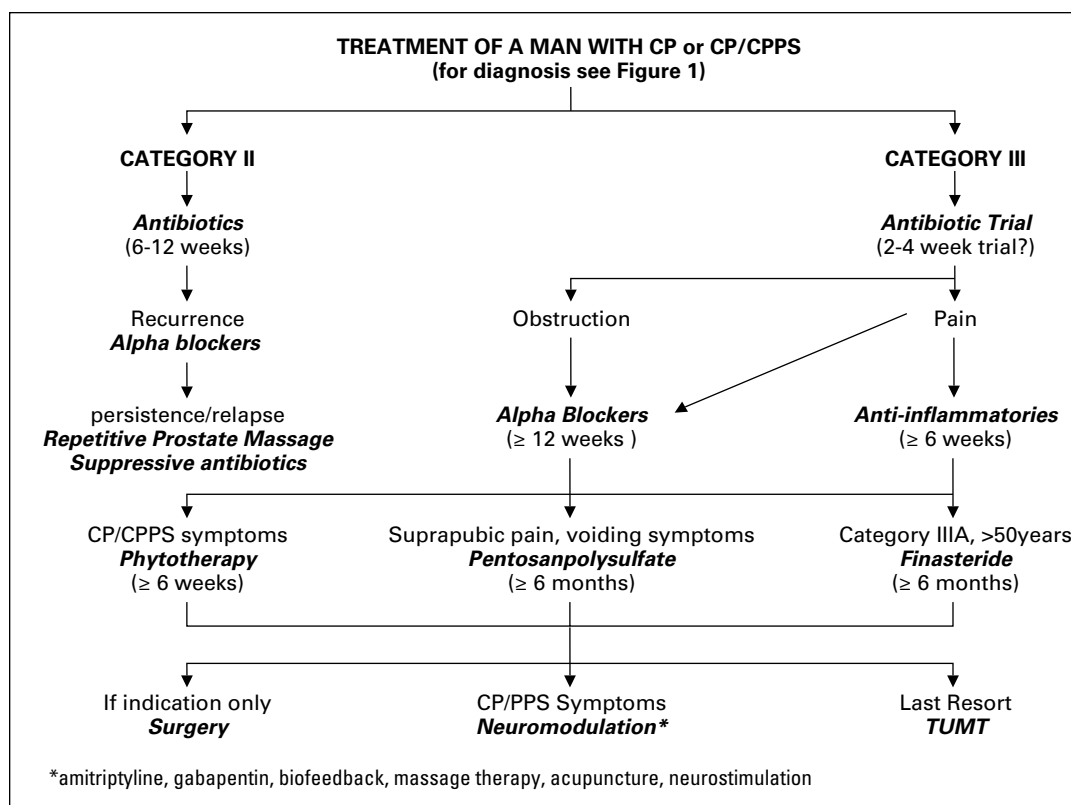


Fig. 3. A best-evidence approach algorithm to manage chronic prostatitis/chronic pelvic pain syndrome.

- low-dose antimicrobial suppression (3:A); or
- radical TURP or open prostatectomy if all other options have failed (4:C).

3. Chronic prostatitis/chronic pelvic pain syndrome (NIH category III)

The introduction of an internationally accepted classification system,¹² a validated outcome index, the NIH-CPSI,⁷ and the significant number of randomized placebo controlled clinical trials published over the last decade and a half¹¹ has permitted best-evidence based guideline recommendations. Twenty-three clinical trials²⁹⁻⁵⁴ were available at time of this guideline development. These English-language trials evaluated medical therapies using a prospective, randomized controlled design; these trials were used to support these recommendations. These have been recently reviewed and analyzed.¹¹ We also used a literature search strategy.¹¹ In addition, a best-evidence based treatment algorithm was used (Fig. 3).

a. Antimicrobials

Antimicrobials cannot be recommended for men with longstanding, previously treated CP/CPPS (1:A). However, uncontrolled clinical studies suggest that some clinical ben-

efit can be obtained with antimicrobial therapy in antimicrobial naïve early onset prostatitis patients (4:D).

