Chronic Prostatitis/Chronic Pelvic Pain Syndrome in Elderly Men
Toward Better Understanding and Treatment

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Abstract

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is the most common of the prostatitis syndromes. It is characterised by pelvic pain, with or without voiding symptoms. CP/CPPS accounts for 2 million office visits in the US alone. Recent epidemiological studies have shown that CP/CPPS can affect men at any age, including those in their 80s. The aetiology is unknown but proposals include infectious, autoimmune, neurologic and psychiatric causes. Men with CP/CPPS are much more likely to have had a past medical history of cardiovascular, neurologic, psychiatric or infectious disease (particularly sinusitis) as compared with asymptomatic individuals. Although leucocytes are commonly found in the prostatic fluid of these men, they do not correlate with the symptoms.

The clinical evaluation now includes a validated, self administered symptom score, the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI), which was designed as an outcome measure for treatment trials. This can aid in diagnosis and follow-up of patients’ response to therapy.

Treatment for CP/CPPS is empiric and limited by a lack of randomised, placebo-controlled clinical trials. Antimicrobials are commonly used to treat the symptoms of CP/CPPS. However, the finding that asymptomatic men have equal or greater numbers of bacteria which localise to the prostatic fluid, compared with men with CP/CPPS, has raised doubts about the contribution of infection to the symptoms. Other commonly used drugs include α-adrenoceptor antagonists, anti-inflammatory drugs, tricyclic antidepressants and anticholinergic agents. The adverse effects of these medications are a concern in older men with CP/CPPS. Other therapies available include minimally invasive procedures such as microwave thermotherapy and transurethral needle ablation, and now neuromodulation devices.

Although much progress has been made, particularly in the last 7 years, considerable work still remains to be done to determine the aetiology and...
Prostatitis is a term that refers to several clinical syndromes. These range from well-defined bacterial infections to poorly defined chronic pelvic pain, to asymptomatic inflammation in the prostate found in pathology specimens. The traditional classification of prostatitis included acute prostatitis, chronic bacterial prostatitis, chronic non-bacterial prostatitis and prostatodynia.\(^1\)

A more recent classification was adopted in 1995 after a US National Institutes of Health (NIH)-sponsored consensus conference (see table 1).\(^2\) In the current system, category I and II reflect acute and chronic bacterial prostatitis, respectively. Together, both account for ≤5–10% of all cases.\(^3\) These cases are clearly associated with bacterial infection and will have a urine culture that grows uropathogens. Acute prostatitis is characterised by the sudden onset of fever and dysuria, whereas chronic bacterial prostatitis typically is characterised by relapsing episodes of urinary tract infections (UTIs), usually with the same organism seen on urine cultures. These patients are usually asymptomatic between infections. Category IV refers to asymptomatic inflammatory prostatitis that is diagnosed incidentally during a work up for infertility, an elevated prostate-specific antigen (PSA) or benign prostatic hyperplasia (BPH). The most common type of prostatitis and the least understood is category III.

Table III, known as chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), constitutes the vast majority (>90%) of cases and is divided into IIIA and IIIB. IIIA refers to the presence of white blood cells (WBCs) in either semen, post-prostate massage urine specimen (VB3) or expressed prostatic secretion (EPS). This corresponds to the previously used classification of chronic non-bacterial prostatitis. Category IIIB is comparable to the formerly used term prostatodynia, and refers to patients with pelvic pain but no evidence of inflammation in semen, VB3 or EPS specimens. The new classification does not correlate exactly with the old system, mostly because the use of seminal fluid and VB3 as sources of leucocytes will increase the number of men considered to have inflammation compared with the traditional system which distinguished chronic non-bacterial prostatitis from prostatodynia on the basis of an examination of EPS alone.\(^4\)

The symptom that distinguishes CP/CPPS from other voiding dysfunction is the presence of pain.\(^5\) The current NIH definition of CP/CPPS is that of genitourinary pain in the absence of uropathogenic bacteria detected by standard microbiological methods.\(^2\) There has been an increase in interest in CP/CPPS starting with the consensus conference in 1995. To facilitate research in the natural history and epidemiology of CP/CPPS, as well to start to develop treatment trials, the NIH formed the Chronic Prostatitis Collaborative Research Network (CPCRN) in October 1997.\(^6\) One of the findings of this group is that CP/CPPS is not limited to younger and middle aged men as previously thought. In the CPPS study, the average age of the men was 42 years, with a range of 20–82 years. Of the cohort, 39% were aged >45 years and 13% were >55 years of age.

