Chronic prostatitis and chronic pelvic pain syndrome (CP/CPPS)

Introduction to chronic prostatitis and chronic pelvic pain syndrome (CP/CPPS).
Riccardo Bartoletti, Nicola Mondaini, Carlo Pavone, Nicola Dinelli, Domenico Prezioso

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Mercoledì 21 Novembre aprirà il Congresso con una Sessione di Chirurgia Prostatica in diretta dal Policlinico di Modena, cui seguirà la “Giulia ni Lecture” sulle Lesioni Preneoplastiche e la Cerimonia Inaugurale.

Il tema principale riguardante le Neoplasie della Prostata, verrà approfondito per mezzo di sette Corsi, suddivisi nelle varie giornate.


Infine verranno assegnati, come consuetudine, 4 premi per le Migliori Comunicazioni (uno per ogni disciplina) nonché premi per il Miglior Poster e per il Miglior Video.

Nuova Dead line per l’invio dei contributi scientifici: mercoledì 15 Agosto 2007 entro le ore 24

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Programma scientifico

Mercoledì 21 novembre
10.00 Inizio registrazione
11.30 Inaugurazione del Congresso
12.00 Chirurgia in diretta dal Policlinico di Modena
16.00 Giuliani Lecture - Le lesioni preneoplastiche
19.30 Giuliani Lecture - I modelli predittivi

Giovedì 22 novembre
9.00 Sala a Corso - Imaging e Biopsia prostatica
   Sala b Corso - Riabilitazione uro-andrologica
   Sala c Corso - Nuovi approcci terapeutici
   Sala d Corso - Rene
13.30 Lunch Time (eat and meet the professor)
   Area poster Poster meet the author
14.30 Sala a Video
   Sala b Comunicazioni selezionate
   Sala c Comunicazioni
   Sala d Comunicazioni
15.30 Sala a Simposio
   Sala b Simposio
16.30 Sala a Simposio
   Sala b Simposio
17.30 Sala plenaria La SIUrO incontra i pazienti
18.30 Sala plenaria Assemblea ordinaria

Venerdì 23 novembre
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8.30 Sala d Corso infermieri
10.30 Coffe break time
11.00 Sala plenaria Corso - Gli effetti secondari delle terapie radicali: la congiura delle verità parziali?
12.30 Sala plenaria Lettura Auro - Chemioprevenzione
13.00 Sala plenaria Lettura SIU
13.30 Lunch Time (eat and meet the professor)
   Area poster Poster meet the author
14.30 Sala a Video
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18.00 Sala plenaria Conferenza - New directions in image guided radiotherapy for intermediate and high risk prostate cancer
19.30 Sala plenaria Conferenza Prof. Roach - Casi clinici

Sabato 24 novembre
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10.30 Coffe break time
11.00 Sala plenaria Corso - Epidemiologia, etiopatogenesi e marker del CaP
12.30 Sala plenaria Corso - CaP indolente: il sorvegliato speciale del prossimo futuro
13.30 Lunch Time (eat and meet the professor)
   Area poster Poster meet the author
14.30 Sala a Video
   Sala b Comunicazioni selezionate
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15.30 Sala plenaria Premiazioni
16.00 Sala plenaria Workshop - Le mille facce della chemioterapia
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Registrazione: Tribunale di Milano n.289 del 21/05/2001
Direttore Responsabile: Pietro Cazzola
Direzione Generale: Armando Mazzù
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Consulenza grafica: Piero Merlini
Impaginazione: Clementina Pasina
Stampa: Parole Nuove s.r.l. - Via Garibaldi 58
20047 Brugherio, Milano - Italy

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Prostatitis is the most frequently diagnosed illness in men under 50, accounting for about 8% of all consultations with urologists. Estimates based on published studies suggest that the incidence of prostatitis in the population is somewhere between 4% and 11%.

In 1995 the National Institutes of Health (NIH) classified prostatitis into 4 main categories: 1) acute bacterial; 2) chronic bacterial; 3) pelvic pain syndrome; 4) asymptomatic inflammatory.

The aetiological agent most often involved is bacterial, particularly the category of Gram (-) bacteria, followed by Gram (+), chlamydiae and mycoplasms; however many cases of prostatitis are caused by bacteria which are difficult to isolate or by actiopathogenic mechanisms which are immunological, neurological, psychosomatic or anatomical in nature.

An observational study was recently done on the Italian territory in order to estimate the incidence and risk factors of chronic prostatitis /chronic pelvic pain syndrome (CP/CPPS). The disease incidence estimation was 13.8%. Cigarette smoking, high caloric diet with low consumption of fruit and vegetables, constipation, meteorism, slow digestion, sexual relationship with more than one partner and coitus interruptus were more likely in CP/CPPS patients than in controls (p<0.001). CP/CPPS had a negative influence on sexual desire, erectile dysfunction and premature ejaculation (p<0.001). The Meares Stamey test was positive in 13.3% of patients and 2.9% of controls.

KEY WORDS: Prostatitis; Definition; Epidemiology; Risk factors.
Prostatitis is caused by bacteria which are difficult to isolate or by aetiopathogenic mechanisms which are immunological, neurological, psychosomatic or anatomical in nature.

There are still aspects of this illness which need to be better understood and more clearly defined; a lot of misinformation and confusion results from the way the problem is handled not only by general practitioners but also by medical specialists (6). In practice patients with prostatitis often ask the doctor for advice about what type of diet, lifestyle and habits can prevent a worsening of the symptoms and of the illness.

Sportsmen, cyclists in particular, often want to have information about the effects of their sporting activity on the prostate gland, whether or not they have prostatitis. The role of perineal microtrauma in the aetiopathology of prostatitis has long been suspected. However the few studies which have looked at the effect of sporting activity on PSA levels have not shown significant differences in the marker in relation to physical exercise in general (7, 8). However there are reports in which patients aged over 50 have significantly higher total PSA levels after cycling, highlighting the need to abstain from cycling prior to PSA measurement (9, 10). Other authors correlate the presence of prostatitis with ano-rectal illnesses or alterations of the gastro-intestinal apparatus such as Crohn disease, alimentary allergies, and irritable bowel syndrome (IBS).

Prostatitis is a complex illness, for which there are no precise clinical parameters and which is mainly defined on the basis of symptoms, and this has meant that a psychosomatic aetiology of the illness has been often hypothesised.

The use of symptomatological scores such as the “National Institutes of Health Chronic Prostatitis Symptom Index” (NIH-CPSI) together with the “International Index of Erectile Dysfunction” allows a more accurate definition of the patient’s situation, particularly in terms of monitoring the medical treatment. The NIH-CPSI questionnaire was designed by Litwin in 1999 for

