Where do we stand with chronic prostatitis? An update

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Chronic prostatitis remains a difficult management problem, which reflects the fact that its aetiology remains incompletely understood. It is a common condition that is characterized by protracted symptoms and high morbidity. Although lacking a reliable diagnostic test, antibiotic therapy remains the mainstay of treatment in the majority of cases.

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Chronic prostatitis is a clinical syndrome of enigmatic aetiology and uncertain management, and remains the Cinderella of prostatic disorders. It is diagnosed by a combination of clinical findings, microscopy and culture of expressed prostatic secretions (EPS), segmented urine samples, and in some cases prostate biopsy. It has a high prevalence of approximately 5–16%, accounting for over 2 million hospital visits per year in the US (Litwin et al, 1999; McNaughton-Collins et al, 2002), and is estimated to account for up to a quarter of all visits to urologists. The sickness impact of chronic prostatitis is equivalent to that of acute myocardial infarction, Crohn's disease and angina (Wenniger et al, 1996). In spite of this high morbidity, chronic prostatitis still has inadequate clinical evidence. The multiplicity of aetiological theories is testimony to the uncertain aetiology of prostatitis (*Table 1*), and the diagnostic criteria are weak.

TABLE 1.
Various proposed causes of chronic prostatitis

Deviational or excessive sexual practices
Perineal trauma (horse riding, bicycles)
Alcoholism
Gonococcal infection
Almost any other bacteria that has been isolated from expressed prostatic secretions: gram-negative organisms (*Escherichia coli*, *Pseudomonas* spp, *Klebsiella* spp) and gram-positive organisms (*Enterococcus* spp, mycoplasma, chlamydia). Recently coagulase-negative staphylococcus, anaerobes, diphtheroids, *Corynebacterium* spp, and several others have been implicated
Viruses, cell-wall deficient organisms, cryptic unculturable organisms
Chemical-induced inflammation from intraprostatic reflux of urine and its metabolites
Immunological triggers
Neurogenic causes

CLASSIFICATION AND DIAGNOSIS

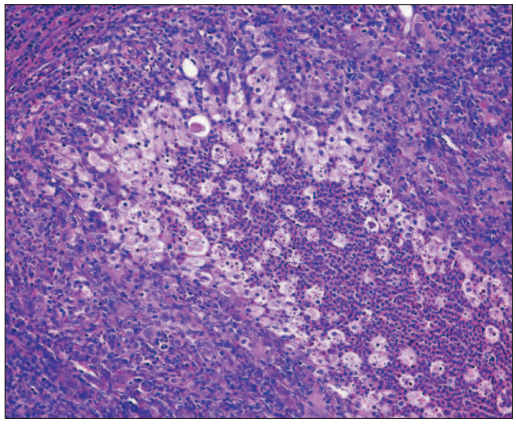
The National Institutes of Health (NIH) International Collaborative Network classified prostatitis into four categories (Kreiger et al, 1999) (*Table 2*). This classification recognizes pain as the primary component of the syndrome. The exclusion criteria for diagnosis of prostatitis include the presence of urogenital cancer, active

TABLE 2.
National Institutes of Health classification of prostatitis

I	Acute bacterial prostatitis	
II	Chronic bacterial prostatitis	
III	Chronic prostatitis/chronic pelvic pain syndrome	a Inflammatory
		b Non-inflammatory
IV	Asymptomatic inflammatory prostatitis	

From Kreiger et al (1999)

Figure 1. Non-specific granulomatous prostatitis.



urethritis, urethral stricture or neurogenic bladder dysfunction.

Acute bacterial prostatitis

The patient with this condition is usually aged 20–45 years and is visibly ill with serious sepsis. It is marked by the sudden onset of fever, chills and malaise associated with dysuria, frequency, poor stream, and discomfort or pain in the pelvis and lumbosacral spine. The bladder is tender on palpation and the prostate found to be enlarged, hot and very tender. It may harbour an abscess that may require drainage. Urine and blood cultures are often positive and antimicrobial therapy should be guided by this. Computed tomography (CT) scans are preferred (as they are less unpleasant) to transrectal ultrasound (TRUS) for imaging if a prostatic abscess is suspected.