Several studies have looked at the prevalence of prostatitis by age in population based studies. Using data from the Health Professionals Follow-Up study of >30 000 individuals, Collins et al. found that 16% of men reported having a history of prostatitis. Of these men, the age of first treatment increased steadily up to 60 years.\(^7\) In a longitudinal study of a cohort of men from Olmsted County, Minnesota, USA, Roberts et al.\(^8\) found that the age specific incidence of chronic prostatitis remained low until the fifth decade, and then markedly increased after the age of 60 years, with an even greater incidence

Table I. National Institutes of Health classification of prostatitis syndromes\(^2\)

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Acute bacterial prostatitis</td>
</tr>
<tr>
<td>II</td>
<td>Chronic bacterial prostatitis</td>
</tr>
<tr>
<td>IIIA</td>
<td>Chronic prostatitis/chronic pelvic pain syndrome</td>
</tr>
<tr>
<td>IIIB</td>
<td>Non-inflammatory (no leucocytes in VB3, EPS or semen)</td>
</tr>
<tr>
<td>IV</td>
<td>Asymptomatic inflammatory prostatitis</td>
</tr>
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\(\text{EPS} = \text{expressed prostatic secretion}; \text{VB3} = \text{post-prostate massage urine specimen}.\)
after the age of 70 years. The cumulative probability of having chronic prostatitis reached 9% at the age of 85 years. Those with a history of prostatitis had an increased risk of recurrent episodes with age, being 20%, 38% and 50% among men 40, 60 and 80 years old, respectively. In two counties in Ontario, Canada, Nickel et al. found that prostatitis symptoms as determined on the pain and voiding domains of the NIH Chronic Prostatitis Symptom Index (NIH-CPSI) were present in 11.5% of men <50 years of age who responded to their survey, compared with 8.5% of men >50 years of age. After a peak of 12.8% among men aged 40–49 years, there was a steady decrease each decade to 10.2% for age 50–59 years, 9.1% for age 60–69 years and 6.9% for age 70–74 years. Using questions similar to the NIH-CPSI, Roberts et al. found that overall, 12% of respondents had at least one urogenital pain symptom. The mean pain score was relatively constant with increasing age, but the urinary symptom and quality-of-life impact scores increased with age. Thus, it appears that men can experience symptoms of chronic pelvic pain at any point in their lifetime.

Epidemiological studies have shown that overall CP/CPPS is much more common than previously assumed. This condition accounts for ≤2 million outpatient visits per year, which are 8% of visits to urologists and 1% of primary care visits in the US. The sickness impact for chronic prostatitis is similar to scores reported in the literature for patients with myocardial infarction and Crohn’s disease. Collins et al. used the 12-item Short Form (SF-12) to evaluate the mental and physical health of CP/CPPS patients and found that the mental component summary score for CP/CPPS patients was lower than that observed in the most severe subgroups of congestive heart failure and diabetes mellitus. Recent data also indicate that there is a substantial cost associated with prostatitis, with 25% of patients reporting loss of work time over the past 3 months, 49% reporting lost leisure time and 13% reporting hospitalisation at some point in their lives because of the condition.

1. Aetiology

Whereas category I and II prostatitis are caused by bacteria including Escherichia coli, Klebsiella, Enterobacter and Pseudomonas, the aetiology of category III prostatitis is unknown. Many causes have been proposed including infectious, autoimmune, neurologic and psychiatric diseases (see Table II). As part of the CPCRN, an epidemiological study was performed that tested some of these hypotheses. The men in the CPCRN cohort with CP/CPPS were compared with a group of 120 asymptomatic individuals. Patients and control individuals did not differ in age, education, employment status or sexual history. Patients reported a significantly greater lifetime prevalence of non-specific urethritis as well as several other items in their self-reported medical history. This included a 6-fold greater incidence of cardiovascular disease, which was predominantly hypertension. Patients also reported a 5-fold greater history of neurological disease and a 2.5-fold greater history of psychiatric disease than control individuals. Hematopoietic, lymphatic or infectious disease, specifically sinusitis, was twice as common in the patients as in the control individuals.

Is there a relation between infection and sexual activity? A Finnish population-based study by Mehik et al. reported on 1832 (75%) respondents to a non-NIH questionnaire of men in the two most northern provinces of Finland. Interestingly, divorced and single men had a lower risk than married men, independent of age. The authors speculated that this difference might be because of the exposure of married men to potential pathogens from their wives’ genital tract. Despite these findings and those of the CPCRN epidemiology study, other studies to date have failed to identify an ongoing infection in these men from any sexually transmitted organisms including Chlamydia trachomatis, Ureaplasma

| Table II. Possible aetiological factors in chronic prostatitis/chronic pelvic pain syndrome |
|---------------------------------|---------------------------------|
| Non-specific urethritis         | (Occult) infection              |
| Cardiovascular disease*         | Neurological disease*            |
| Psychiatric conditions          | Environmental factors           |
| Autoimmune disorder             | Functional somatic syndrome     |
| Interstitial cystitis           |                                 |
| a. May be particularly important in older men. |
urealyticum, Mycoplasma hominis or Trichomonas vaginalis.\textsuperscript{16,24-28}

The symptoms of pelvic pain and voiding dysfunction are similar to those that occur with a true bacterial infection. Therefore, it is not surprising that one of the most common theories of aetiology is that of an occult infection. This idea has also been bolstered by the discovery of fastidious microbes as the cause of other previously poorly characterised conditions such as \textit{Helicobacter pylori} for stomach ulcers and \textit{Tropheryma whippelii} for Whipple’s disease.\textsuperscript{29} One limitation to isolating organisms in prostatitis patients may be the culture method itself. Shoskes et al.\textsuperscript{30} suggested that increasing culture time from 2 to 5 days yields 7.5% more positive cultures, and that these cultures correlated with inflammation secondary to Gram-positive bacteria. The longer culture time seemed to make the biggest difference in cultures of semen and EPS, indicating that there may be local environmental factors in these fluids that may inhibit their growth initially, but can be overcome by the longer incubation time.