### Table 1.

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>Difference between the two groups (p)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range)</strong></td>
<td>34.9 (24-43)</td>
<td>36.3 (28-41)</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Level of education</strong></td>
<td></td>
<td></td>
<td>0.60</td>
</tr>
<tr>
<td>Elementary school</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle school</td>
<td>68 (8.8)</td>
<td>11 (6.9)</td>
<td></td>
</tr>
<tr>
<td>College</td>
<td>480 (62.9)</td>
<td>117 (77.1)</td>
<td></td>
</tr>
<tr>
<td>Degree</td>
<td>216 (28.3)</td>
<td>24 (16.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Cigarette smoking</strong></td>
<td>551 (72.1)</td>
<td>71 (46.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Alcohol consumption</strong></td>
<td>482 (63.0)</td>
<td>78 (51.0)</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>Diet (mean daily proportional consumption)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meat/fish/eggs</td>
<td>35%</td>
<td>45%</td>
<td>0.06</td>
</tr>
<tr>
<td>Milk/cheese</td>
<td>28%</td>
<td>15%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pasta/rice/cake</td>
<td>45%</td>
<td>15%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vegetables</td>
<td>15%</td>
<td>35%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fruits (n° pieces/daily-mean)</td>
<td>1.4</td>
<td>3.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Drink (ml/daily-mean)</td>
<td>1500</td>
<td>1800</td>
<td>0.79</td>
</tr>
<tr>
<td>Coffee (n° cups/daily-mean)</td>
<td>3</td>
<td>4</td>
<td>0.70</td>
</tr>
<tr>
<td>Daily spice use (mean)</td>
<td>605 (79.2)</td>
<td>99 (65.1)</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Sexual behaviour</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 partner</td>
<td>329 (43)</td>
<td>97 (64)</td>
<td>0.059</td>
</tr>
<tr>
<td>&gt;1 partners</td>
<td>435 (57)</td>
<td>55 (36)</td>
<td></td>
</tr>
<tr>
<td><strong>Contraceptive methods</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No contraceptive methods</td>
<td>245 (32)</td>
<td>61 (40)</td>
<td>0.65</td>
</tr>
<tr>
<td>Coitus interruptus</td>
<td>313 (41)</td>
<td>33 (22)</td>
<td>0.001</td>
</tr>
<tr>
<td>Condom</td>
<td>138 (18)</td>
<td>43 (28)</td>
<td>0.73</td>
</tr>
<tr>
<td>Others</td>
<td>68 (9)</td>
<td>15 (10)</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>Concomitant diseases</strong></td>
<td>25 (3.2)</td>
<td>3 (1.8)</td>
<td>0.90</td>
</tr>
<tr>
<td><strong>Concomitant pharmacological treatments</strong></td>
<td>15 (2.0)</td>
<td>2 (1.0)</td>
<td>0.89</td>
</tr>
</tbody>
</table>
use in aetiological and clinical studies, and as a diagnostic tool to define both the patient's symptoms and their quality of life (11). A new definition of prostatitis was recently introduced by the International Continence Society (ICS) and is a classification system which mainly considers pelvic pain but does not take into account all the other aspects of the illness (12).

It is therefore necessary to define patients with non-specific clinical symptoms in terms of their status (diet, related illnesses, lifestyle, sexual activity, physical activity, work) and in terms of their illness, both subjectively (NHI-CPSI, IPPS, VAS, IEFF-5) and objectively (an evaluation which defines the clinical situation and the results of microbiological tests).

The decision about which clinical and microbiological tests are more appropriate for identifying the illness is not based on any guidelines. The decision about which clinical and microbiological tests are more appropriate for identifying the illness is not based on any guidelines. An observational study was recently done on the Italian territory in order to estimate the incidence and risk factors of chronic prostatitis /chronic pelvic pain syndrome (CP/CPPS). Seven-hundred-fourty-six patients out 5540 male urological outpatients and 152 healthy volunteers were evaluated through an accurate analysis of lifestyle, medical history, subjective symptoms and microbiological tests, from January to June (2002).

The disease incidence estimation was 13.8%. Cigarette smoking, high caloric diet with low consumption of fruit and vegetables, constipation, meteorism, slow digestion, sexual relationship with more than one partner and coitus interruptus were more likely in CP/CPPS patients than in controls (p<0.001) (Table 1). CP/CPPS had a negative influence on sexual desire, erectile dysfunction and premature ejaculation (p<0.001). The Meares Stamey test was positive in 13.3% of patients and 2.9% of controls. Therefore this tests should be recommended for all patients, particularly those without previous antibiotic treatment. In some controls bacteria were localized in the prostate but no symptoms were reported. This raises three questions: 1) Are bacteria in the prostatic fluids relevant for the diagnosis of CP/CPPS? 2) Should these subjects be considered as category IV prostatitis? 3) Are bacteria in the prostate important for the genesis of CP/CPPS or do bacteria colonize just inflamed tissue? What is the cause and what is the consequence?

The main question raising by evaluating the low incidence of bacterial disease is: why do Italian Urologists currently treat CP/CPPS with antibiotics? Moreover the information collected from this study should be considered extremely important because related to how often the illness is reported and also indicate the extent of the social problem in Italy. In fact CP/CPPS has a high incidence among urological outpatients. It is a multifactorial disease related to diet, lifestyle, gastrointestinal and ano-rectal diseases, and impairment of sexual activity. Further studies are needed to better characterize the aetiology of the individual patient in order to define the optimal approach of diagnosis and treatment.

Moreover a recent hypothesis of the aetiology of prostate carcinoma has suggested that chronic prostatitis may cause or speed up the development of prostate cancer. Clinical tests might therefore be necessary for patients classified as ‘at risk’ in standard international classifications (rising PSA and PSA >2.5 ng/ml).

**References**

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**Summary**

Chronic prostatitis (CP) has been described as one of the most common illnesses in men aged ≤50, showing a significant impact on patients' quality of life comparable with other chronic diseases, such as unstable angina or Crohn's disease. CP also is a social and economic problem due to its high incidence in the young male population and to the absence of evidence for the effectiveness of treatment. Today, however, although validated outcome questionnaires are available to follow prostatitis patients, diagnostic and treatment options are based on experience, expert opinion and poor clinical trial data. More extensive and better-designed epidemiological studies are needed to evaluate and describe prostatitis patient clinical characteristics, in order to carry out correct and useful treatment. The aim of this report is to present the new Associazione Italiana Sindromi Pelvico Prostatiche questionnaire (AISPEP-Q) in order to provide a tool for increasing knowledge in prostatitis patient characteristics and design future epidemiological studies.

**Key words:** Chronic Prostatitis; CP/CPPS; Questionnaire; Symptom Score; Quality of Life.

**INTRODUCTION**

Chronic prostatitis (CP) is one of the most important infectious diseases in young fertile males and has been indicated as one of the major medical healthcare problems not only in urology but also in everyday general medicine (1). Epidemiological research had demonstrated that 35% to 50% of men are affected by prostatitis at some time in their life (2-4). The prevalence of prostatitis has been reported from 9 to 12%, according to country (5). Rizzo et al., in a prospective and descriptive study, have recently reported a prevalence of prostatitis in Italy of 12.8% of all urological visits (6). However, the real incidence and prevalence of prostatitis is underestimated, due to the lack of international guidelines to help physicians on how best to evaluate and treat patients with suspected prostatitis. Moreover, the impact that prostatitis seems to have on patients’ quality of life is very similar to that caused by other chronic diseases, such as unstable angina and Chron's disease, with billions of dollars being spent every year in USA and other countries (7). The development of a new classification, carried out in 1995 by the US National Institutes of Health (NIH) (8) and reviewed after 3 years (9), allowed a better systematization of the treatment options to the benefit of patients (4). Today, however, although validated outcome questionnaires are available to follow prostatitis patients, diagnostic and treatment options are based on...
experience, expert opinion and poor clinical trial data. More extensive and better-designed epidemiological studies are needed to evaluate and describe prostatitis patient clinical characteristics, in order to carry out correct, useful treatment. In 2003, in Italy, a non profit association, called AISPEP (Associazione Italiana Sindromi Pelvico Prostatiche), was set up by a group of volunteers affected by chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), with the aim of raising awareness of this suffering male condition, to provide a web forum for support and information and stimulate clinicians to plan new research. During its three years’ activity the AISPEP web site and its related forum has become an important meeting point for all Italians affected by this condition, working together with similar foreign associations. AISPEP has recently developed a website questionnaire, in Italian, in co-operation with a number of specialists, in order to collect the different symptomatic and behavioral characteristics of the patients affected by chronic prostatitis, especially by collecting a large amount of information useful to a more extensive comprehension of the causes and predisposing factors involved in this disease. The aim of this report is to present the AISPEP questionnaire (AISPEP-Q) in order to provide a tool for increasing knowledge in prostatitis patient characteristics and design future epidemiological studies.