b. Alpha-blockers

Alpha-blockers cannot be recommended as a first line monotherapy (1:A). However, there is some evidence that alpha-blocker naïve men with moderately severe symptoms who have relatively recent onset of symptoms may experience benefit (1:A). Alpha-blocker therapy appears to provide benefit in a multimodal therapeutic algorithm for men with voiding symptoms (2:C). Alpha-blockers must be continued for over 6 weeks (likely over 12 weeks).

c. Anti-inflammatory

Anti-inflammatory therapy is helpful for some patients, but is not recommended as a primary treatment (1:B); however, it may be useful in an adjunctive role in a multimodal therapeutic regimen (2:C).

d. Phytotherapies

Phytotherapies (specifically quercetin and the pollen extract, cernilton) are optional recommendations for first line (2:B)

and combination multimodal therapy (3:C).

e. Other medical therapies

Other medical therapies, such as 5-alpha-reductase inhibitor therapy, pentosanpolysulfate and pregabalin, while not recommended as primary monotherapy (1:A), may provide benefit in selected patients (older men with LUTS for 5-ARI therapy, men with associated pain perceived bladder pain and irritative voiding symptoms for pentosanpolysulfate and neuropathic type pain for pregabalin).

f. Other potential medical therapies

Muscle relaxants, saw palmetto, corticosteroids, and tricyclic antidepressants have all been suggested⁶ and used, but recommendations will have to wait for results from properly designed randomized placebo controlled trials (4:D).

g. Physiotherapies

A number of physical therapies have been recommended,⁶ but they also suffer from a lack of prospective controlled data obtained from properly designed controlled studies. Prostatic massage, perineal or pelvic floor massage and myofascial trigger point release has also been suggested as a beneficial treatment modality for patients, however focused pelvic physiotherapy has yet to be shown to provide more benefit compared to SHAM physiotherapy. Biofeedback, acupuncture and electromagnetic therapy also show promise, but like all the other physical therapeutic modalities, require sham controlled trials before recommendations can be made (3:C).

h. Psychotherapies

Psychological support and therapy has been advocated based on new psycho-social modelling of this syndrome.⁵⁵ This treatment ideally would include a cognitive behavioral therapy program. A referral to a psychologist or psychiatrist should be considered mandatory in patients with severe depression and/or suicidal tendencies.

i. Surgery

The evidence for surgical therapies has been reviewed.⁶ A number of minimally invasive therapies such as balloon dilation, neodymium:Yag laser, transurethral needle ablation, microwave hyperthermia and thermotherapy have been suggested (at this time, not recommended, 2:A). Further assessment of heat therapy employing sham controls, standardized inclusion exclusion criteria and validated symptom outcome measures are recommended. Pudendal nerve blocks or neurectomy surgery have been suggested for CPP that can be shown to be secondary to pudendal nerve entrapment (3:C). Other surgery, such as radical transurethral resection of the prostate and total prostatectomy, should not be encouraged and is not recommended (4:D) at this time for CP/CPPS since no definitive clinical series or long-term follow-up has ever been presented.

j. Multimodal Therapy (UPOINT)

A number of uncontrolled clinical studies have strongly suggested that multimodal therapy is more effective than monotherapy in patients with long-term symptoms.^{56,57} Individualized personal therapy algorithms directed toward