Newer studies have also increasingly used molecular techniques to try to answer the question of infection in these patients. In a recent study using polymerase chain reaction (PCR), several unusual organisms were identified.\textsuperscript{31} Using PCR on the pellet of samples from CPPS patients and control individuals, investigators found that the most common species discovered were from the genera Paenibacillus and Proteobacterium and were much more common in men with CPPS. Shoskes and Shahed\textsuperscript{32} found that performing PCR on EPS detected the presence of bacterial DNA in category IIIA patients in 23 (70\%) of 33 specimens, whereas the culture was positive (for Gram-positive bacteria) in only 17 (51\%) of 33 specimens. Only 2 of 14 category IIB patients had bacterial DNA. Nevertheless, 13 (57\%) of the total patients with bacterial DNA improved with antimicrobials while patients who lacked bacterial DNA by PCR did not improve with antimicrobials.

Further questions to the answer are: (i) if bacteria are present in the prostate of men with pelvic pain, are they responsible for the symptoms? and (ii) are bacteria present in the prostates of men without symptoms? Hochreiter et al.\textsuperscript{33} compared PCR results of prostatic tissue samples searching for bacterial DNA from radical or open prostatectomy specimens with samples from healthy organ donor prostates. In the former group, they found samples with inflammation that correlated with the presence of bacterial DNA by PCR, while a negative PCR result was seen in the healthy group with no inflammation. They concluded that healthy prostates contain no flora. Another study also found that bacterial RNA in the prostate was not specific for men with prostatitis and was also found in men undergoing implantation of radioactive seeds for prostate cancer.\textsuperscript{34} A recent study by Krieger et al.\textsuperscript{35} supports the association between bacterial DNA and inflammation. Sterile prostate biopsies were retrieved from radical prostatectomy specimens and category III patients using perineal approach. Bacterial DNA was detected by PCR in 20\% of prostates with cancer, and 46\% of prostates with chronic prostatitis. DNA sequences from typical and non-typical uropathogenic bacteria were found. This finding was contrary to the authors’ hypothesis that older men, i.e. older prostates, would have higher bacterial rates, as they might have been catheterised or had UTIs in the past. The authors concluded that bacteria might be associated with prostate disorders, but not necessarily a reflection of the medical history.

The most recent evidence does not support a role for the bacteria that can be detected by standard culture methods as being pathogenic in men with CP/CPPS. In a case control study as part of the CPCRN, Nickel et al.\textsuperscript{36} found no difference in the rates of positive cultures localising bacteria to the prostate between men with CP/CPPS and asymptomatic men. This argues against commonly detected bacteria as a cause of the symptoms of chronic prostatitis and points out that bacteria seem to be normally found in the prostate of asymptomatic men.

Whether or not there is an ongoing infection or a remote infection, a common finding in patients with CPPS is that of ongoing inflammation. The 1995 classification retains the distinction between men with leucocytes in EPS, VB3 or semen and those without leucocytes. Several studies indicate that the inflammatory response in men with CP/CPPS may be autoimmune. The EPS of CP/CPPS patients contain markers for cytotoxic T cells, a cell type not typical of antimicrobial immunity, but more consis-
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Does inflammation correlate with symptoms? In the CPCRN cohort study, the presence of WBCs correlated poorly with symptoms. This study looked at 278 men with CP/CPPS. Category IIIA was defined as ≥5 WBCs in EPS or >1 in VB3 or semen. Urethral inflammation was defined as ≥1 WBC in first voided urine (VB1). Of these patients, 56% had urethral inflammation, 51% had ≥5 WBCs in EPS and 87% were classified as category IIIA. None of the symptom index measures, including subsets for pain, urinary and quality of life, were different for WBCs subgroups. The overall rank correlation between WBCs and urinary symptoms was not significant and weak. Another argument against the association of inflammation and symptoms is that category IIIB patients have symptoms but no inflammation, and conversely category IV patients have inflammation but no symptoms.

