# STUDY OF TERAZOSIN IN THE TREATMENT OF CHRONIC PROSTATITIS

by

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*To my wonderful parents, Cheah Eng Wee and Goh Chow Nai,*
*my lovely sister, Phaik Kin,*
*and adorable brother, Phee Kheng*

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| ABP | Acute bacterial prostatitis |
| ANOVA | Analysis of variance |
| BOO | Bladder outlet obstruction |
| BPH | Benign prostatic hyperplasia |
| CBP | Chronic bacterial prostatitis |
| CP | Chronic prostatitis |
| CPPS | Chronic pelvic pain syndrome |
| DNA | Deoxyribonucleic acid |
| EMG | Electromyography |
| EPS | Expressed prostatic secretion |
| IPSS | International Prostate Symptom Score |
| LUTS | Lower urinary tract symptoms |
| NBP | Non bacterial prostatitis |
| NIH | National Institutes of Health |
| NIH-CPSI | National Institutes of Health – Chronic Prostatitis Symptom Index |
| PQS | Pressure flow study |
| PSA | Prostate specific antigen |
| PVR | Post void residual volume |
| Qmax | Peak urinary flow rate |
| QOL | Quality of life |
| SD | Standard deviation |
| SEM | Standard error of mean |
| UDS | Urodynamics |

| | |
|---|---|
| VB1 | First voided urine specimen (First urine) |
| VB2 | Second voided urine specimen (Midstream urine) |
| VB3 | Third voided urine specimen (Post massage urine) |
| Vd | Volume of distribution |
| WBC | White blood cell |

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# PENILAIAN TERAZOSIN UNTUK RAWATAN PENYAKIT PROSTATITIS KRONIK

## ABSTRAK

Walaupun prostatitis kronik merupakan jenis penyakit prostatitis yang paling biasa, tetapi ia paling kurang difahami. Sehingga kini, masih belum terdapat rawatan yang dibukti berkesan untuk penyakit ini. Oleh yang demikian, kajian ini bertujuan untuk menilai keberkesanan terazosin, suatu drug penghalang reseptor $\alpha_1$ untuk rawatan prostatitis kronik.

Sebelum kajian di atas dilaksanakan, indeks prostatitis kronik iaitu, "National Institutes of Health – Chronic Prostatitis Symptom Index" (NIH-CPSI), yang disyorkan oleh National Institutes of Health Amerika Syarikat untuk digunakan dalam penyelidikan prostatitis, telah dikaji dalam populasi tempatan. Daripada kajian ini, NIH-CPSI didapati memuaskan dari segi validiti dan reliabiliti bagi ukuran simptom pesakit, maka adalah sesuai bagi penilaian pesakit dalam kajian di atas. Peralatan urodinamik, iaitu Urodesk 300 yang mengukur kadar aliran air kencing serta tekanan dalam pundi kencing, abdomen dan uretra pula dikaji dari segi ketepatan and kejituannya. Peralatan urodinamik juga didapati sesuai bagi penilaian pesakit dalam kajian di atas.

Seterusnya, suatu kajian prevalens prostatitis kronik di Pulau Pinang, Malaysia telah dijalankan. Daripada 3147 subjek yang disoalselidik, sebanyak 8.7% didapati menghidap penyakit prostatitis kronik. Penilaian klinikal yang merangkumi pemeriksaan fizikal, "ultrasound" and ujian kencing telah dijalankan ke atas subjek yang menghidap prostatitis kronik. Dalam penilaian ini, didapati bahawa 75% juga

memenuhi kriteria klinikal untuk prostatitis kronik, manakala 25% menghidap penyakit lain seperti batu karang ginjal dan varikosil. Hasil soal selidik tersebut juga menunjukkan bahawa sebanyak 8.0% daripada subjek yang terlibat mempunyai simptom urinari.

Bagi meningkatkan kefahaman penyakit ini, kajian urodinamik ke atas pesakit-pesakit prostatitis kronik telah dijalankan. Sebanyak 41.2% pesakit mempunyai masalah pundi kencing, seorang pesakit mempunyai "bladder outlet obstruction" dan seorang pesakit mempunyai "detrusor sphincter pseudodyssynergia". Purata kadar aliran kencing maksimum didapati lebih rendah manakala "post void residual urine" lebih tinggi berbanding dengan kumpulan sukarelawan yang sihat. Suatu kaedah analisis kromatografi cecair prestasi tinggi juga telah dibangunkan untuk menganalisis kepekatan terazosin dalam plasma manusia dan seterusnya kajian farmakokinetik terazosin telah dijalankan.

Bahagian terakhir kajian ini melibatkan suatu kajian "randomized double-blind" dengan kawalan placebo. Dalam kajian ini, seramai 100 orang pesakit prostatitis kronik, berumur antara 20 dan 50 tahun diberikan terazosin atau placebo secara rawak selama 14 minggu. Keberkesanan terazosin dinilai dengan menggunakan NIH-CPSI. Terazosin didapati mengurangkan skor NIH-CPSI lebih banyak ($p=0.01$) berbanding dengan placebo, iaitu sebanyak 57% berbanding dengan 37%. Terazosin juga mengurangkan skor domain individu NIH-CPSI (simptom sakit, urinari dan kesan ke atas kualiti hidup) dan "International Prostate Symptom Score" lebih banyak berbanding dengan placebo. Daripada keputusan kajian ini, didapati bahawa terazosin lebih berkesan daripada placebo untuk rawatan penyakit prostatitis kronik.