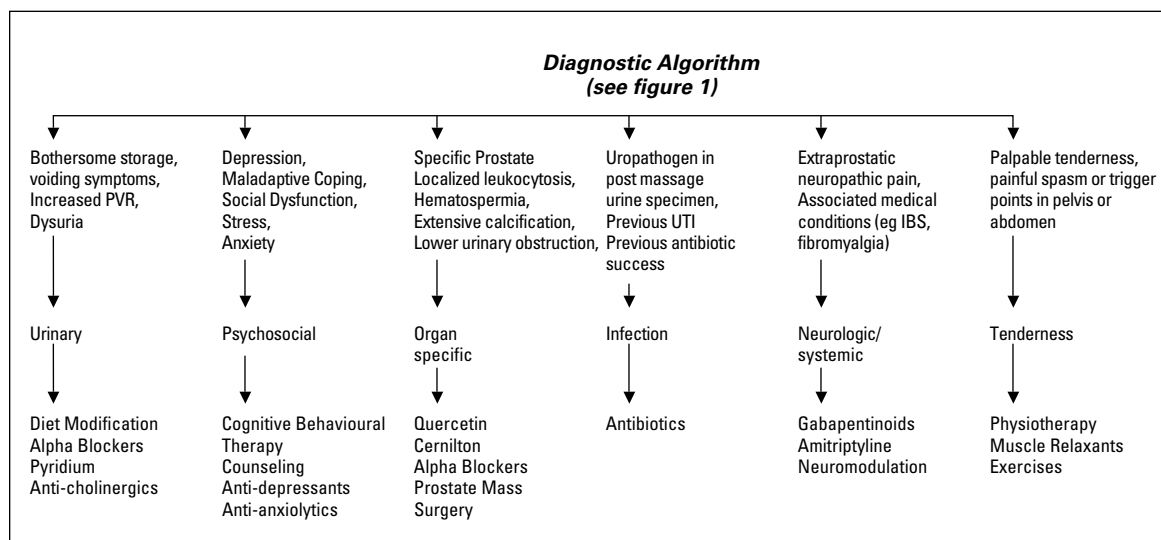


Fig. 4. A clinical phenotype directed treatment (UPOINT) approach for chronic prostatitis/chronic pelvic pain syndrome.

Table 1. Summary of recommendations (Level of Evidence: Grade of Recommendation)**EVALUATION****I. Acute Bacterial Prostatitis (NIH Category I)**

- 1) History (Mandatory 4:C)
- 2) Physical examination (Mandatory 4:C)
- 3) Urinalysis and culture/sensitivity (Mandatory 2:A)
- 4) Initial imaging of the prostate (not recommended 3:B)
Ultrasound optional (2:A) if suspicion for prostatic abscess is entertained.

II. Chronic Bacterial Prostatitis (NIH Category II)

- 1) History (Mandatory 4:C)
- 2) Physical examination (Mandatory 4:C)
- 3) 4-glass or 2-glass test for culture. (Recommended 3:A)
- 4) Culture of semen (Not recommended 3:D)
- 5) Imaging of the prostate (Not recommended 3:B); optional (4:D) only in highly selected patients
- 6) Urodynamics (Optional in selected cases only 4:D)

III. Chronic Prostatitis/Chronic Pelvic Pain Syndrome (NIH Category III)

- 1) History (Mandatory 4:C)
- 2) The NIH-CPSI instrument (Recommended 3:A)
- 3) Physical examination (Mandatory 4:C)
- 4) 4-glass or 2-glass test for WBC count and culture (Recommended 3:A)
- 5) Semen analysis and culture (Not recommended 3:D)
- 6) Flow rate, post-void residual and other urodynamic studies (Optional 3:C)
- 7) Serum PSA (Not recommended 3:B)
- 8) Routine imaging of the prostate (Not recommended 3:D)
- 9) Cystoscopy (Not recommended 4:D)
- 10) Psychological evaluation in selected patients (Optional 3:B)

IV. Asymptomatic Prostatitis (NIH Category IV)

- 1) No evaluation unless considering antimicrobial therapy for elevated PSA or infertility. (Recommended 3:C)

TREATMENT**I. Acute bacterial prostatitis (NIH Category I)**

- 1) Antimicrobials: Patients with severe symptomatic febrile acute bacterial prostatitis: Aminoglycosides in combination with ampicillin, broad spectrum penicillin in combination with a beta-lactamase inhibitor, a 3rd generation cephalosporin or a fluoroquinolone is required until defervescence and normalization of associated urosepsis. (Recommended 2:A). Following resolution of severe infection and for less severely ill patients, outpatient oral fluoroquinolones for 2-4 weeks are appropriate. (Recommendation 4:B)
- 2) Hospitalization if indicated (Recommended 3:B)
- 3) Urinary drainage if indicated (Recommended 3:B)
- 4) Imaging if indicated (Recommended 4:A)
- 5) Drainage of prostatic abscess if indicated (Recommended 4:A)