Although WBCs do not correlate with symptoms, other markers of inflammation are present that may have a stronger association. Several groups of researchers have measured the levels of inflammatory mediators in the EPS of men with chronic prostatitis. Hochreiter et al. reported that levels of IL-8 and epithelial neutrophil activating factor-78 (ENA-78) were significantly elevated in categories IIIA, IV and I prostatitis patients as compared with control individuals and category IIIB prostatitis patients. These cytokines are direct mediators of leucocytic chemotaxis and activation. An association was shown between leucocytes and levels of IL-8, but not between cytokines and pelvic pain. The ultimate role in pain of these cytokines is questionable because of no increase in their levels in category IIIB patients. Also, it cannot be conclusively said if these cytokines are released after WBCs activation or precede and stimulate their arrival. The Northwestern group also found elevated levels of IL-1β and tumour necrosis factor (TNF-α) levels in EPS in category IIIA as opposed to category IIIB patients and control individuals. No correlation between these cytokines and WBCs was noted. Elevated levels of TNF-α and IL-1β have also been reported in the seminal plasma of men with chronic prostatitis as compared with asymptomatic control individuals. Ruggieri et al. found no correlation between levels of IL-1β and TNF-α in seminal plasma and symptoms in CP/CPPS patients. However, Hochreiter et al. found that cytokine levels in EPS changed in association with symptoms. In the absence of antimicrobial treatment, 80% of patients showed increased cytokines (by a mean of 1.725%) when symptoms developed and a mean decrease of 49% when symptoms disappeared. Increases or decreases in cytokine levels also correlated with WBC levels in EPS. When antimicrobials were given, in 93% of the cases cytokine levels decreased (mean decrease 51%) regardless of changes in symptoms or inflammatory status.

Correlation between IL-10 and both pain severity and quality-of-life measures has been reported. IL-10 has been shown to be involved in the pathogenesis of several autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus, myasthenia gravis and asthma. Thus, it is also possible that while static measurements of immune mediators may not correlate with symptoms, changes in the levels of these mediators may be clinically meaningful.

Another marker of inflammation is reactive oxygen species (ROS). Neutrophils release ROS, which are free radicals, in response to antigenic stimulation. Release of such species (O2, HO, H2O2) or oxidative stress, within the prostatic fluid of category III patients, is a hot concept for investigation. Oxidative stress in EPS, as a marker of tissue injury, secondary to pathogenic bacterial infection, was studied by Shahed and Shoskes. Their premise was that infection by Gram-positive bacteria in category IIIA, and not prostatic colonisation, results in...
oxidative stress, since tissue injury by definition follows infection and not colonisation. Thus, after antimicrobial treatment for infection, the oxidative stress would be reduced, proving Gram-positive bacteria to be true pathogens. Less oxidative stress levels were independent of leucocyte count in the EPS, and therefore not a marker per se of leucocytes, but rather a marker of tissue injury. Less oxidative stress was subsequently detected in the EPS after clinically successful treatment with oral antimicrobials or antioxidants. Increased ROS levels and low antioxidant levels in seminal plasma of men with CPPS compared with control individuals were also reported by Pasqualotto et al. Thus, the concept of non-WBC inflammation must be considered in future models of prostatitis.

The presence of pain leads to the question of whether there is a neurologic cause for the symptoms. Zerrmann et al. found significant abnormalities in the coordination of voiding and activity in the pelvic floor/external urethral sphincter in >80% of men with symptoms of pelvic pain. This kind of dysfunction is classically found in patients with a supra-sacral spinal cord lesion, which raises the question as to whether these men have a subclinical neural injury in the spinal cord that would contribute to such dyssynergy and thus pelvic pain. Also, some chronic pelvic pain patients respond to sacral neurostimulation supporting the idea that whatever the inciting insult, there may be a common pathway to nerve dysfunction in these patients. An association has also been made between nerve growth factor (NGF) and CP/CPPS. NGF is a protein produced by cells in a target organ, which is then absorbed by sympathetic and small sensory fibres via a tyrosine kinase A (trkA) receptor, and transported retrograde to the cell body. NGF has been implicated in inflammation that may lead to hyperalgesia by mechanisms including sensitising nociceptors, elevating levels of substance P and calcium gene related peptide, which may cause histamine release from mast cells and central sensitisation. NGF levels have been shown to correlate with pain in men with CP/CPPS. Although in the study by Miller et al. there was no difference in levels of seminal plasma NGF in men with CP/CPPS and control individuals, our studies and others have demonstrated increased NGF compared with control individuals in both seminal plasma and post massage urine.

Although pain is the common symptom in these patients, there may be psychological and even environmental factors that may affect how the patient perceives the pain. In a study by Mehik et al., men >50 years of age had a 3-fold greater risk of having or having had prostatitis than their younger cohort. Of these men, 63% had their worst symptoms during the winter months of November-March, while very few (3%) had their worst symptoms in the summer. The authors concluded that the higher prevalence they reported might in part be owing to the cold climate. The authors also reported that psychological stress was a common finding in this population. Self-assessment of personality showed that these men were more nervous and busy than healthy control individuals. They also showed fears of having a sexually transmitted disease and suicidal thinking was more common. A Korean study found that longer exposure to sunlight was protective against developing symptoms of CPPS. The authors also found that a lower education level was associated with a higher incidence of CPPS. Overall, the psychological health of men with CPPS appears to be inferior to those of the healthy population. Although it is unlikely that depression is a cause of the original symptoms, it certainly may be a result of the chronic pain and disability, and may make the perception of the symptoms worse.