Chronic bacterial prostatitis

These patients present with long-term (>3 months) discomfort or pain in the pelvis with varying voiding or sexual symptoms in the absence of a documented urinary tract infection. The differentiation between NIH categories II, IIIa and IIIb has traditionally been based on the Meares–Stamey four-glass localization test (Meares and Stamey, 1968). This consists of collection of initial voided urine (VB_1), mid-stream or second voided urine (MSU/VB_2) which represent urethral and bladder specimens respectively, followed by collection of EPS during prostate massage. Finally a further voided urine sample is collected after the massage (VB_3).

The diagnosis of type II prostatitis is based on a positive culture on the EPS, or higher concentrations of growth in VB_3 than that cultured in previous samples. The finding of inflammatory cells in the EPS or VB_3 differentiates categories IIIa and IIIb. Although the test is the basis of the current classification system, urologists have largely abandoned it as it is complicated, impractical and has high false-positives and false-negatives. Nickel et al (2001) also demonstrated that there is no difference of benefit in treating category II and category III prostatitis with a fluoroquinolone antibiotic for 12 weeks, seriously questioning the relevance of 'bacterial prostatitis' as determined by the Meares–Stamey test. Nickel (2000) has proposed a modification of the Meares–Stamey test termed the 'pre- and post-massage test', which involves microscopy and urine culture before and after prostatic massage. Although this appears to be currently popular among urologists, a diagnostic test that will lead to a validated classification and rational treatment strategies is urgently required (Nickel, 2000).

Chronic non-bacterial prostatitis or chronic pelvic pain syndrome

These patients present differently from those with chronic bacterial prostatitis, with pain in the suprapubic region, tip of the penis and lower back, perineal discomfort, dysuria, frequency, a weak urinary stream and pain on ejaculation. The combination of EPS and VB_3 culture are most useful for diagnosis; additionally a longer culture period of 5 days rather than the conventional 2 days yield a further 7.5% of positive bacterial cultures.

16S rRNA gene-based polymerase chain reaction (PCR) studies have demonstrated good correlation of inflammation with bacterial gene detection, which suggests bacteria have a role in the pathogenesis of chronic prostatitis. Statistically significant levels of elevated pro-inflammatory (interferon-γ (IFN-γ), interleukin-2 (IL-2)) and anti-inflammatory (IL-10) cytokines have been found in chronic prostatitis (Miller et al, 2002). Seminal plasma samples of category IIIa prostatitis shows elevated IL-1β, tumour necrosis factor (TNF)-α, IL-6 and IL-8 compared to IL-1β, TNF-α and IL-8 but not IL-6 in type IIIb prostatitis (Orhan et al, 2001).

Prostate biopsy specimens have also been studied using PCR techniques; initial results indicate that 46% of patients and 20% of controls (men with prostate cancer) are positive for 16s ribosomal DNA; the viability of the bacteria in these specimens is being currently assessed (Krieger and Riley, 2002). Animal models have also been developed by orally administering Sprague–Dawley rats with a phyto-oestrogen, isoflavone, which induces severe inflammation in the dorsolateral aspect of the rat prostate; this may influence interpretation of prostate biopsy specimens in humans. A positive RT-PCR test for bacterial genomic fragments may indicate a positive response to antibiotics whereas a negative test may indicate the appropriateness of anti-inflammatory and neuromuscular therapies instead; however, this is not practical yet as the RT-PCR is currently unavailable in routine clinical practice.

Asymptomatic inflammatory prostatitis

This group of men have a diagnosis made from prostatic biopsies for elevated prostate specific antigen (PSA) (*Figure 1*) workup for infertility, and are asymptomatic; consequently treatment is not warranted.

TREATMENT

Acute bacterial prostatitis

Patients who can tolerate oral fluids and do not have a spiking temperature can be managed on an outpatient basis with oral fluoroquinolones for 4 weeks. Addition of an α-blocker and anti-inflammatory agents often provides some symptomatic relief, the former by reducing prostatic smooth muscle tone (Narayan et al, 2002). Those who require hospitalization require prompt hydration and intravenous antibiotics (commonly a fluoroquinolone, gentamicin, a cephalosporin, vancomycin, or penicillin alone or in combination); the initial antibiotics can be changed after microbiology reports are available if appropriate and to oral therapy when possible.

Urethral catheterization is not recommended as it is acutely uncomfortable and may provoke the development of epididymitis and even prolong the course of the disease. In case of painful acute retention, a suprapubic catheter is preferred. Transurethral incision and drainage of a prostatic abscess may be required, and usually provides rapid relief from acute symptoms.