**AISPEP Questionnaire Description**

The questionnaire was completed in July 2005 by the AISPEP team and the group of specialists. It was turned into a web format. Internet consultation on the AISPEP web site was activated in Italy on January 24 2006. By November 24, 141 questionnaires useful for prospect statistical evaluation had been collected. The questionnaire in Italian is given in Appendix 1. The AISPEP-Q consists of 93 questions and is divided into eight different subscales (Table 1).

**AISPEP-Q implementation**

The AISPEP questionnaire was implemented as an extension module of the PHP-Nuke Content Management System. PHP-Nuke is a free software, released under the GNU-GPL License. It is a customizable CMS (Content Management System) that integrates all the instruments that are used to create an information site/portal. PHP-Nuke utilizes the duo PHP + MySQL, which is a hinge of its own structure, very often being accompanied by the Apache web server. The goal of this software is an automated web site to distribute news and articles and collect data and information from users. The AISPEP site is based on PHP-Nuke and the questionnaire is reserved for registered users. The data are stored in a relational database (MySQL) and are available for statistics of all kinds. Users have to give a valid e-mail address to register and cannot use the same address for two different registrations. Furthermore, AISPEP strongly discourages users from registering more than once with different e-mail addresses. Each registered user can fill in the online questionnaire only once. Therefore, it is reasonable to say that each patient has filled in the questionnaire only once and that each collected questionnaire comes from a different patient. Although the questionnaire is filled in by registered users, AISPEP cannot associate these users with their replies. The procedure is similar to the election process: we know who has voted, but the vote is secret, in order to ensure members privacy. When the users start filling in the questionnaire, they read the following advice: “You are asked to fill in the questionnaire with accuracy and honesty. It is impossible to track down the user who filled in the questionnaire: users’ IDs are listed and saved in order to prevent multiple deliveries, but it is impossible to track down the replies of any single user. Certain questions only require as single answer while others allow multiple ones. When you finish data entry, the system will show you a summary of your answer and you can check them and ensure you did not make any mistakes or miss out any answer”.

**Subscale descriptions**

The first section

In this section patients are asked to respond to personal information data in 9 questions about age, height, weight, place of birth and of residence, married status, number of sons/daughters, education level and type of profession.

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Subscale topic</th>
<th>Questions number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>personal information</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>anamnestic data</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>life habits</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>pain description</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>urinary symptoms</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>sexual habits</td>
<td>19</td>
</tr>
<tr>
<td>7</td>
<td>quality of life</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>patient knowledge about prostatitis</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>93</td>
</tr>
</tbody>
</table>

*Table 1.*

The table shows the AISPEP-Q subscales and their topics. The number of questions is also shown.
The second section
It consists of 26 questions about anamnestic data of the patients concerning the time of prostatitis diagnosis, time of presenting symptoms, who made the diagnosis, how many specialists visited the patients, the level of information that the specialist gave to the patients and the level of patient satisfaction and which diagnostic examinations the patients had before being diagnosed. Additional questions are about past urinary tract infection, catheters use, perineal traumas, varicocele, discom- pathies, neurological illness, depression, diabetes, arthritis, eye inflammation, oral infections, intestinal problems, irritable bowel syndrome, allergies, therapies or surgical treatments, episodes of acute prostatitis, isolated bacteria, in case of bacterial prostatitis, and in which biological material they were isolated.

The third section
The third section concerns the life habits in 11 questions, about sports, meals, use of alcoholic beverages, smoking, anabolizing drugs, driving, sedentary life, stress, holidays.

The fourth section
The fourth section is about painful symptoms in 8 questions. It includes questions about pain location, description, when patients started to feel pain, monthly frequency, ejaculation pain, difficulties in orgasm manifestation, fecal problems.

The fifth section
The fifth section describes urinary symptoms: 10 questions. Urinary burning, urethral burning beyond voiding, urinary efforts and interruption, decrease in urinary flow, urinary urgency, nocturia, hematuria.

The sixth section
The sixth section involves 19 questions about the sexual sphere: age of first intercourse, gender related intercourse, presence of a stable partner, number of sex partners in the last six months, number of partners up to now, type of sexual practice, number of monthly intercourses, difficulties in maintaining erection, worries about sexual intercourse, presence of premature ejaculation before and after appearance of prostatic symptoms, frequency of masturbation, use of 5-PDI and their effects, hemospermia and change in sperm consistency, fertility.

The seventh section
Quality of life in 8 questions. This section concerns to what symptoms extent impact patients' life: in normal activities, in social life, in sexual life, how much the patient thinks about his symptoms, problems about discussion with partner, friends and family, reaction to being forward to live with present symptoms for the rest of one's life.

The eighth section
The last section is about the knowledge that patients have about prostatitis, about who informed the patients and who they share/discuss their problems with.

DISCUSSION
According to the most recent observation studies performed in Italy (6,10), CP seems to represent a very common diagnosis in urological practice, but very little is known about general patient conditions, way of life, risk factors, etiological causes and sexual and quality of life impact in patients with CP (11). From this consideration, our idea started off creating a very detailed and exhaustive questionnaire about CP. Considering that up to now an Internet survey seems to be the easiest way of collecting the most extensive data in the shortest time, we set up this AISPEP-Q and in 10 months we received 141 completed surveys collected on-line and tabulated at the central site. As expected, the responding population consisted of relatively young men from all over Italy (mean 30.3 years). This fact will allow the AISPEP and the authors to evaluate a national population in a short time. Additionally, the questionnaire will collect a large amount of data concerning not only symptoms but also the performed clinical and laboratory investigations, therapies carried out, co-morbidities, sexual dysfunctions and quality of life details. The setting-up group hope that the analysis of the data will focus on the possibility for better separation of CP/CPPS men from normal subjects. Future aims will be to validate and extend the questionnaire to other international populations of patients affected by CP/CPPS (English version) with the hope of collecting data able to demonstrate similar symptoms, quality of life impact, and risk factors from these different populations and confirm that CP is a pathology affecting young fertile men. Base of conducting patient surveys by Internet has been well demonstrated up to now.

ACKNOWLEDGEMENTS
We are grateful to all AISPEP members for their support and to Professor John Denton for manuscript language revision.

REFERENCES
### APPENDIX 1

The Italian version of AISPEP-Q.