# ABSTRACT

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is the most common form of prostatitis but yet the least understood. There is at present, no evidence based therapeutic plan for the management of these patients. Hence, the present study aimed to evaluate the efficacy terazosin, an $\alpha_1$-blocker for treatment of CP/CPPS.

Prior to the above study, the National Institutes of Health – Chronic Prostatitis Symptom Index (NIH-CPSI), a prostatitis specific index, recommended by the US National Institutes of Health for research trials, was evaluated in the local population. The NIH-CPSI was demonstrated to have satisfactory reliability and validity as an outcome measure and hence found to be suitable for patient assessment in the terazosin treatment study. The urodynamics equipment, Urodesk 300, on the other hand, was validated for its within- and between-day precision and accuracy with respect to the urinary flow rate and volume, together with pressure within the bladder, abdomen and urethra. The urodynamics equipment was also demonstrated to give reliable outcome measures.

In the next part of the study, the prevalence of CP/CPPS in Penang, Malaysia was determined. Of the 3147 subjects surveyed, 8.7% were found to have CP/CPPS. In addition, thorough clinical evaluation of those found to have CP/CPPS confirmed that 75% of subjects who met the survey criteria also met clinical criteria for CP/CPPS. The clinical evaluation, which included physical examination, ultrasound and urinalysis found that 25% of the patients who met the survey criteria could be excluded due to other urological conditions such as urinary stones and varicocele. The survey also

demonstrated that the prevalence of lower urinary tract symptoms was 8.0% in the population studied.

To achieve a better understanding of this condition, the urodynamic profile of CP/CPPS patients was evaluated. A high proportion (41.2%) of CP/CPPS patients had various bladder abnormalities, one each had bladder outlet obstruction and detrusor sphincter pseudodyssynergia. Additionally, peak urinary flow rate was significantly lower while post void residual urine volume was significantly higher than those of the control group. An assay method for determining plasma terazosin levels was also developed and subsequently a pharmacokinetic study of terazosin was conducted in the local population.

In the final part of the study, a randomized double-blind placebo-controlled study was conducted. A total of 100 CP/CPPS patients aged 20 to 50 years, were randomized to receive either terazosin or placebo for 14 weeks. Treatment efficacy was assessed primarily by the NIH-CPSI. Terazosin was found to reduce the NIH-CPSI total score (57% reduction) significantly greater ($p=0.01$) than placebo (37% reduction). Terazosin was also effective in reducing the scores of the individual NIH-CPSI domains of pain, urinary and quality of life impact as well as the IPSS score when compared to placebo. Thus, the present study found that terazosin was more effective than placebo in the treatment of patients with CP/CPPS.

# CHAPTER 1. INTRODUCTION

## 1.1 PROSTATITIS

### 1.1.1 INTRODUCTION

Prostatitis is a major healthcare issue (Nickel et al, 1999a), being the third most important prostate disease after prostate cancer and benign prostatic hyperplasia (BPH). Unlike prostate cancer and BPH, which usually inflict older men, prostatitis affects men of all ages with major economic implications (Calhoun et al, 2001). Patients experience a negative impact on their quality of life similar to patients with unstable angina, a recent myocardial infarction, or active Crohn's disease (Wenninger et al, 1996). A catch-all term to describe an array of symptoms that include pain in various places, urinary problems, and sexual dysfunction, prostatitis reflects a lack of knowledge not only regarding its origin but also its treatments, that led urologists to call the diagnosis a "wastebasket of clinical ignorance" (Vastag, 2001). At present, physicians and urologists do not have an evidence-based therapeutic plan for 90% of prostatitis patients, when there is no definite microbiological etiology (Collins et al, 2000a).

### 1.1.2 DEFINITION OF PROSTATITIS SYNDROMES

Prostatitis encompasses a heterogeneous group of infectious and non-infectious disorders, most of which are not sufficiently evaluated to determine their etiology. The diagnostic classification system for prostatitis syndromes has been updated recently from the traditional classification system (Drach et al, 1978). According to the most recent classification to date, prostatitis can be divided into four categories as shown in Table 1.1.

Table1.1 National Institutes of Health Classification of Prostatitis (Nickel et al, 1999a)

| Category | Name | Description |
|---|---|---|
| I | Acute bacterial prostatitis (ABP) | Acute infection of the prostate gland |
| II | Chronic bacterial prostatitis (CBP) | Recurrent urinary tract infection/chronic infection of the prostate |
| III | Chronic abacterial prostatitis/chronic pelvic pain syndrome (CP/CPPS) | Discomfort or pain in the pelvic region/variable voiding and sexual symptoms/no demonstrable infection |
| IIIA | Inflammatory chronic pelvic pain syndrome | Excessive number of white cells in semen/EPS/VB3 |
| IIIB | Non-inflammatory chronic pelvic pain syndrome | Insignificant number of white cells in semen/EPS/VB3 |
| IV | Asymptomatic inflammatory prostatitis (AIP) | Evidence of inflammation in biopsy/semen/EPS/VB3, no symptoms |

The (US) National Institutes of Health recognized the limited understanding of the etiology for most patients previously diagnosed with chronic prostatitis and the possibility that organs other than the prostate gland may be important in the pathogenesis of this syndrome (Nickel et al, 1999a).