II. Chronic Bacterial Prostatitis (NIH Category II)

- 1) Oral fluoroquinolone therapy for susceptible bacteria for 4-6 weeks. (Recommended 2:A)
- 2) Trimethoprim-sulfamethoxazole (or other antimicrobials) for fluoroquinolone resistant bacteria. (Recommended 3:B)
- 3) Treatment refractory patients:
 - intermittent antimicrobial treatment of acute symptomatic cystitis; (Recommended 3:A)
 - low-dose antimicrobial suppression; (Recommended 3:A)
 - radical TURP or simple prostatectomy (as a last resort if all other options have failed). (Recommended 4:C)

III. Chronic Prostatitis/Chronic Pelvic Pain Syndrome (NIH Category IIIb)

- 1) Antibiotic therapy for newly diagnosed, antimicrobial naïve patients (Recommended 4:D); Antibiotic therapy for patients who have failed previous antibiotic therapy (Not recommended 1:A)
- 2) Alpha-blocker as first line mono-therapy (not recommended 1:A); Alpha-blocker therapy for newly diagnosed, alpha-blocker naïve patients with voiding symptoms as part of a multi-modal treatment strategy (Optional 1:A)
- 3) Anti-inflammatory monotherapy (Not-recommended 1:B); Anti-inflammatory therapy as part of a multimodal treatment strategy (Optional 2:C)
- 4) The phytotherapies quercetin and pollen extract (recommended 2:B) but are likely most effective as a part of a multimodal treatment strategy (3:C)
- 5) Five alpha-reductase inhibitor monotherapy. (Not recommended 1:A); Five alpha-reductase inhibitor therapy in older men with lower urinary tract symptoms and/or as part of a multimodal treatment strategy (Optional 2:C)
- 6) Individualized multimodal therapy directed towards to defined clinical phenotype. (Recommended 3:C)
- 7) Minimally invasive therapies such as TUNA, laser therapies, etc. (Not recommended 2:A)
- 8) Invasive surgical therapies such as TURP and radical prostatectomy. (Not recommended 4:D)
- 9) The following potentially effective therapies can be considered in selected patients (Optional 4:D)
 - Heat therapy in the form of microwave
 - Biofeedback
 - Physical therapy
 - Psychotherapy (Mandatory for severe depression and/or suicidal tendencies)
 - Acupuncture
 - Electromagnetic stimulation
 - Muscle relaxants (diazepam, baclofen, cyclobenzaprine)
 - Neuromodulating agents (gabapentinoids, tricyclic antidepressants)
 - Pudendal nerve modulation

IV. Asymptomatic Inflammatory Prostatitis (NIH Category IV)

- 1) Definitive therapy (Not recommended: 3:A)
- 2) Antimicrobial therapy for selected patients with elevated PSA, infertility or manipulation (biopsy) warrants consideration. (Optional 3:C)

clinically defined presenting phenotypes (UPOINT) have been proposed⁵⁸ and the early results of such a strategy look promising.⁵⁹ Based on the fact that monotherapies provide (at best) modest efficacy, a multimodal approach using specific clinical phenotypes to choose therapies is considered an optional recommendation.⁵⁸ An algorithm has been proposed (Fig. 4).

4. Asymptomatic prostatitis (NIH category IV)

Therapy is not indicated (3:A) since these patients by definition are asymptomatic. However, antimicrobial therapy for selected patients with category IV prostatitis associated with elevated PSA, infertility and those planned for prostate biopsy may warrant consideration (3:C).

Competing interests: J. Curtis Nickel reports being an investigator/consultant for Glaxo-Smith-Kline, Johnson and Johnson, Pfizer, Watson, Ferring, Taxis and consultant for Farr Labs, Astellas, Triton, Trillium Therapeutics, Cernelle.

This paper has been peer-reviewed.

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