1. **Dati personali**
   1. **Età**
      - 15-19
      - 20-24
      - 25-29
      - 30-34
      - 35-39
      - 40-44
      - 45-49
      - 50-54
      - 55-59
      - 60-64
      - 65-69
      - 70-74
      - 75 e oltre

2. **Altezza**
   - Fino a 160 cm
   - 161-170
   - 171-180
   - 181-190
   - Oltre 190 cm

3. **Peso**
   - Fino a 60 kg
   - 61-70
   - 71-80
   - 81-90
   - 91-100
   - Oltre 100 kg

4. **Regione di nascita**
   - Abruzzo
   - Basilicata
   - Calabria
   - Campania
   - Emilia-Romagna
   - Friuli-Venezia Giulia
   - Lazio
   - Liguria
   - Lombardia
   - Marche
   - Molise
   - Piemonte
   - Repubblica di San Marino
   - Sardegna
   - Sicilia
   - Toscana
   - Trentino-Alto Adige
   - Umbria
   - Valle d’Aosta
   - Veneto

5. **Regione di residenza**
   - Abruzzo
   - Basilicata
   - Calabria
   - Campania
   - Emilia-Romagna
   - Friuli-Venezia Giulia
   - Lazio
   - Liguria
   - Lombardia
   - Marche
   - Molise
   - Piemonte
   - Repubblica di San Marino
   - Sardegna
   - Sicilia
   - Toscana
   - Trentino-Alto Adige
   - Umbria
   - Valle d’Aosta
   - Veneto

6. **Stato civile**
   - Celibe
   - Sposato
   - Vedovo
   - Separato/divorziato

7. **Figli**
   - 0
   - 1
   - 2
   - 3
   - Più di 3

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**Correspondence:** Sandra Mazzoli, STDs Center, Santa Maria Annunciata Hospital Via dell’Antella, 58 - 50011 Bagno a Ripoli, Florence, Italy; E-mail: smazzoli@libero.it
8. Grado di istruzione
   Scuola elementare
   Scuola media inferiore
   Scuola media superiore
   Laurea

9. Professione
   Studente In cerca di occupazione Lavoratore dipendente Lavoratore autonomo Imprenditore Libero professionista Dirigente Pensionato

2. Anamnesi del paziente
1. Da quanto tempo ti è stata diagnosticata una prostatite?
   No, non mi è stata diagnosticata una prostatite
   Meno di 6 mesi
   Più di 6 mesi, meno di un anno
   Più di 1 anno, meno di 3 anni
   Più di 3 anni, meno di 5 anni
   Più di 5 anni

2. Da quanto tempo manifesti i sintomi?
   Non ho sintomi
   Meno di 6 mesi
   Più di 6 mesi, meno di un anno
   Più di 1 anno, meno di 3 anni
   Più di 3 anni, meno di 5 anni
   Più di 5 anni

3. Da chi ti è stata diagnosticata?
   No, non mi è stata diagnosticata una prostatite
   Medico di base
   Urologo
   Andrologo
   Altro specialista

4. Da quanti specialisti sei stato visitato dall’inizio della malattia?
   Nessuno
   Uno
   Due
   Tre
   Quattro
   Più di quattro

5. In che misura ritiensi di essere stato informato dal tuo medico/specialista sulla tua patologia?
   Per niente
   Poco
   Sufficientemente
   Molto
   Totalmente

6. Ti ritiensi soddisfatto delle cure e dell’attenzione ricevute dal tuo medico/specialista?
   Per niente
   Poco
   Sufficientemente
   Molto
   Totalmente

7. A quali esami diagnosticici sei stato sottoposto dal tuo medico/specialista prima di giungere alla diagnosi di prostatite?
   Esplorazione rettale
   Tesi delle urine
   Urinocultura
   Spermocultura

8. Hai avuto in passato ricorrenti infezioni alle vie urinarie?
   No
   Sì

9. Sei mai stato cateterizzato?
   No
   Sì

10. Hai avuto in passato traumi al perineo (zona tra scroto e ano)?
    No
    Sì

11. Sei stato operato di varicocele?
    No
    Sì

12. Hai tuttora un varicocele?
    No
    Sì

13. Soffri di discopatie?
    No
    Sì

14. Soffri di malattie neurologiche?
    No
    Sì

15. Soffri di depressione?
    No
    Sì

16. Sei affetto da diabete?
    No
    Sì

17. Soffri di problemi alle articolazioni e/o ai tendini?
    No
    Sì

18. Soffri di ricorrenti infiammazioni agli occhi?
    No
    Sì
19. Hai frequenti infezioni (stomatiti, afte, ecc.) del cavo orale?
   No
   Sì

20. Soffri di problemi intestinali?
   Stitichezza
   Diarrea
   Emorroidi
   Altro

21. Soffri di sindrome del colon irritabile?
   No
   Sì

22. Soffri di allergie?
   No
   Sì

23. A quali delle seguenti terapie/interventi sei stato sottoposto?
   Antiinfiammatori
   Antibiotici
   Alfalitici
   Antidepressivi
   Miorilassanti
   Prodotti fitoterapici
   Massaggio prostatico
   Termoterapia
   Infiltrazioni transperineali
   Elettrostimolazione con sonda anale
   Biofeedback
   Agopuntura
   Fisioterapia
   TUIP
   TURP
   TUNA

24. Hai mai avuto episodi di prostatite acuta?
   No
   Sì

25. Nel caso di prostatite batterica, quali microrganismi sono stati isolati?
   Germi comuni (stafilococco, streptococco, enterococco...)
   Chlamydia trachomatis
   Micoplasmi urogenitali
   Gonococco
   HPV
   Altro

26. Nel caso di prostatite batterica, dove sono stati isolati i microrganismi?
   Nella normale urinocoltura
   Nel liquido seminale
   Nel secreto prostatico
   Nel primo getto delle urine
   Nel tampone uretrale (senza massaggio prostatico)
   Nel tampone uretrale (dopo massaggio prostatico)
   Nelle urine dopo massaggio prostatico

3. **Abitudini di vita**

1. Fai una regolare attività sportiva?
   Mai
   Raramente
   Qualche volta
   Spesso
   Sempre

2. Che tipo di attività?
   Ciclismo
   Pesiistica
   Jogging
   Atletica
   Nuoto
   Ginnastica
   Alpinismo
   Windsurf
   Calcio
   Equitazione
   Motociclismo
   Altro

3. Fai pasti regolari durante il giorno?
   Mai
   Raramente
   Qualche volta
   Spesso
   Sempre

4. Fai uso eccessivo di bevande alcoliche?
   Mai
   Raramente
   Qualche volta
   Spesso
   Sempre

5. Di quali bevande alcoliche?
   Birra
   Vino
   Superalcolici

6. Fumi?
   Sigarette
   Tabacco (pipa)
   Sigaro
   Altro

7. Attualmente o in passato hai fatto uso di sostanze anabolizzanti?
   No
   Sì

8. Fai abitualmente lunghi viaggi in macchina?
   Mai
   Raramente
   Qualche volta
   Spesso
   Sempre

9. Il tuo lavoro ti costringe a stare seduto per molte ore?
   Mai
   Raramente
   Qualche volta
   Spesso
   Sempre
10. Hai osservato una possibile connessione tra periodi di intenso stress e comparsa di sintomi prostatici?
   Mai
   Raramente
   Qualche volta
   Spesso
   Sempre

11. Hai osservato un calo evidente dei sintomi prostatici in corrispondenza di periodi di prolungato relax e lontananza dalle preoccupazioni quotidiane (per esempio in periodi di vacanze)?
   Mai
   Raramente
   Qualche volta
   Spesso
   Sempre

4. Sintomi dolorosi
   1. Avverti dolore nelle seguenti parti del corpo?
      Perineo (zona tra testicoli e ano)
      Testicolo destro
      Testicolo sinistro
      Punta del pene
      Base del pene
      Uretra
      Sotto i fianchi, all’altezza della vescica
      Ano
      Parte bassa della schiena
      Addome
      Osso sacro
      Glutei
      Cosce
      Ginocchia
      Polpacci
      Piedi
   2. Quale aggettivo descrive meglio il tuo dolore?
      Insignificante
      Lieve
      Moderato
      Intenso
      Insopportabile
   3. Da quanto tempo avveriti i tuoi sintomi dolorosi?
      Non ho dolore
      Meno di 6 mesi
      Più di 6 mesi, meno di un anno
      Più di un anno, meno di 3 anni
      Più di 3 anni, meno di 5 anni
      Più di 5 anni
   4. Per quanto tempo in media avveriti i sintomi dolorosi durante l’arco di un mese?
      Mai
      1-5 giorni
      6-10 giorni
      11-20 giorni
      Più di 20 giorni
   5. Avverti dolore o fastidio durante e/o dopo l’iacuazione?
      Mai
      Raramente
      Qualche volta
      Spesso
      Sempre