Categories I and II are similar to the traditional classification of acute and chronic bacterial prostatitis, respectively. Category III, which is referred to as chronic prostatitis (CP) or chronic pelvic pain syndrome (CPPS), consists of two subcategories, namely, IIIA, which is inflammatory in nature and is known traditionally as non-bacterial prostatitis (NBP), and IIIB, which is non-inflammatory in nature, is known as prostatodynia. This new category III together with category IV, which is asymptomatic prostatitis address the major problems and omissions of the traditional and historic classification system (Drach et al, 1978) employed for the past few decades. The new classification system is dependent on microscopic and culture evaluation of prostate-specific specimens (i.e. expressed prostatic fluid, ejaculate, postprostate massage urine, and/or prostate biopsy). However, the new classification system still suffers from the limitations imposed by an inadequate understanding of the relevance of white blood cells, lack of standardization of leukocyte investigation techniques, and lack of comparable cutoff points for "elevated numbers", as well as a lack of understanding of the true clinical relevance of any microorganisms detected in these specimens (Nickel et al, 1999a).

Bacterial prostatitis is characterized by symptoms of urinary tract infection, positive cultures of urine or prostatic secretions, and inflammatory cells in prostatic secretions. Acute bacterial prostatitis (ABP) causes intense symptoms, as well as constitutional

findings. Chronic bacterial prostatitis (CBP) on the other hand, has a more insidious onset with less pronounced prostatic inflammation. In addition, patients have irritative or obstructive genitourinary symptoms and relapsing or persistent urinary tract infections (Meares, 1992).

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) occurs in men with no history of urinary tract infection and negative bacterial cultures of urine and prostatic fluid. The new NIH consensus definition of CP/CPPS recognizes that pain is the main symptom (with variable voiding and sexual dysfunction) and is the optimal criterion to differentiate patients with CP/CPPS from control patients or patients experiencing other genitourinary problems (e.g. benign prostatic hyperplasia). The definition of CP/CPPS, proposed by the 1995 NIH Workshop on Chronic Prostatitis (Nickel et al, 1999a) is based on the "presence of genitourinary pain in the absence of uropathogenic bacteria detected by standard microbiological methodology". However, it is recognized that some patients experience only obstructive and irritative voiding symptoms without pain. This syndrome is categorized into inflammatory (based on the presence of leukocytes in expressed prostatic secretion, postprostatic massage urine, or semen) or non-inflammatory (no leukocytes in similar specimens). Asymptomatic inflammatory prostatitis (category IV) is a new category that accounts for men with prostatic inflammation detected during evaluation of another disorder (Kohnen & Drach, 1979; Nickel et al, 1999b).

Of men referred for symptoms consistent with prostatitis, only about 10% have ABP or CBP (De la Rossette et al, 1993a). Most of the remainder have CP/CPPS, being the least

understood category. Thus, much of the present discussion is focused on this category of prostatitis.

### 1.1.3 EPIDEMIOLOGY OF PROSTATITIS

Epidemiology is concerned with understanding the distribution and determinants of diseases in populations. To discuss the epidemiology of prostatitis effectively, an operational definition of prostatitis is essential. Until recently, the epidemiology of prostatitis was uncertain and limited by the murkiness inherent in the term "prostatitis" discussed previously. Thus, the new NIH classification and definition of prostatitis provides uniform definition of prostatitis that will facilitate research in epidemiology.

In the past 3 years, epidemiological research has determined that prostatitis is a very common and important disease. Prostatitis was reported to account for 2 million out-patient visits per year and 8% of urology visits in the United States (US) (Collins et al, 1998a). Urologists in the US saw an average of 173 patients with prostatitis per year (Moon, 1997). In Canada, urologists saw an average of 260 patients with prostatitis per year, one third of whom was newly diagnosed (Nickel et al, 1998). However, these studies were retrospective in nature, based on urologist/physician/general practitioner visits and without specific criteria for diagnosis of prostatitis. The prevalence rate of prostatitis in the general population was estimated to be 5% to 9% (Moon et al, 1997; Roberts et al, 1998; Mehik et al, 2000; Nickel et al, 2001a). Unfortunately, the few prevalence studies were from single, often tertiary referral centers in North America and Western Europe. It is difficult to determine if these observations could be generalized to other geographic areas such as Asia. In addition, the available studies are difficult to

interpret and compare, partly because, as mentioned above, a uniform definition of prostatitis has been lacking until recently.

## 1.1.4 ETIOLOGIES AND PATHOGENESIS OF PROSTATITIS

### 1.1.4.1 ACUTE BACTERIAL PROSTATITIS

The most common cause of ABP is infection by gram-negative organisms. Strains of *Eschericha coli* were identified in 80% of infections. *Pseudomonas aeruginosa, Serratia, Klebsiella, and Proteus* were identified in 10% to 15% and enterococci in 5% to 10% of infections (Meares, 1992). Commonly, infections are caused by a single organism, but occasionally by two or more. Besides enterococci, other gram-positive organisms are believed to be commensals of the anterior urethra, which only become pathogenic under certain circumstances. Obligate anaerobic bacteria seldom cause prostatic infection. Several theories exist for the pathogenesis of bacterial prostatitis. It probably evolves from ascending urethral infections or reflux of infected urine into prostatic ducts that empty into the posterior urethra (Kirby et al, 1982). Other possibilities include invasion by rectal bacteria (by direct extension or lymphogenous spread) and hematogenous infection.

### 1.1.4.2 CHRONIC BACTERIAL PROSTATITIS

CBP has the same etiologic organisms as ABP. Its pathogenesis includes stasis of refluxed infectious material, with resultant ductal fibrosis and stone formation, thereby, promoting chronicity (Doble, 1994).