Furthermore, there is a growing perception that CPPS may be one manifestation of a series of disorders labelled functional somatic syndromes. As compared with the general population, functional somatic syndromes and psychological disorders were significantly more prevalent among men with CPPS. The symptoms of functional somatic syndrome included irritable bowel syndrome, chronic headache, fibromyalgia, and non-specific dermatological and rheumatological symptoms. These findings are also similar to those with interstitial cystitis in which patients were found to be 100 times more likely to have inflammatory bowel disease and 30 times more likely to have lupus than the general population.
population. This again raises the question of whether the two entities are either related, or the same process. A significant question to address in the definition, evaluation and treatment of CP/CPPS is whether this is the same syndrome as IC.

Both IC and CP/CPPS are clinical syndromes characterised by chronic pelvic pain and voiding dysfunction. Neither has an identifiable objective parameter such as histological, biochemical or radiological findings with which to make the diagnosis. Traditionally, the majority of patients diagnosed with IC are female, while the diagnosis of chronic prostatitis is necessarily made in males. Currently accepted clinical diagnostic criteria for IC and prostatitis allow for men with pelvic pain and voiding symptoms to be included in either diagnosis. A good example is that one of our patients qualified for inclusion in both the Interstitial Cystitis Data Base cohort and CP/CPPS. Clinically, IC and CP/CPPS are often similar if not indistinguishable. In addition to the symptoms, both are known to have a detrimental impact on quality of life. Studies have documented the similarity in seeing glomerulations with hydrodistention under anaesthesia in patients with both IC and prostatitis. The importance of this comparison is diminished with more recent data indicating that glomerulations are not pathognomonic of IC. However, pain with bladder filling is a hallmark of IC and also has been reported in 45% of men with CP/CPPS. Urodynamic findings common to both groups include sensory urgency and poor relaxation of the pelvic floor with bladder contractions and voiding.

The aetiology and much of the pathogenesis of both IC and CP/CPPS are unknown. However, many of the theories of aetiology of CP/CPPS have also been applied to IC and vice versa. As in CP/CPPS, the idea of occult infection as a cause of IC has been popular. One recent report identified Ureaplasma urealyticum in 48% of patients diagnosed with IC and 90% of these patients improved after antimicrobials. Another popular theory in the pathogenesis of IC has been that of a ‘leaky epithelium’ in the bladder caused by a deficiency of glycosaminoglycans on the bladder epithelium. Although this has not been tested in the prostate, it has been noted that the prostate does contain surface mucus and the question has been raised as to whether changes in the prostatic epithelium, from infection or even reflux, could be responsible for patient symptoms. The concept of a neurogenic aetiology and especially neurogenic inflammation is well established in IC. C fibres are sensory nerves associated with pain transmission and also innervate mast cells. These sensory nerves release substance P which is a nociceptive neurotransmitter that produces pain and also stimulates mast cells to release their contents, including histamine and tryptase. Elevated levels of substance P containing neurons have been found in the bladder of patients with IC. Mast cells may also release their contents in response to cytokines, bacterial toxins, hypoxia and stress among other stimuli. Elevated numbers of mast cells have been reported in patients with IC as well as elevated levels of histamine in the bladder wall. Mastocytosis has been suggested in CP/CPPS. The idea of an autoimmune response has also been widely theorised for IC.

Data on aetiological mechanisms of CP/CPPS specifically in elderly men are very limited. Most studies do not stratify for age in their evaluation, especially those looking at biomarkers. Several areas may be particularly important in the elderly. One is neurological causes, as with aging there can be spinal degeneration, which based on the CPCRN epidemiological study may play a role in CP/CPPS. This study also highlighted the association between a history of cardiac disease and CP/CPPS, which would be expected to be more common in the elderly. The work by Mehik et al. on pain perception found a difference between young and older patients. Whether or not there are differences in aetiology and pathogenesis in CP/CPPS in young versus older men is not known, and will await the discovery of what these factors are in any population.

2. Evaluation

There is no accepted standard evaluation for men with CP/CPPS. However, the results of a recent symposium on CP/CPPS outlining suggestions for evaluation have been published (see table III). Mandatory measures include history, physical examination including digital rectal examination, urinalysis and urine culture. In the older man with
The commended investigation is determination of post-void residual urine. This is especially important in older men given the greater risk of retention from BPH than in younger men with CP/CPPS.

There are many optional investigative procedures as outlined in a recent summary statement by Nickel.[84] The role of imaging studies is controversial, but prostatic ultrasound may be especially helpful in men who have pain after ejaculation, to look for lesions such as prostatic and mullerian remnant cysts. Patients with urethral discharge should have a urethral swab. Urodynamics can be used in men whose voiding symptoms are refractory to treatment. They should be performed in men with elevated residual urine to assess the reason for difficulty emptying the bladder. In older men, the finding of elevated residual urine is likely to be more common than in younger individuals, either because of prostatic obstruction or reduced bladder contractility. It is important also to further evaluate abnormalities in the workup and not to ascribe these findings necessarily to the CP/CPPS alone. Two findings that are particularly relevant to older men are haematuria and an elevated PSA. Haematuria, microscopic or gross, should not be attributed solely to prostatitis but be further evaluated with cystoscopy and a study of the upper urinary tracts. PSA measurement is not standard in the evaluation of CP/CPPS, but is done frequently as a screening test for prostate cancer in men >40 years of age in African Americans or those with a family history of prostate cancer, or age ≥50 years in other individuals. PSA is slightly elevated in men with CP/CPPS compared with asymptomatic individuals,[91] but not enough to account for PSA >4.0, which should prompt a prostate biopsy. The main goal of the evaluation of patients with category III or CP/CPPS is to try to find a treatable cause of the symptoms. Unfortunately, in the vast majority of men, no such cause will be identified.