6. Hai maggiore difficoltà a raggiungere l’orgasmo a causa dei tuoi sintomi?
   Mai
   Raramente
   Qualche volta
   Spesso
   Sempre

7. Avverti una variazione dei tuoi sintomi dopo l’ evacuazione delle feci?
   No, nessuna variazione
   Sì, avverto un miglioramento
   Sì, avverto un peggioramento

5. Sintomi urinari
   1. Avveriti spesso la sensazione di non aver completamente svuotato la vescica appena dopo aver finito di urinare?
      Mai
      Raramente
      Qualche volta
      Spesso
      Sempre
   2. Avveriti bruciore durante la minzione?
      Mai
      Raramente
      Qualche volta
      Spesso
      Sempre
   3. Avveriti bruciore all’uretra? (non durante la minzione)
      Mai
      Raramente
      Qualche volta
      Spesso
      Sempre
   4. Ti capita di doverti sforzare per iniziare la minzione?
      Mai
      Raramente
      Qualche volta
      Spesso
      Sempre
   5. Durante la minzione ti capita di interrompere e riprendere la minzione più volte?
      Mai
      Raramente
      Qualche volta
      Spesso
      Sempre
   6. Hai osservato una diminuzione nell’intensità del getto urinario?
      Mai
      Raramente
      Qualche volta
      Spesso
      Sempre
   7. Quante volte senti il bisogno di urinare prima che siano passate due ore dall’ultima minzione?
      Mai
      Raramente
Qualche volta
Spesso
Sempre

8. Ti capita di sentire improvvisamente un bisogno impellente di urinare?
Mai
Raramente
Qualche volta
Spesso
Sempre

9. Ti capita di alzarti durante la notte per urinare?
Mai
Raramente
Qualche volta
Spesso
Sempre

10. Hai mai osservato la presenza di sangue nelle urine?
Mai
Raramente
Qualche volta
Spesso
Sempre

6. **Sfera sessuale**
1. A quale età hai avuto il primo rapporto sessuale?
   Non ho mai avuto rapporti sessuali
   Meno di 16 anni
   Tra i 16 e i 19 anni
   Tra i 20 e i 24 anni
   Tra i 25 e i 29 anni
   Tra i 30 e i 35 anni
   Oltre i 35 anni

2. Nella tua vita sessuale hai rapporti:
   Non ho rapporti sessuali
   Esclusivamente con donne
   Esclusivamente con uomini
   Con entrambi

3. Hai un/una partner fisso/a?
   No
   Sì

4. Con quanti partner hai avuto rapporti negli ultimi sei mesi?
   Nessuno
   Uno
   Due
   Da 3 a 5
   Più di 5

5. Quanti partner sessuali hai avuto fino ad oggi?
   Nessuno
   Uno
   Due
   Da 3 a 5
   Da 6 a 10
   Più di 10

6. Quali tipi di rapporto sessuale pratichi?
   Stimolazione manuale
   Vaginale protetto
   Vaginale non protetto
   Anal proptetto
   Anal non protetto
   Orale protetto
   Orale non protetto

7. Quanti rapporti sessuali hai in media durante il mese?
   Nessuno
   1 - 5
   6 - 10
   11 - 15
   16 - 20
   21 - 25
   Più di 25

8. Hai difficoltà ad ottenere e mantenere un’eruzione sufficientemente valida per un rapporto sessuale?
   Mai
   Raramente
   Qualche volta
   Spesso
   Sempre

9. Durante il rapporto sessuale, sei preoccupato della tua prestazione sessuale?
   Mai
   Raramente
   Qualche volta
   Spesso
   Sempre

10. Prima della comparsa dei sintomi prostatici, avevi problemi di eiaculazione precoce?
    Mai
    Raramente
    Qualche volta
    Spesso
    Sempre

11. Dopo la comparsa dei sintomi prostatici, hai avuto problemi di eiaculazione precoce?
    Mai
    Raramente
    Qualche volta
    Spesso
    Sempre

12. Durante il rapporto sessuale, sei solito cercare di ritardare l’iaculazione?
    Mai
    Raramente
    Qualche volta
    Spesso
    Sempre

13. Con quale frequenza ti masturbi?
    Mai
    Raramente
    Circa 1 o 2 volte a settimana
    Circa tutti i giorni
    Più volte al giorno
14. Quando ti masturbi, sei solito cercare di ritardare l'eiaculazione?  
   Mai  
   Raramente  
   Qualche volta  
   Spesso  
   Sempre  

15. Fai uso di prodotti farmaceutici (Viagra, Cialis, Levitra) per migliorare le tue prestazioni sessuali?  
   Mai  
   Raramente  
   Qualche volta  
   Spesso  
   Sempre  

16. Che effetto producono tali farmaci sulle tue prestazioni sessuali?  
   Non utilizzo i suddetti farmaci  
   Nullo  
   Limitato  
   Discreto  
   Notevole  

17. Hai mai notato la presenza di sangue nello sperma?  
   No  
   Sì  

18. Hai mai notato un cambiamento di colore e/o con sistenza dello sperma?  
   No  
   Sì  

19. In questo momento della tua vita ti ritieni fertile?  
   No  
   Sì  

7. **Qualità della vita**  
1. Quanto i tuoi sintomi ti impediscono di condurre le tue normali attività quotidiane?  
   Per niente  
   Poco  
   Abbastanza  
   Molto  
   Moltissimo  

2. Quanto i tuoi sintomi incidono sulla tua vita sociale?  
   Per niente  
   Poco  
   Abbastanza  
   Molto  
   Moltissimo  

3. Quanto i tuoi sintomi condizionano la tua vita sessuale?  
   Per niente  
   Poco  
   Abbastanza  
   Molto  
   Moltissimo  

4. Quanto ti capita di pensare ai tuoi sintomi?  
   Per niente  
   Poco  
   Abbastanza  
   Molto  
   Moltissimo  

5. Quale sarebbe il tuo stato d’animo se dovessi trascorrere il resto della vita con i sintomi che avverti?  
   Molto soddisfatto  
   Soddisfatto  
   Moderatamente soddisfatto  
   Indifferente  
   Moderatamente insoddisfatto  
   Insoddisfatto  
   Terribilmente insoddisfatto  

6. Temi che i tuoi sintomi possano dar luogo ad una malattia di maggiore gravità?  
   Per niente  
   Poco  
   Abbastanza  
   Molto  
   Moltissimo  

7. Provi vergogna o timore nel parlare dei tuoi sintomi al tuo partner sessuale?  
   Per niente  
   Poco  
   Abbastanza  
   Molto  
   Moltissimo  

8. Provi vergogna o timore nel parlare dei tuoi sintomi agli amici e/o familiari?  
   Per niente  
   Poco  
   Abbastanza  
   Molto  
   Moltissimo  

8. **Conoscenze sulla prostatite**  
1. Da chi hai avuto informazioni sulla prostatite?  
   Medico di base  
   Medico specialista  
   Famiglia, parenti  
   Amici  
   Partner  
   Giornali  
   AISPEP  
   Internet  
   Programmi radiofonici e/o televisivi  
   Altre fonti  

2. Con chi parli di questo problema?  
   Medico di base  
   Medico specialista  
   Famiglia, parenti  
   Amici  
   Partner  
   Gruppi di discussione su Internet  
   Altro personale sanitario
Prevalence of sexual dysfunction in men with chronic prostatitis/chronic pelvic pain syndrome.