### 1.1.4.3 CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME

Although CP/CPPS is the most common condition, it remains a condition of uncertain etiology and is rarely associated with any other infection in the urinary tract. Although urine cultures are negative, recent studies suggest that the etiology of CP/CPPS may be of bacterial origin. Krieger et al (1996a) found bacterial DNA in 77% of prostate biopsies in patients who had no evidence of bacteriuria or bacterial prostatitis by traditional clinical tests. Specific polymerase chain reaction assays detected *Clamydia trachomatis*, *Mycoplasma hominis* and *Trichomonas vaginalis* in 8% of patients. In a follow-up study (Krieger et al, 2000), bacterial DNA sequences were found in 19.6% of patients with prostatic cancer and 46.4% of patients with CP/CPPS, suggesting that DNA sequences may not be specific to CP/CPPS only. Thus, it is clearly premature, as the authors pointed out, to conclude that the presence of bacterial DNA sequences are associated with prostatitis symptoms.

*Clamydia trachomatis* (De la Rossette et al, 1993a; Bruce & Reid, 1989; Polleti et al, 1985), *Ureaplasma urealyticum* (Ohkawa et al, 1993), *Mycoplasma hominis*, and *Trichomonas vaginalis* (Meares, 1992) have been implicated in previous studies. However, failure to document an immune response in patients reported to have *Ureaplasma* or *Clamydia* (Shortliffe et al, 1992; Schachter, 1985), negative results from other studies (Berger et al, 1989; Doble et al, 1989), possible problems in identification of organisms, and possible urethral contamination of samples (Polleti et al, 1985), raise questions about the etiologic role of these organisms in CP/CPPS. Gram-positive organisms have been suggested (Drach, 1974; Nickel & Costerton, 1992; Lowentrit et al, 1995; Berger et al, 1997) but are generally agreed to be commensals rather than

pathogens (Anderson & Weller, 1979). Thus, the role of an infectious agent in CP/CPPS has not been established.

Other hypothesized causes of chronic prostatitis include chemical prostatitis resulting from intraprostatic urinary reflux (Kirby et al, 1982). Urate appeared to be the chemical agent eliciting the inflammatory response (Persson & Ronquist, 1996). An autoimmune response (Moon, 1998) and a viral etiology have also been implicated (Doble et al, 1991), but the results of these studies were inconclusive.

CP/CPPS may result from tension myalgia of the pelvic floor (Sinaki et al, 1977), or an increased tension in the muscles of the bladder neck and prostatic urethra. Urodynamic and neuromuscular studies have provided conflicting results on the pathophysiology of CP/CPPS. Some studies have indicated that CP/CPPS is caused by abnormal external sphincter activities (striated muscles) (Siroky et al, 1981; Osborn et al, 1981; Hellstrom et al, 1987; Zerman et al, 1999; Clemens et al, 2000), whilst others suggested abnormal internal sphincter activities or sympathetic dyssynergia (Barbalias et al, 1983; Barbalias, 1990; De la Rossette et al, 1992; Theodorou et al, 1999). Mayo et al (1999) on the other hand, found that only few patients (2%) referred to the Prostatitis Clinic had bladder outlet obstruction, suggesting that these patients had neither voiding abnormalities nor dyssynergia.

## 1.1.5 CLINICAL FEATURES

### 1.1.5.1 ACUTE BACTERIAL PROSTATITIS

ABP typically presents with a sudden onset of fever, chills, general malaise and pain in the lower back, rectum, or perineum. Most patients also have intense irritative and obstructive genitourinary symptoms. Rectal palpation usually discloses an exquisitely tender, swollen prostate gland that is partially or totally firm, irregular, and warm to the touch. The prostatic expressate is packed with leukocytes and fat-laden macrophages, and a large number of the bacterial pathogen grow on culture. Because ABP is usually accompanied by bacteriuria, the pathogen generally can be identified by culture of the voided urine.

### 1.1.5.2 CHRONIC BACTERIAL PROSTATITIS

CBP often presents with urinary tract infections caused by recognized uropathogens, objective evidence of inflammation, and a prostatic focus of infection (Krieger & McGonagle, 1989). CBP is characterized by recurrent urinary tract infections caused by the same bacterial species. Patients are often asymptomatic between episodes of bacteriuria and seldom have abnormalities on physical examination. Chills and fevers are unusual, unless an acute exacerbation of the chronic infection occurs. Some men have dysuria or other voiding complaints, ejaculatory pain, hemospermia, or pelvic pain.

### 1.1.5.3 CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME

Inflammatory and non-inflammatory CP/CPPS produce similar systems. Chronic pelvic pains are the most prominent urogenital symptoms of CP/CPPS (Krieger et al, 1996b). The most frequent and discriminatory site of pain is perineal (Alexander & Trissel, 1996; Nickel & Sorensen, 1996). Other sites include suprapubic, testicular, penile,

rectal, and lower back. Urinary symptoms are also prevalent and they include urgency, nocturia, frequency, dysuria, weak urinary stream, hesitancy, post void dribbling and interrupted flow. Although pelvic pains seem to be most discriminatory, some patients experience only irritative and obstructive voiding symptoms, without accompanying pain (Nickel et a, 1999a). Sexual dysfunction may include painful ejaculation, difficulty getting and maintaining erection, difficulty reaching ejaculation, premature ejaculation, lack of interest in sexual activity and hemospermia (Krieger et al, 1996b). There is no history of bladder infections. Urogenital physical examination is unremarkable. The prostate may be normal, tender or boggy on digital rectal examination, and patients may experience tenderness in periprostatic tissues and "tight" anal sphincter on digital rectal examination. Uroflow studies are abnormal in about 30% of cases (De la Rossette et al, 1993a), whilst cystometry and pressure flow studies yield variable results.