Chronic bacterial prostatitis

Robust randomized controlled trials on the treatment of chronic prostatitis are currently lacking. Various and diverse potential therapies have been proposed, and those that have at least some evidence or theoretical basis are listed in *Table 3*. The management strategies may be considered to be either curative or suppressive, with surgical options reserved for cases that fail adequate conservative therapy.

Curative approach: This is recommended for all men with positive cultures at presentation, and is achieved by a 12-week course of co-trimoxazole which has a 30% cure rate, or fluoroquinolones (ciprofloxacin or levofloxacin) which have a 75% cure rate (Nickel, 1999; Weidner et al, 1999).

Suppressive treatment: This is recommended in the presence of persistent positive cultures when the patient has become asymptomatic after a curative course of antibiotics. Nitrofurantoin, trimethoprim or a cephalosporin is recommended for 6–12 weeks after which the patient is evaluated again (Nickel, 1999). Repeated prostatic massages with further courses of antibiotics have been recommended for persistent symptoms after an initial curative course of antibiotics.

The long-term efficacy of long-term antimicrobials in the relief of symptoms and prevention of recurrence is unknown, but microbiological eradication of bacteria occurs in 92% of men after 3 months of therapy and in 70–80% of men evaluated after 12–24 months (Weidner et al, 1999); cure rates are better with fluoroquinolones than with trimethoprim. The rationale for prostatic massage is based on the presumption that bacterial pockets exist in blocked prostatic ducts or within microabscesses, which may be induced to drain by massage.

Surgical approaches: Transurethral resection of the prostate (TURP) or even total prostatectomy is used when conservative measures fail. It is indicated and particularly effective in the presence of persistent positive cultures in association with bladder outflow obstruction as in bladder neck stenosis, benign prostatic enlargement or urethral stricture (Barnes et al, 1982). When retropubic prostatectomy is undertaken the patient must be clearly made aware that such therapy may result in adverse sequelae such as erectile dysfunction or incontinence and may not relieve symptoms. The various surgical options available that are backed by some evidence of efficacy are listed in *Table 4*.

TABLE 3.
Potential pharmacological therapies for chronic prostatitis or chronic pelvic pain syndrome

Treatment category	Examples
Antibiotics	Quinolones, trimethoprim
α-blockers	Tamsulosin, doxazosin, terazosin
Prostatic massage	Repeated massage
Anti-inflammatory	Non-steroidal anti-inflammatory agents
Pain control measures	Gabapentin, amitriptyline
Biofeedback	Perineal (electromyography or pressure probes)
Phytotherapy	Quercetin, saw palmetto, pollen extract
α-reductase inhibitors	Finasteride
Muscle relaxants	Diazepam, baclofen
Physical therapy	Massage therapy, air rings or 'donuts'
Psychotherapy	Exploration of related psychopathologies
Alternate therapies	Meditation, acupuncture, coping skills
Heparinoids	Pentosan polyphosphate
Other medications	Capsaicin, allopurinol

adapted from Nickel et al (2000)

Chronic non-bacterial prostatitis

Appropriate treatment for NIH category IIIa and IIIb prostatitis remains uncertain, as the aetiology of these processes remains unknown. As alluded to earlier, Nickel et al (2001) demonstrated that fluoroquinolone antibiotics may be of benefit to both type II and III chronic prostatitis, irrespective of the Stamey localization test, and so may α-blockers (Barbalias et al, 1998;

Narayan et al, 2002). The rationale for antibiotics rests on the possibility that the causative agents are difficult-to-culture organisms or hitherto unknown aetiological agents that may remain sensitive to antibiotics. These are prescribed for 6 weeks and continued for a further 6 weeks if symptomatic improvement occurs (Nickel, 1999).

Agents currently recommended for bacterial prostatitis are used on their own or in combination with agents effective against chlamydia and ureaplasma (e.g. tetracyclines). Many urologists favour a combination of antibiotics to cover most suspected organisms, an α-blocker, and a muscle relaxant such as diazepam, known as Nickel's 'triple therapy' (Nickel, 1999). Others add anxiolytics or pain modulators such as amitriptyline, 5-α-reductase inhibitors and a non-steroidal anti-inflammatory agent coupled with pelvic floor exercises, biofeedback, relaxation therapies and prostate massage (Barbalias et al, 1998). Tricyclic antidepressants, gabapentin, and muscle relaxants have also been tried with varying outcome; mostly poor and unsupported by large properly designed trials. 'Alternative therapies' such as phytotherapy with agents such as quercetin, a bioflavonoid, is gaining popularity with reported symptom relief in 67% but there are no large, well-designed randomized controlled trials to support this. Finasteride has also been reported to be beneficial in reducing symptom scores (Leskinen et al, 1999). Acupuncture may be of some benefit.