3. Treatment

Currently used treatments for CP/CPPS are empiric (see table IV). Limitations include lack of a clear aetiology to guide appropriate therapy, and a dearth of randomised, placebo-controlled trials to support the treatments that are already being used. McNaughton Collins et al.[92] reviewed the available

| Table III. Clinical, laboratory, and imaging evaluations for chronic prostatitis/chronic pelvic pain syndrome |
|---|---|---|
| **Mandatory** | **Recommended** | **Optional** |
| History (includes Post-void Localisation studies: 2- (VB2, NIH-CPSI) residual volume VB3) or 4-glass (VB1, VB2, EPS, VB3) test | Physical examination | Imaging: transrectal ultrasound examination |
| Urinalysis and culture | Urethral swab | Urodynamics studies |
| EPS = expressed prostatic secretion; NIH-CPSI = National Institutes of Health Chronic Prostatitis Symptom Index; VB1 = first voided urine; VB2 = midstream urine; VB3 = post-prostate massage urine specimen. |

**Symptoms of CP/CPPS,** the digital rectal examination is very important to look for prostate nodules that should prompt a biopsy to rule out prostate carcinoma. Recommended evaluation includes the assessment of symptoms, which has been greatly facilitated by the CPCRN with the development of the NIH-CPSI, a self-administered validated symptom index.[85] Originally designed as an outcome measure for use in treatment trials, it is also very useful for symptom assessment in the office and also is now available in Spanish translation.[86] The index has nine questions divided into domains of pain, urinary symptoms and quality of life. Scoring can be used to identify areas to target in history and to follow-up clinically patients’ progress.

Other recommended investigations include some form of lower urinary tract localisation studies. The evaluation of chronic prostatitis has traditionally used the Meares-Stamey four glass test (VB1, midstream urine [VB2], EPS, VB3).[87] Nickel[88] has advocated using the pre- and post-prostate massage urine for culture and microscopic examination. The correlation between leucocytes in the EPS and VB3 has been confirmed, so the use of VB3, which is easier to obtain, provides a surrogate marker.[89] The utility of four glass localisation cultures for diagnosis of category III has been called into question by the findings that asymptomatic men have a similar amount and localisation of bacteria on this test as do symptomatic men with CP/CPPS.[36] Urine should be sent for cytology to rule out bladder cancer or carcinoma in situ as a cause of the symptoms,[90] which is particularly more relevant in older men compared with men aged 20–30 years. Another recommended investigation is determination of post-
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literature from 1966 to March 1999 and found 14 randomised and/or controlled treatment trials in CP/CPPS. One recent advance has been the proposal of a uniform set of inclusion and exclusion criteria for research trials in CP/CPPS. To facilitate research studies that include comparable groups of patients and allow for comparisons, the second International Prostatitis Consensus Conference adopted the criteria that had been developed for use in the NIH sponsored CPCRN cohort study. These guidelines have recently been used in studies such as the CPCRN randomised clinical trial to evaluate four treatments: ciprofloxacin alone, tamsulosin alone, ciprofloxacin with tamsulosin, and placebo.

Among the most commonly used treatments of CP/CPPS are antimicrobials. Although there is a clear rationale for use in category I and II, the use of antimicrobials for category III is less well supported. In category III prostatitis, 40–50% of patients responded to a 2–4 week therapeutic trial. Fluoroquinolones have been the drug of choice because of good prostate penetration, good bioavailability and equivalence between oral and parenteral formulations. There does not seem to be a difference in response to 4 weeks of antimicrobial therapy in category III prostatitis compared with an 8 or 12 week course. Thus, an initial 4-week course can be attempted, and patients who respond can be treated for an additional 2–4 weeks, while in those who do not respond, the treatment can be stopped. In older men it is important to look at the urine or VB2 results. If there is a bacterial infection, further evaluation such as bladder ultrasound should be performed to rule out urinary retention and poor bladder emptying as a cause of the UTI.

Another common treatment for CP/CPPS is α-adrenoceptor antagonists. Response rates reported are in the range of 50% with either non-selective α-1 and α-2 adrenoceptor antagonists or selective α-1 adrenoceptor antagonists. A recent study examined the use of tamsulosin and found that this more selective α-adrenoceptor antagonist may also be beneficial in CP/CPPS.