### 1.1.6 LABORATORY DIAGNOSIS OF VARIOUS CATEGORIES OF PROSTATITIS

Despite being an important disease, little information is available on the optimal approach to its diagnosis (Collins et al, 2000a). ABP is generally recognized easily because its clinical manifestations are dramatic and characteristic; in contrast, the clinical features of chronic prostatitis syndromes are highly variable and inexact. Indeed many signs, symptoms and physical findings in cases of CBP, inflammatory and non-inflammatory CP/CPPS are often indistinguishable. The medical history and physical findings may suggest diagnosis but are not confirmatory.

Histological examination of prostatic tissue generally is required for diagnosing unusual forms of prostatitis such as granulomatous prostatitis. However, the histological changes

seen in CBP or CP/CPPS are not sufficiently specific to confirm a diagnosis. Kohnen and Drach (1979) reviewed 169 consecutive cases of surgically resected hyperplastic prostates and found an incidence of inflammation of about 98%. Nickel et al (1999b) identified inflammation in all 80 patients with a diagnosis of BPH who underwent transurethral resection of the prostate. Clearly, prostatic inflammation is an extremely common histological finding in patients with no symptoms of prostatitis and is of questionable use in the diagnosis of prostatitis syndromes.

1.1.6.1 LOWER URINARY TRACT LOCALIZATION STUDIES (4-GLASS TEST)

The Meares and Stamey (1968) 4-glass test (**Appendix 1.1**) has been the definitive test to differentiate between bacterial from nonbacterial, and inflammatory from non-inflammatory prostatitis. It is however, contraindicated in ABP, where it is painful for the patient and may cause bacteriemia. This method, called the lower urinary tract localization study, is based on comparison of quantitative colony counts from specific aliquots of urine specimens obtained before and after prostatic massage (**Table 1.2**). Finding at least 10 leukocytes per high power field (400X magnification) in prostatic secretions indicates inflammation (Drach et al, 1978). Anderson and Weller (1979) observed a five-fold increase in leukocytes and an eight-fold increase in lipid-laden macrophages in expressed prostate secretions of men with NBP compared with control subjects. Unfortunately, the lower urinary tract localization study has never been properly validated, and few urologists and almost no primary care physicians use it routinely in clinical practice (Collins et al, 2000b). The reasons include its cumbersome nature, its low yield, the perception that it results in many false negatives and false positives, as well as its poor diagnostic value.

**Table 1.2** Interpretation of the 4-glass test

| Test specimen | | VB1 | VB2 | EPS | VB3 |
|---|---|---|---|---|---|
| Cat II | WBC | - | +/- | + | + |
| | Culture | - | +/- | + | + |
| Cat IIIA | WBC | - | - | + | + |
| | Culture | - | - | - | |
| Cat IIIB | WBC | - | - | - | - |
| | Culture | - | - | - | - |

Cat = NIH Classification Category

WBC = white blood cell

VB1 = first voided urine specimen

VB2 = second voided specimen or midstream specimen

EPS = expressed prostatic secretion

VB3 = third voided urine or post massage urine

The interpretation of the culture results from the four aliquots collected depends on a comparison of the quantitative bacterial counts of the specimens. To clearly document cases of urethritis, prostatitis or cystitis, the counts for the appropriate specimens must differ by at least one to two orders of magnitude to be considered significant. If the count of the first voided urine specimen (VB1), significantly exceeds the count of either expressed prostatic secretion (EPS) or post massage urine (VB3), then urethritis or significant colonization is present. If the count of either EPS or VB3 significantly exceeds VB1, then bacterial prostatitis is present. If the count of the second voided specimen or midstream urine specimen (VB2), significantly exceeds all other specimens, or all four aliquots show heavy growth, then true cystitis or bladder infection is present. In this case, the results cannot be interpreted with respect to the presence or absence of bacterial prostatitis. Therefore, the patient should be placed on an antibacterial regimen (e.g. nitrofurantoin) that will sterilize the bladder urine but which is known not to diffuse into the prostatic fluid and the localization study can be repeated in four or five days when the bladder urine is sterile.

### 1.1.6.2 POTENTIAL DIAGNOSTIC TESTS OF CP/CPPS

Alexander et al (1998) found a strong correlation between levels of interleukin-β and tumor necrosis factor-α in the semen of men with CP/CPPS. This finding suggests that seminal proinflammatory cytokines may provide an objective measure of disease in these patients. However, the lack of correlation between cytokine levels and the leukocyte count in expressed prostatic secretions suggests that cytokine levels do not distinguish a meaningful subpopulation of symptomatic patients

Investigators have hypothesized that immunologic analysis may be a better diagnostic tool than the lower urinary tract localization study (Meares & Stamey, 1968). Two small studies (Wishnow et al, 1982; Shortliffe & Wehner, 1986) suggested that immunologic analysis of prostatic fluid for antigen-specific antibodies might aid in the differential diagnosis between bacterial and non-bacterial prostatitis. However, neither study provided the sensitivity or specificity required.

Zinc has been examined as a marker of prostatic secretary function. Marmar et al (1980) found that zinc levels in men with CP/CPPS and men with bacterial prostatitis were significantly lower that those in controls and men with prostatodynia. The investigators concluded that measurement of zinc levels might help in the differential diagnosis and classification. In contrast, Zaichick et al (1996) found no differences in zinc levels among patients with CP/CPPS, BPH and healthy controls.