Surgical treatment by TURP is not often effective since the peripheral zone, which is the major site of the inflammatory process, is not effectively removed by this procedure (Kirby, 1999). Other surgical modalities (*Table 4*) such as transurethral microwave thermotherapy and transurethral needle ablation have been shown to improve symptom scores in men with chronic non-bacterial prostatitis in several studies. In the case of transurethral microwave thermotherapy a 74.9% improvement in symptom scores was reported with almost no morbidity (Mene et al, 1997); this was backed up by another study that involved sham controls. However, randomized controlled trials are necessary to confirm this. A limited TURP has been recommended by some (Barnes et al, 1982) in order to remove prostatic calculi and regions affected by prostatitis. Transurethral deroofing or incision of a Müllerian remnant cyst under sonographic control may relieve some cases; care should be taken not to damage the ejaculatory ducts or bladder neck mechanism. The ejaculatory ducts may also be incised simply by using a resectoscope in cases of ejaculatory duct obstruction confirmed by TRUS. Incision of the seminal vesicles has also been anecdotally described. A proposed management algorithm is suggested in *Figure 2*.

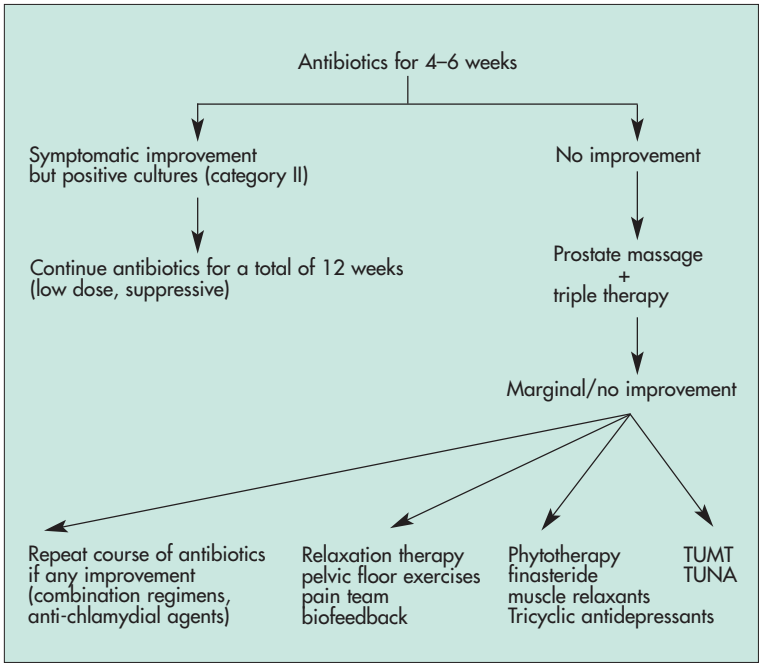
TABLE 4.
Surgical options for chronic prostatitis

Transurethral microwave thermotherapy
Transurethral needle ablation
Laser prostatectomy
Transurethral resection (TURP)
Limited/focal TURP
Retropubic 'total' prostatectomy
Deroofing/incision of Müllerian remnant
Transurethral incision of ejaculatory ducts
Transurethral incision of seminal vesicles

CONCLUSIONS

The aetiology of chronic prostatitis remains an enigma and until more is discovered about the disease treatment will remain empirical, and progress will be slow, by trial and error in clinical studies. From the practical point of view it must be emphasized that a bacterial cause should be diligently sought as the outcome is slightly better in these patients. HM

Figure 2. Management algorithm for category III prostatitis: chronic prostatitis or chronic pelvic pain syndrome. TUMT = transurethral microwave therapy; TUNA = transurethral needle ablation.



Conflict of interest: none.

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KEY POINTS

- Prostatitis is a common condition that causes a high degree of morbidity.
- Although the aetiology of the condition remains poorly understood, all efforts should be made to establish a microbiological diagnosis.
- Antibiotic therapy should be prescribed for a minimum of 6–12 weeks in order to achieve microbiological eradication.
- Surgical options may provide symptomatic relief in treatment failures, particularly in cases of concurrent bladder outflow obstruction.
- More basic science research is urgently required in this field.