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Objective: The aim of this study was to assess the prevalence of sexual dysfunction in men with chronic prostatitis/chronic pelvic pain syndrome.

Materials and Methods: A group of 399 patients with symptoms suggesting prostatitis without urethral discharge attending an outpatient Prostatitis Clinic was considered. All were evaluated by the same urologist according to a protocol comprising medical history, physical and transrectal ultrasound examination. Patients had a urethral swab, a four-specimen study and culture of the seminal fluid. Patients were classified according to NIDDK/NIH on the basis of the results of the microbiologic and microscopic four-specimen study and of the culture of the seminal fluid. Subjective symptoms were scored by CPSI questionnaire and by non validated general assessment questions inquiring loss of libido, quality of erection, premature loss of erection, pain on ejaculation, hemospermia, pyospermia, premature ejaculation, and presence of semen abnormalities.

Results: Of all the patients evaluated, 138 (34%) had erectile and 220 ejaculatory dysfunctions (55%). Loss of libido, premature ejaculation and presence of semen abnormalities were more frequent in subjects younger than 50 years. Rates of impaired erection and of semen abnormalities were significantly higher in patients with bacterial chronic prostatitis with respect to patients with chronic pelvic pain syndrome. Premature ejaculation was more frequent (p=0.02) in patients with 10-30 leukocytes (36%) or >30 leukocytes (32%) in VB3 urine than in those with 10 or less leukocytes (22%). Painful ejaculation was significantly associated to the sonographic demonstration of enlargement (p=0.000), asymmetry (p=0.001) or inflammatory changes (p=0.038) of the seminal vesicles, whereas hemospermia was significantly associated to asymmetry (p=0.000) or inflammatory changes (p = 0.013, respectively) of the seminal vesicles. Men with erectile (p=0.001) and ejaculation dysfunction (p=0.001) had more severe CPSI scores than men without such complaints.

Conclusions: Although mental distress and impaired quality of life related to illness could contribute to sexual dysfunction observed in patients with CP/CPPS, the presence of erectile and ejaculatory disorders is more frequently related to symptoms and imaging suggestive of a more severe inflammatory condition.

Key words: Chronic prostatitis; Chronic pelvic pain syndrome; Sexual dysfunction; Erectile dysfunction; Ejaculatory disorders.
INTRODUCTION
Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and sexual dysfunction are both conditions affecting the quality of life in men. Although ejaculation discomfort is usually described as a specific symptom of CP/CPPS, the available literature exploring the possible relation between CP/CPPS and sexual dysfunction is scant and the impact of CP/CPPS on sexual function in men is probably underestimated. The aim of this study was to further assess the prevalence of sexual dysfunction in men with CP/CPPS and discuss the relationship between sexual dysfunction and CP/CPPS.

MATERIALS AND METHODS
A group of 399 patients with symptoms suggesting prostatitis without urethral discharge attending an outpatient Prostatitis Clinic was considered. All were evaluated by the same urologist according to a protocol comprising a thorough history including standard symptom evaluation and sexual history and physical and transrectal ultrasound examination. Subjective symptoms were scored by the Chronic Prostatitis Symptom Index (CPSI) questionnaire (1) containing four questions regarding pain or discomfort, two questions regarding urination and three questions related to quality of life. Sexual function was evaluated by non validated general assessment questions inquiring loss of libido, quality of erection, premature loss of erection, pain on ejaculation, hemospermia, pyospermia, premature ejaculation, and presence of semen abnormalities.

Patients had a urethral swab for bacterial culture and additional swabs for identification of \textit{C. trachomatis}, \textit{T. vaginalis}, \textit{U. urealyticum}, \textit{M. hominis} and \textit{Candida spp}. Patients underwent a four-specimen study according to Meares and Stamey (quantitative bacteriological culture and microscopy of first voided urine VB1, midstream urine VB2, expressed prostatic secretion EPS and urine after prostatic massage VB3) (2) and culture of the seminal fluid.

Patients were classified according to the National Institute of Diabetes and Digestive and Kidney Disease/National Institute of Health (NIDDK/NIH) classification (3) on the basis of the results of the microbiologic and microscopic four-specimen study and of the culture of the seminal fluid.

RESULTS
In all, 399 men with chronic prostatitis/chronic pelvic pain syndrome had an evaluable answer to the questions related to the presence of sexual dysfunction. Of the 399 men, 138 (34%) had erectile and 220 ejaculatory dysfunctions (55%). Some sexual dysfunctions were more frequent in younger subjects (less than 50 years): loss of libido (10/213 vs 2/186; p=0.019), premature ejaculation (70/213 vs 40/186, p=0.000) and presence of semen abnormalities (27/213 vs 13/186, p=0.001).

In particular 113 patients were classified in NIH category II (chronic bacterial prostatitis), 156 in category III a and 130 in category III b. The distribution of the prevalence of the different disorders of erection or ejaculation in patients classified in different NIH categories of chronic prostatitis/chronic pelvic pain syndrome is shown in Table 1. The rate of impaired erection and of semen abnormalities were significantly higher in patients with chronic prostatitis with respect to patients with category III a and III b chronic pelvic pain syndrome. No significant difference was shown for loss of libido, premature loss of erection, pain on ejaculation, hemospermia, pyospermia and premature ejaculation.

Of 351 patients 222 had 10 or less leukocytes in VB3 urine, 101 had more than 10 and less than 30 leukocytes and 28 had more than 30 leukocytes. Premature ejaculation was more frequent (p=0.02) in patients with 10-30 leukocytes (36%) or > 30 leukocytes (28%) in VB3 urine than in those with 10 or less leukocytes (22%), whereas no correlation was observed with erectile dysfunctions and other ejaculation disorders.

At transrectal sonography the presence of enlargement,
asymmetry or inflammatory changes of the seminal vesicles was observed in 153 (38%), 148 (37%) 149 (37.3%), respectively.

The presence of painful ejaculation and hemospermia was significantly associated to the sonographic demonstration of asymmetry (p=0.001 and p=0.000, respectively) or of inflammatory changes (p=0.038 and p=0.013, respectively) of the seminal vesicles. Painful ejaculation was also significantly associated (p=0.000) to an enlargement of the seminal vesicles. Sonographic abnormalities were not related to any erectile dysfunction and to other ejaculatory complaints. Men with erectile and ejaculation dysfunction had more severe CPSI scores (p=0.001 and p=0.001 respectively) than men without such complaints. The presence of erectile and ejaculation dysfunction was related to significantly higher scores for domains of pain (p=0.000 and p=0.001 respectively) and quality of life (p=0.007 and p=0.001 respectively), whereas scores for lower urinary tract symptoms (LUTS) domain were not significantly different in patient with or without erectile and ejaculation dysfunction (Table 2).

In particular the presence of erectile impairment (p=0.006, p=0.021), premature loss of erection (p=0.001, p=0.010) ejaculatory pain (p=0.000, p=0.000), hemospermia (p=0.000, p=0.002), premature ejaculation (p=0.000, p=0.000) and abnormalities of semen (p=0.000, p=0.001) were associated with significantly more severe scores for respectively pain and quality of life domains.