Several studies have examined the role of ultrasonography as a diagnostic test for CP/CPPS. Doble and Carter (1989) found that seven of eight ultrasonographic signs were significantly associated with the presence of symptoms of CP/CPPS compared

with controls; sensitivity and specificity were calculated for each sign. Although the sensitivity of ultrasonography increased with higher leukocyte counts, the signs were not sufficiently specific to different clinical groups.

In summary, there is no gold standard diagnostic test for CP/CPPS other than the standard textbook lower urinary tract localization study (4-glass test). The methodological quality of the available studies of other diagnostic tests is weak. Moreover, the studies used only small sample sizes.

## 1.1.7 OUTCOME MEASURES

### 1.1.1.7 PROSTATITS SPECIFIC INDEX

Prostatitis is a disease in which quantification of symptoms is paramount in following a patient's progress. In a disease characterized primarily by symptom complexes, some form of symptom assessment instrument is a prerequisite to determine and validate criteria for disease categories, to perform epidemiological surveys (i.e. natural history and population-based studies), and to evaluate the efficacy of various therapeutic interventions.

Neal and Moon (1994) developed a simple questionnaire (four questions only) that appeared helpful for assessing and following patients with CP/CPPS before and after treatment with an alpha-1 blocker. Krieger et al (1996b) developed a 21-question symptom questionnaire, which consists of 3 domains namely, pain, urinary and sexual dysfunction. Another prostatitis-specific questionnaire, the Symptom Severity Index was developed and validated by Nickel and Sorensen (1996). None of the above symptom scores was regarded as the gold standard, but the work of these authors

provided an important foundation for the development of the National Institutes of Health – Chronic Prostatitis Symptom Index (NIH-CPSI) (Litwin et al, 1999). The NIH-CPSI is a properly validated prostatitis-specific symptom index, which examines the main domains of prostatitis such as pain, urinary and quality of life impact. It is a nine-question questionnaire that is simple, easy and quick to administer and useful in research studies and clinical practice. The NIH International Prostatitis Collaborative Network (IPCN) suggested that the outcome measures in prostatitis research trials should include this index. The NIH-CPSI clearly differentiates CP/CPPS from two control populations: patients with no genitourinary symptoms and patients with benign prostatic hyperplasia. However, the index has not been assessed in other populations or for its sensitivity for determining significant clinical changes.

### 1.1.7.2 THE INTERNATIONAL PROSTATE SYMPTOMS SCORE

The International Prostate Symptom Score (IPSS) is a commonly used instrument in multicenter international clinical trials to assess treatment outcomes in BPH. It consists of seven questions related to incomplete voiding, frequency, interrupted stream, urgency, weak stream, straining and nocturia, and a disease-specific quality of life question (Barry et al, 1992). Each question is rated from 0 ("not at all") to 5 ("almost always"). The total IPSS is the sum of items 1-7 (range 0-35) and it assesses the overall severity of lower urinary tract symptoms. It has been evaluated for reliability, validity and sensitivity to clinical change in BPH, but it was later found that it was not specific to the disease. Because patients with CP/CPPS experience similar lower urinary tract symptoms such as frequency and urgency (Alexander & Trissel, 1996), the IPSS has been used as one of the outcome measures in previous trials even though it has not been validated for this purpose.

### 1.1.7.3 UROFLOWMETRY

Uroflowmetry measures the flow rate of the external urinary stream by volume per unit time in ml/s. The urinary flow rate and pattern reflect the final results of the micturition process consisting of detrusor function, bladder neck opening and urethral conductivity. An abnormal flow rate indicates impaired voiding but does not determine the exact location of the suspected dysfunction. The maximum flow rate is the maximum measured value of the urine flow rate and is the most important single parameter in uroflowmetry. Interpretation of maximum flow rate values requires familiarity with the flow curve pattern, the voided volume, age, sex, artifacts and circadian rhythms. Maximum urine flow rate is highly dependent on the volume voided. Detrusor muscle when stretched, achieves an optimal performance, but if stretched further, it becomes inefficient. Haylen et al (1988) described the maximum flow rate as having a linear relationship with square root of voided urine volume, whereas Drach et al (1979) suggested that maximum flow rate has a linear relationship with voided volume. Abrams (1997) recommended that the volume voided should be in the range of 200-500 mls, and the lowest acceptable flow rate is 21 ml/s for males of 14-45 years old. However, it is difficult to determine if these values can be generalized to other populations. Because it is simple, fast and non-invasive, uroflowmetry is commonly used as a screening tool prior to more complicated urodynamic studies, as well as an outcome measure in clinical trials including those of BPH and CP/CPPS (De la Rossette et al, 1992; Neal & Moon, 1994; Barbalias et al, 1998; Lacquaniti et al, 1998). Flow rates should be evaluated not only with consideration of normal values in the population of interest, but also with machine reliability. Even though most commercially available flowmeters have acceptable accuracy, clinicians should seek independent information on the reliability of their machines, both from the standpoint of accuracy and precision.

## 1.1.8 TREATMENT

### 1.1.8.1 ACUTE BACTERIAL PROSTATITIS

ABP is quite easily managed with a wide spectrum of antibiotic coverage (usually parenteral) and in many incidences involves some form of lower urinary tract drainage (preferably suprapubic tube). Preferred initial therapy in the nonallergic patient is trimethoprim-sulfamethoxazole (TMP-SMX). There is evidence that the new fluoroquinolone agents such as ciprofloxacin, norfloxacin, ofloxacin, and enoxacin have excellent efficacy in the treatment of ABP (Meares, 1992).