One of the considerations for the use of α-adrenoceptor antagonists in older men is that of adverse effects. α-Adrenoceptor antagonists can cause marked hypotension, syncope, dizziness and lightheadedness or vertigo, especially when standing. Marked orthostatic effects are most frequently seen with the first dose, but can also occur following dosage increases. In placebo-controlled trials for BPH, the incidence of these symptoms with the non-selective α-1 adrenoceptor antagonist doxazosin 1 mg was low (0.3%) and did not increase with increasing dosage to 8 mg/day. The incidence of discontinuation of treatment because of hypotension or orthostatic symptoms was 3.3%. Other adverse reactions seen with doxazosin and placebo had <1% incidence, but of possible clinical interest were angina pectoris (0.6% and 0.7%, respectively), postural hypotension (0.3% and 0.3%, respectively), syncope (0.5% and 0.0%, respectively) and tachycardia (0.9% and 0.0%, respectively). Thus, one significant consideration before starting α-adrenoceptor antagonists is to check resting blood pressure.

Another factor to consider α-adrenoceptor antagonists in older men is that of concurrent coronary disease, as hypotension in these men may produce decreased cardiac perfusion. These cardiovascular effects are much less often observed with tamsulosin used to treat symptomatic BPH. One of the reasons for this may be that the proportion of the α-1B receptor subtype increases with advancing age in human blood vessels. Tamsulosin is a selective antagonist of α-1A and α-1D receptors so does not bind to α-1B receptors in the blood vessels of older men.

There have been few clinical trials of anti-inflammatory therapy for chronic prostatitis and only one was a randomised, double-blind, placebo-con-

Table IV. Treatment options for chronic prostatitis/chronic pelvic pain syndrome

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<tr>
<th>Limited course of antimicrobials</th>
<th>α-Adrenoceptor antagonists&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Anti-inflammatory drugs</th>
<th>Pentosan polysulfate</th>
<th>Finasteride&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Quercetin</th>
<th>Tricyclic antidepressants</th>
<th>Anticholinergic drugs&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Gabapentin</th>
<th>Minimally invasive surgical therapies&lt;sup&gt;b&lt;/sup&gt; microwave thermotherapy, transurethral needle ablation</th>
</tr>
</thead>
</table>

<sup>a</sup> Use with caution in elderly men because of possible adverse effects.

<sup>b</sup> May be particularly useful in elderly men.

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trolled trial. Small studies of non-conventional anti-inflammatory medications have been reported using promelase\cite{106} and nimesulide.\cite{107} In 2001, a randomised, placebo-controlled trial of rofecoxib, a cyclo-oxygenase 2 (COX-2) inhibitor, was completed.\cite{108} The theory for the use of a COX-2 inhibitor in CP/CPPS comes from the association of the COX-2 subtype of the cyclo-oxygenase enzyme with inflammation. COX-1 is the constitutive isofrom found in virtually all cell types; the COX-2 isofrom is undetectable in most tissues, but is rapidly induced in inflammation.\cite{109} In vivo, COX-2 can continue to be synthesised for days or weeks given the persistence of an appropriate stimulus.\cite{110} Compared with healthy men, EPS and semen of men with CP/CPPS have higher levels of the inflammatory cytokines IL-1\beta and TNF-\alpha.\cite{41,42} These cytokines up-regulate COX-2 gene expression, which may further contribute to inflammation.\cite{111}

In the rofecoxib trial,\cite{108,112} a total of 161 patients were randomised to treatment with rofecoxib 50mg, 25mg, or placebo. The NIH-CPSI total, domain and pain scores significantly decreased from baseline in all groups, and although the mean scores numerically favoured the rofecoxib groups, the difference was not statistically significant between groups. There was a trend for a higher percentage of patients with a 25% or 6-point improvement in NIH-CPSI total score on rofecoxib versus placebo, with the difference being significant for the 50mg rofecoxib group (p < 0.05). Patient global assessment of pain, response to therapy and disease activity also favoured rofecoxib over placebo (p < 0.05, p = 0.07, p = 0.06, respectively). Rofecoxib was generally well tolerated. Of interest is that there appeared to be a better response in category IIIB patients, or those without inflammation in their prostatic secretions, compared with category IIIA. This leads one to reconsider the importance of inflammation in this condition and what the precise site of action of rofecoxib was in those patients who improved.

There are other drugs which are not NSAIDs but likely exert an anti-inflammatory effect in treating the symptoms of CP/CPPS. Pentosan polysulfate is a semisynthetic mucopolysaccharide that is chemically and structurally similar to the naturally occurring sulphated polysaccharides that form a protective barrier in the urinary epithelium. Beneficial effects have been reported with oral dosages of 200mg twice daily\cite{113} and 100mg three times daily.\cite{114} A randomised, placebo-controlled trial compared pentosan polysulfate 900 mg/day orally for 16 weeks with placebo: there was a moderate or marked clinical global improvement with pentosan polysulfate (36.7%) compared with placebo (17.8%) [p = 0.04].\cite{115} The idea of a common aetiology for IC and CP/CPPS has been again raised by these data, as pentosan polysulfate, has been widely used in women with IC.