**DISCUSSION**

Chronic prostatitis has been suggested as an important organic cause of premature ejaculation being found in 52% of the patients with premature ejaculation (4). A recent survey demonstrated that in Turkish men with CPPS the incidence of sexual problems was higher than in the normal population: premature ejaculation was found in 77.3% of the patients with CPPS and in 15.2% was associated to erectile dysfunction (5).

A study among men diagnosed as having chronic prostatitis by the analysis of expressed prostatic secretions demonstrated an overall prevalence of sexual dysfunctions of 49%, with premature ejaculation and erectile dysfunction accounting for 26% and 15% respectively (6). Smith et al. reported erectile dysfunction and decreased libido respectively in 43% and 24% of the men with prostatitis (7). Sexual dysfunction is even common in men with CPPS refractory to treatment with up to 92% of men presenting with sexual dysfunction, including ejaculatory pain in 56%, decreased libido in 66% and erectile and ejaculatory dysfunction in 31% (8).

Approximately 20% of sexually active men with LUTS suggestive of benign prostatic hyperplasia also complaining of prostatitis-like symptoms have a higher prevalence of erectile dysfunction and reduced ejaculation than men with LUTS only (9).

The correlation between CP/CPSS and sexual dysfunction is still unexplained (10). According to some Authors CP/CPSS impairs the overall quality of life and it is this that contributes to or causes erectile dysfunction (11). Also mental distress has been related to prostatitis, men with prostatitis being described as busy and nervous and tending to have a meticulous attitude. Marital difficulties or divorce (that are attributed to their illness), fear of having a sexually transmitted disease and suicidal thinking were reported more frequently by patients with prostatitis than by healthy men (12). Also partners of patients with CP/CPSS present symptoms of depression and similar sexual dysfunctions, such as pain upon intercourse or vaginismus (7).

According to such hypotheses a trigger point release/paradoxical relaxation training protocol was applied in CP/CPSS patients obtaining significant improvement in pelvic pain and urinary symptoms but also in libido, ejaculatory pain, erectile and ejaculatory dysfunction (8). Also acupuncture proved to be a safe, effective, and durable treatment in improving symptoms and quality of life of men with CP/CPSS (13).

If mental distress and impaired quality of life certainly contributes to sexual dysfunction observed in men with CP/CPSS organic factors also play a role in the pathogenesis of this disturbances. In fact in our study erectile and ejaculatory disorders are more frequent in CP than in CPPS III A and B and are significantly correlated to the presence of symptoms and imaging suggestive of a severe inflammation of the genital tract.

Inflammation of the prostate is mediated through the cytokine-induced expression of several factors such as chemokines, inducible nitric oxide synthase, and cyclooxygenase-2. An imbalance toward increased pro-

### Table 2.

**CPSI scores in relation to sexual dysfunction.**

<table>
<thead>
<tr>
<th></th>
<th>N° pts</th>
<th>CPSI-Pain</th>
<th>CPSI-LUTS</th>
<th>CPSI-QoL</th>
<th>CPSI-Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erectile dysfunction</td>
<td>Without</td>
<td>261</td>
<td>9.7-3.2</td>
<td>3.3-2.5</td>
<td>7.5-2.8</td>
</tr>
<tr>
<td></td>
<td>With</td>
<td>138</td>
<td>10.8-3.3</td>
<td>3.6-2.3</td>
<td>8.3-2.8</td>
</tr>
<tr>
<td>Sig</td>
<td></td>
<td>0.001</td>
<td>0.295</td>
<td>0.007</td>
<td>0.001</td>
</tr>
<tr>
<td>Ejaculation dysfunction</td>
<td>Without</td>
<td>179</td>
<td>8.6-2.8</td>
<td>3.4-2.5</td>
<td>7.1-2.7</td>
</tr>
<tr>
<td></td>
<td>With</td>
<td>220</td>
<td>11.3-3.2</td>
<td>3.5-2.4</td>
<td>8.4-2.8</td>
</tr>
<tr>
<td>Sig</td>
<td></td>
<td>0.000</td>
<td>0.700</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>
inflammatory and decreased anti-inflammatory cytokines determines the outcome of the inflammatory process (14, 15). The role of low-grade chronic systemic infection-induced inflammation in endothelial and erectile dysfunction has been implicated through impaired nitric oxide availability (16-19).

In conclusion sexual dysfunction related to CP/CPPS appear to result from an interplay between psychological factors and dysfunction in the immune, neurological and endocrine systems.