### 1.1.8.2 CHRONIC BACTERIAL PROSTATITIS

Treatment for CBP usually requires long-term therapy with antibiotics. The class of antibiotics that are recommended is the fluoroquinolones. They have an affinity for the prostate gland and seem to accumulate well there. Additionally, there is the added benefit of a broad spectrum activity, covering the usual and unusual uropathogens in addition to some of the more fastidious microorganisms, such as *Clamydia*, *Mycoplasma* and *Ureaplasma* species. Most authors agree that four weeks is a minimum period of time necessary to eradicate a prostate infection, while others extend this to 8-12 weeks (Neal, 1998).

### 1.1.8.3 CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME

CP/CPPS is however, more difficult to treat. In the last 30 years, a multitude of treatments for CP/CPPS have been investigated. Some appeared to be successful, but on closer examination the studies utilized small sample sizes, were uncontrolled and brief with undefined populations and unvalidated outcome measures. To date, there is no well-designed placebo-controlled study that provides significant evidence of the

fficacy and safety of any device or treatment in the management of CP/CPPS (Nickel, 000).

ersson and Ronquist (1996) theorized that backflow of urine into prostatic ducts aused prostatic inflammation by increasing concentrations of metabolites that contain urine and pyrimidine bases. Subsequently, a double-blind controlled study of llopurinol treatment in 54 men was performed (Persson et al, 1996). Although this mall trial showed improvements in patient-reported symptoms, investigator-graded rostate pain as well as biochemical variables, the data provided, the measures used, and ne statistics presented do not conclusively support the idea that changing the amounts f purine and pyrimidine bases in urine and prostatic secretions would relieve the ymptoms (Nickel et al, 1996). A randomized controlled trial found that compared to lacebo, quercetine, a naturally occurring bioflavonoid, was well tolerated and produced ignificant improvements in NIH-CPSI symptom scores (Shoskes et al, 1999). lowever, the study only involved 15 patients and the 1-month follow-up period was elatively short. Finasteride has been found to reduce symptoms in patients with nflammatory CPPS compared to placebo (Leskinen et al, 1999). However, pain ratings id not differ significantly between groups. Although the authors speculated that a eduction in prostate volume may alleviate symptoms, the mechanism by which nasteride would improve symptoms in patients with CP/CPPS remains unknown.

rostate massage, which has been employed for decades in the treatment of prostatic isorders, has recently seen a resurgence (Nickel et al, 1999c). The technique of epetitive massage, in theory, empties the prostatic ducts of inspissated secretions and resumably pockets of infection that may be harboured by obstructed regions of the land (Neal, 1998). This treatment combined with concomitant antibiotic usage, may

fford a treatment alternative for refractory patients (Nickel et al, 1999d). Other ublished studies recommended treatments that included pollen extract (Buck et al, 989), trice-weekly ejaculation (Yavascaoglu et al, 1999), pentonsan polysulphate Nickel et al, 2000), non steroidal anti-inflammatory medications (Pontari, 1999), ntibiotics (Nickel et al, 2001b), and a combination of biofeedback, pelvic floor elaxation techniques and bladder training (Clemens et al, 2000). However, none of hese studies were randomized placebo-controlled.

he literature also contains many reports of surgical procedures for CP/CPPS such as ansurethral and "subtotal" prostate resection (Meares, 1986), transurethral incision of he prostate (Kaplan et al, 1994), and hyperthermia (Servadio & Leib, 1991; Nickel & orenson, 1994; Nickel & Sorensen, 1996). However, drug therapy is generally referred as the majority of patients are sexually active.

his wide variety of treatments being investigated, is a reflection of patients' and inicians' frustration with respect to management of CP/CPPS. Therapy is totally mpirical and ineffective in many cases. In 1998, the International Prostatitis ollaborative Network developed a list of treatment modalities that should be evaluated properly designed trials in any future research endeavour. The treatment modalities in rder of priority are outlined in **Table 1.3.**

*ole of α-1 blockers*

ecause symptom complexes of CP/CPPS and BPH overlap (e.g. frequent urination, octuria, incomplete emptying, urgency, hesitancy, terminal dribbling, intermittency, eak stream), investigators have hypothesized that drug therapy for BPH may help

Table 1.3 Prioritizations* of treatments for chronic prostatitis/chronic pelvic pain syndrome (Nickel et al, 1999a)

| Treatment Category | Rank | Priority rating (mean score) |
|---|---|---|
| Antimicrobials (e.g. antibiotics) | 1 | 4.4 |
| Alpha-blockers (e.g. terazosin) | 2 | 3.7 |
| Prostatic massage (repetitive) | 3 | 3.3 |
| Anti-inflammatories (NSAIDS, hydroxyzine) | 3 | 3.3 |
| Pain control measures (e.g. gabapentine, tizanidine) | 4 | 3.1 |
| Biofeedback (e.g. perineal) | 5 | 2.7 |
| Phytotherapy (e.g. saw palmetto, quercetine) | 6 | 2.5 |
| Alpha-reductase inhibitors (e.g. finasteride) | 7 | 2.5 |
| Muscle relaxants (e.g. diazepam, baclofen) | 8 | 2.4 |
| Devices (TUMT, TUNA, laser) | 9 | 2.2 |
| Physical therapy (massage therapy, air rings/donuts | 10 | 2.1 |
| Psychotherapy | 10 | 2.1 |
| Alternate therapy (e.g. meditation, coping skills, acupuncture | 11 | 2.0 |
| Heparinoids (e.g. pentonsan polysulfate) | 12 | 1.8 |
| Capsaisin | 12 | 1.8 |
| Allopurinol | 13 | 1.5 |
| Surgery (TURBN, TURP, radical prostatectomy) | 13 | 1.5 |

NSAIDs = non-steroidal anti-inflammatory drugs; TUMT = transurethral microwave thermotherapy; TUNA = transurethral needle ablation; TURBN = transurethral resection of bladder neck; TURP = transurethral resection of prostate.