Finasteride, a 5-\alpha reductase inhibitor, may also have anti-inflammatory effects. In patients with category IIIA prostatitis, 6 months of therapy with finasteride compared with placebo resulted in a 50% improvement in global assessment in 44% of patients receiving finasteride and 27% of placebo recipients.\cite{116} Finasteride is an attractive medication to use in older men with CP/CPPS because it can also be effective on BPH,\cite{117} which can be concurrent in men with symptoms of CP/CPPS. A previous long-term study indicated that the use of finasteride could reduce the risk of acute urinary retention or operation for bladder outlet obstruction.\cite{117} A study from the NIH indicated that the combination of finasteride and doxazosin could reduce the long-term risk of adverse events from bladder outlet obstruction such as worsening symptoms, recurrent UTI, urinary retention and renal failure.\cite{118} Another compound that has anti-inflammatory effect is the flavonoid quercetin. In a randomised, placebo-controlled trial, quercetin produced significant reduction in NIH-CPSI symptom scores (p = 0.003) and was generally well tolerated.\cite{119}

Many other drugs are used for CP/CPPS, as evidenced by the NIH sponsored CPCRN study,\cite{6} but these lack controlled trials to document their efficacy. Some of the more commonly used drugs to treat CP/CPPS include tricyclic antidepressants, such as amitriptyline. These are thought to block pain by inhibiting the central neuronal reuptake of norepinephrine and serotonin, potentiating the inhibitory effect of these substances on central pain processing receptors.\cite{120,121} Anticholinergics such as oxybutynin or tolterodine are used to treat the increased urinary frequency. Tricyclic antidepressants also have possible anticholinergic side effects.
There is some theoretical concern in using anticholinergic drugs in older men for fear of causing difficulty emptying the bladder if there is concomitant BPH. A study looked at using anticholinergic drugs to actually help treat the symptoms of BPH and found them to have good safety profile with very little risk of precipitating urinary retention. Of more concern is the possibility of central nervous system effects from anticholinergic medications in elderly men, and this must be monitored closely. Newer anti-epileptic drugs, such as gabapentin, have also proven to be useful in treating neuropathic pain and have been used in CP/CPPS.

Some surgical and minimally invasive options are also available. In patients who have CP/CPPS and documented smooth sphincter/bladder neck dyssynergy, incision of the bladder neck has excellent results. In this study, 74% of men had pelvic pain, so although the study said they were misdiagnosed as chronic prostatitis, they would indeed meet the clinical definition. The point is that they had a treatable lesion causing the pelvic pain. Microwave thermotherapy has been applied both transrectally and transurethrally with good results reported when used for CP/CPPS. Transurethral needle ablation (TUNA) delivers low level radiofrequency energy at 490 kHz to heat the tissue and selectively ablate the prostatic tissue. While TUNA has been shown to be effective in the treatment of BPH, reports on its use for treatment of CP/CPPS have been mixed. A prospective, non-randomised trial in 42 patients reported excellent results in terms of improved symptom score and decreased leucocyte count in EPS, while another recent study found no significant treatment difference compared with the sham treatment group. A promising surgical procedure for CP/CPPS is sacral neuromodulation, in which a neuroprosthetic sacral nerve stimulation device is surgically implanted after successful percutaneous trial stimulation. Of the ten patients with chronic pelvic pain in a study, six reported significant improvement in pelvic pain symptoms at 19 months follow-up. Pelvic floor physical therapy is also a good option in these patients.

4. Conclusions

The study of chronic prostatitis has advanced greatly in the past 7 years. In this time, there has been a new classification system, and advances in epidemiology and treatment. It is now recognised that the most common entity that clinicians confront, i.e. the patient with unexplained chronic pelvic pain, is that of category III, now called chronic pelvic pain syndrome. This term is clinically more relevant than the term chronic prostatitis, because it reflects the current thinking that not all pelvic pain in these men is necessarily attributable to the prostate. Chronic prostatitis is no longer just thought as a condition of young or middle-aged men, but one that affects men at any point in life, young or old. Other disease processes are also seen in association with CP/CPPS such as cardiovascular and neurological conditions that may be more common in elderly men, which may provide clues to the aetiology and pathogenesis of the disorder. The significance of inflammation in the prostatic fluid of men with pelvic pain has been called into question, as there is tremendous overlap with asymptomatic men and the leucocyte count does not correlate well with symptoms. Further work into non-leucocyte inflammation is required, and the need for the subcategories of IIIA and IIIB must be readdressed. Recent data indicating the prevalence of bacteria on cultures in asymptomatic men has changed the idea of what constitutes a prostate infection and cast doubt on the role of commonly identified organisms in producing the symptoms of CP/CPPS. The theory that older men may harbour more bacteria in their prostate than younger men has been refuted.

The current state of treatment of chronic prostatitis is limited by both a lack of double-blind, randomised, placebo-controlled trials and a lack of understanding of the aetiology and pathogenesis of the condition on which to base rational treatment. However, among the available treatment options, there are some drugs which may be particularly suited for use in older men, such as finasteride and α-adrenoceptor antagonists, although adverse effects must be carefully considered when using the latter agents.

Further randomised, controlled trials sponsored by the NIH are due to begin sometime in 2004. As part of the continuation of the CPCRN, further investigation into the relationship between CP/CPPS and IC is also planned.
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