*Priority rating: 5, highest; 4, high; 3, medium; 2, low; and 1, very low

ome men with CP/CPPS. Alpha-1 blockers are the most widely used drugs in the edical management of BPH and have been investigated for the treatment of CP/CPPS.

ladder outlet obstruction (BOO) associated with BPH not only results from onmalignant enlargement of the prostate caused by increased cellular growth of the landular and stromal components of the gland, but also from the dynamic component f the disease, which is alpha-1 receptor mediated increased smooth muscle tone of the ladder neck and prostate. Physiologic and pharmacological studies provide compelling vidence that the tension of human prostatic smooth muscles contributes to BOO. Raz et l (1992) were among the first investigators to study the physiology and pharmacology f prostatic smooth muscles. Isometric tension studies demonstrated that the rat prostate ontracts in the presence of norepinephrine, an adrenergic agonist. Caine et al (1975) ubsequently demonstrated that the human prostate adenoma and capsule also contract ith the presence of norepinephrine. Caine et al (1976) recognized the therapeutic nplications of pharmacologically altering the tension of prostatic smooth muscles in ales with clinical symptoms of BPH. By blocking sympathetic input on the alpha-1 drenergic receptor, alpha-1 blockers aim to relax the smooth muscles in the prostate, s capsule, and the area around the bladder neck, and by this mechanism, improve inary flow. This, in turn, relieves both irritative and obstructive symptoms of the wer urinary tract.

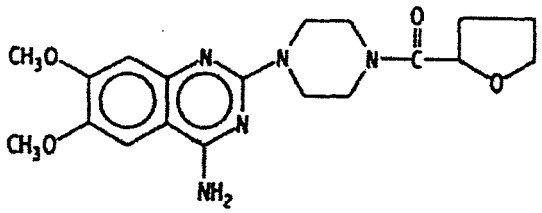
ideo-urodynamic studies have suggested that CP/CPPS symptoms could be attributed functional/dynamic obstruction at the bladder neck. This was evidenced by narrowing the bladder neck during voiding, with complete absence of electromyographic tivity (complete relaxation of the striated urethral sphincter). A sympathetically

nediated contraction of the bladder neck during voiding was thus suggested as the athophysiology of this condition, and hence alpha-blockers were postulated to be eneficial to these patients (De la Rossette, 1992; Barbalias et al, 1983; Barbalias 1990; heodorou et al, 1999). Moreover, it has been shown that dysfunctional voiding may esult in reflux of urine into the prostatic ducts, creating a sterile inflammatory process. f the urine is infected, prostatitis may ensue by the reflux of bacteria into the prostatic cinar system (Hellstrom et al, 1987). Furthermore, a study by Yamanashi et al (2000), ound that terazosin was effective in opening the bladder neck and improving hydraulic nergy profile in men with bladder neck obstruction. $\alpha$-$_1$ blockers, therefore may meliorate prostatitis symptoms whether infectious or not, by reducing the degree of ysfunctional voiding that may be primary or secondary in the pathogenesis. In fact, everal studies have shown that $\alpha$-blockers improved symptoms in CP/CPPS (Osborn et l, 1981; De la Rossette et al, 1992; Neal & Moon, 1994; Barbalias et al, 1998; acquaniti et al, 1998). However, only two of these studies (De la Rossette et al, 1992; acquaniti et al, 1998) were randomized placebo-controlled, of which only the study by acquaniti et al (1998) used a validated symptom score for CP/CPPS. The study by eal and Moon (1994), also used a validated score for CP/CPPS, but the study was not andomized placebo-controlled. More importantly, none of the studies employed the ew NIH consensus definition for CP/CPPS, which recognizes pain as the predominant ymptom.

## 1.2 TERAZOSIN

### 1.2.1 CHEMISTRY

Terazosin, an alpha-1-selective adrenoceptor-blocking agent, is a quinazoline derivative, represented by the following chemical and structural formula: 6,7-demethoxy-2-[4(tetrahydrofuran-2-carbonyl)piperazin-1-yl]-quinazolin-4-ylamine. It is the oldest selective alpha-1 blocker and used widely for the treatment of hypertension and BPH.




### 1.2.2 PHARMACOLOGY

Receptor binding studies have demonstrated that terazosin is highly selective for $\alpha$-$_1$ receptor (Achari & Laddu, 1992). Terazosin selectively blocks postsynaptic $\alpha$-$_1$ receptor without affecting the presynaptic $\alpha$-$_2$ receptor. By blocking the $\alpha$-$_1$ receptor located in vascular smooth muscles, terazosin causes them to relax. This in turn decreases peripheral vascular resistance, resulting in a reduction in blood pressure. Due to its selectivity for postsynaptic $\alpha$-$_1$ receptor, there is minimal reflex increase in heart rate during terazosin therapy. In BPH, as well as in CP/CPPS, there is thought to be $\alpha$-$_1$ receptor mediated increased smooth muscle tone of the bladder neck and prostate. Through blocking the $\alpha$-$_1$ receptor, terazosin will help to improve urinary flow.