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INTRODUCTION

Human prostate pathologies are one of the most impacting clinical problems of the third millennium, both as prostate adenocarcinoma as a cause of morbidity and death in the world and Italian population (1, 2), and as inflammatory conditions of the gland. It is especially the latter inflammatory pathologies that are greatly on the increase in male patients from 20-40 years old, with an important impact in terms of social, health-related and individual costs (3). They have a very high additional impact on fertility and patient quality of life (4). In Italy, in agreement with two recent studies, chronic prostatitis represents one of the emerging problems in young males during fertile age: mean age is usually very low and confirmed by about 30-40 years (5). The main chronic prostatitis characteristics are an early start in symptoms, persistence of symptoms for years, relatively young age of patients, possible impact of STD infections acquired during initial sexual intercourse, and heavy long-term sequelae such as infertility. In 1995 the National Institutes of Health in the USA (NIH) made a new prostatitis classification, now widely accepted, which is a stable point of reference, even though subjected to revision and expansion, dividing prostatitis syndromes into acute and chronic, bacterial and non bacterial (6). Prostatitis syndromes are a major problem in urology and microbiology. Only 5-10% of patients have a bacterial infection. Acute bacterial prostatitis - Cat. I NIH - is rare; only a small subset of patients with chronic prostatitis have evidence of infection with recognized uropathogens - Cat II NIH. Theoretically, etiology involves the whole range of bacterial species, aerobic and anaerobic, yeasts and other cryptic microorganisms (7). A correct microbiological approach includes use of adequate biological materials that have to be homogeneous, quantitatively sufficient, and representative of the site infection organ (8, 9). Collection and sampling have to be simple, not invasive, not bothersome for patients, have a good compliance and not be contaminated by saprofitic microflora. Correct microbiological approaches include, additionally, identification of a low number of bacteria in EPS or post massage urines, which can be pathognomonic of chronic bacterial prostatitis (10, 11). Critical microbiological sample points can be recognized in the immediate/rapid transport to suitable conditions of biological materials, their immediate/rapid culture after collection, and the application of bacteriological techniques also able to quantify a small number of pathogens. Biological materials to be used are: early morning first void urine EMU,
total ejaculate TE, mid stream urine, EPS (expressed prostatic secretion), post prostate massage urine PPMU, prostate biopsy PB, both transrectal and transperineal; this last rarely and mainly utilized to avoid trans-rectal contaminations by gut microflora (12). One of the major microbiological problems in prostatitis bacteriology is “which bacteria can be considered true pathogens”; from this point of view, we can consider different approaches: the “conservative approach” which involves the recognition only of the bacteria present in expressed prostatic secretion - EPS - and bacteria recognized as a cause of recurrent urinary tract infections - UTI. In this case bacteriospermia demonstrates proven infection or high level colonization in these patients. Microbiologically this means cultures of EPS, prostatic biopsies (transperineal) and the Meares-Stamey test (M&S Test) (13). The “aspecific approach” includes the use of single biological materials not in association with the others, like the use of the single urethral swab to identify pathogens as prostatic pathogens, urineculture, semen culture, and EPS. The Meares & Stamey test (Figure 1) in bacterial prostatitis is up to now considered the most important test for diagnosis of bacterial prostatitis (13, 14). Its aim is to establish the true site of infection. In interpreting the results, VB1 sampling of first few drops is important, colony counts in EPS or VB3 have to be > 10 folds greater numbers than in VB1, same bacterium/a in VB2 and EPS or/and VB3. In EPS few colonies point to infection, colony counts in EPS have to be 1-2 logs higher than VB3, because there can be a possible dilution in VB3 and finally VB1 represents the control sample for VB3. Several problems have been identified in running the M&S Test: 1) Possible misinterpretation of VB2 test for colony count amplification due to night latency time, 2) The test is indaginous for the patient and the urologist, 3) Easy contamination of the various biological materials, 4) Samples not quantitatively controllable, 5) Difficult identification of the infection site very frequent (15). To avoid misinterpretation it is advisable to repeat the test for men with inconclusive findings and those with repeated episodes of bacteriuria. Microscopic examination in EPS by leukocytes count has been used in prostatitis patients to define inflammation with the association of the concept that an increased number of leukocytes means a prostatic inflammatory response (11, 15). Several bias impact this test including the right definition of the cut-off level of the test, which is variable in agreement with the authors: abnormal number leukocytes can be >10 / high power microscopic field or >20 / high power microscopic field and in agreement with the use or not of quantitative chamber counts. The test is of poor or little value in EPS in men with possible urethral inflammation (STDs) (16, 17). There is a misleading evaluation of total ejaculate owing to difficulty in distinguishing immature sperm from leukocytes: there can be false positives after ejaculation or false positives due to urethral abnormalities, really frequent in several pathological conditions like urethritis, condilomata, diverticula, uninfected calculi. Difficulty in interpreting microbiological findings includes the presence of contaminating, indigenous microbiota; organisms derived after passage through distally contaminated urethra (i.e. voided urine, urethral swabs, EPS); presence of inhibitory substances in prostatic secretions and total ejaculate; history of multiple courses of antibiotics; presence of difficult-to-culture cell wall deficient/defective bacteria or non cultivable bacteria; interaction with other microorganisms; interaction with the host; production of extra-cellular slime and biofilm formation; environmental stresses in tissues (18-21). All these possible problems lead to inclusion of the use of specialized culture media, specialized stains, special incubation of the culture (microaerofilic and anaerobic), the use of electron microscopy and polymerase chain reaction (PCR) to detect/confirm some microbes (22-24). Bacterial infection of the prostate occurs as a result of ascending urethral infection, reflux of infected urine into prostatic ducts emptying into the posterior urethra or invasion of rectal bacteria through direct extension or by linfogenous
and haematogenous spread, with a frequent host response consisting of polymorphonuclear leukocytes and macrophages in prostatic secretions. Bacterial prostatitis includes, additionally, the concept of a possible concomitant urinary tract infection, something that strongly advocates contemporary screening also of urinoculture (25). Acute bacterial prostatitis is a febrile disease associated with an abrupt onset and genitourinary and constitutional signs and symptoms (3). Chronic bacterial prostatitis is a more subtle illness, very frequently relapsing, due to recurrent urinary tract infections with persistence of bacteria in the prostatic secretory system (3). These facts induce in patients multiple courses of antibacterial therapy, strongly impacting as a microbiological problem, often inducing bacterial persistence and resistance (19). Bacteria involved in prostatitis are described in Table 1. With the intent to solve these problems, in 1997 I introduced a new protocol, a modification of the standard Meares and Stamey test for the microbiological diagnosis of prostatitis, which includes total ejaculate (TE) from each patient. This sampling protocol is illustrated in Figure 2. The introduction of the modified M&S test allowed the resolution of several problems including the fact that no false positive urine culture results were detected, the results obtained from TE were much more positive than in EPS or PMU. Seeing that TE seems to contain from 60 to 80% biological materials of prostatic origin, and excluding a contamination from urethra, these isolates seem to represent the true prostatic/upper genital tract infectious agents. In addition the sampling was, as the initial part of the protocol, a home sampling protocol for the patient with additional very good compliance in the patient population. On the basis of this new protocol we have followed the chronic prostatitis patients attending our Center in Florence and in the last two years have isolated and typed 1,686 bacteria and yeasts from total ejaculate: 371 strains of Gram negatives (22.00%), 1,112 Gram positive (65.9%), 14 yeast strains (0.83%) and 189 Mycoplasmas (11.2%) (Figure 3). The results make up evidence for a sort of microbiological revolution in terms of expression of microbes: Gram positives represent the majority of isolates 66.7%, gram negatives 22%, Mycoplasmas 11.2% (Figure 4). In between Gram positives Enterococcus faecalis is the prevalent species with a prevalence rate of 42.7%. We also note the emergence of coaugulase-negative Staphylococci (CNS), with Staphylococcus haemolyticus and Staphylococcus epidermidis as predominant species. Also Ureaplasma urealyticum is the most expressed among the Mycoplasmas: 161 strains versus 28 Mycoplasma hominis (Figure 5). The emergence of Ureaplasma u. and the gram positives focus on the necessity to set up new therapeutic protocols with different pharmacological compounds including tetracyclines and the newest fluoroquinolones and rifampicin to obtain the best bactericidal concentrations and an optimal penetration in difficult to reach organs like the prostate. These data are the expression of a revolution in microbial isolation which follows the widespread use of large spectrum antibiotics in outpatients. Prostatitis patients represent a sort of enclave of largely and frequently a specifically and empirically treated patients, very often without a microbiological analysis as a base. This fact induces a sort of selection of the colonizing/infecting bacteria to a Gram positive and to difficult microorganisms like Ureaplasma.

**Table 1.**

Bacteria involved in prostatitis.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli</td>
<td></td>
</tr>
<tr>
<td>Other Enterobacteriaceae</td>
<td></td>
</tr>
<tr>
<td><em>Klebsiella</em> <em>spp.</em></td>
<td></td>
</tr>
<tr>
<td><em>Enterobacter</em> <em>spp.</em></td>
<td></td>
</tr>
<tr>
<td><em>Proteus</em> <em>spp.</em></td>
<td></td>
</tr>
<tr>
<td><em>Serratia</em> <em>spp.</em></td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td></td>
</tr>
<tr>
<td>Enterococci</td>
<td></td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td></td>
</tr>
<tr>
<td>Staphylococci</td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus</em> <em>epidermidis</em></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus</em> <em>haemolyticus</em></td>
<td></td>
</tr>
<tr>
<td>Corynebacterium <em>spp</em></td>
<td></td>
</tr>
<tr>
<td><em>Corynebacterium</em> <em>minutissimum</em></td>
<td></td>
</tr>
<tr>
<td><em>Corynebacterium</em> <em>group</em> <em>ANF</em></td>
<td></td>
</tr>
<tr>
<td><em>Corynebacterium</em> <em>seminale</em></td>
<td></td>
</tr>
<tr>
<td>Anaerobic bacteria</td>
<td></td>
</tr>
<tr>
<td>Urogenital Mycoplasmata</td>
<td></td>
</tr>
<tr>
<td><em>Ureaplasma</em> <em>urealyticum</em></td>
<td></td>
</tr>
<tr>
<td><em>Mycoplasma</em> <em>hominis</em></td>
<td></td>
</tr>
<tr>
<td>Other bacteria</td>
<td></td>
</tr>
<tr>
<td><em>Chlamydia</em> <em>trachomatis</em></td>
<td></td>
</tr>
<tr>
<td>Yeasts</td>
<td></td>
</tr>
<tr>
<td><em>Candida</em> <em>albicans</em></td>
<td></td>
</tr>
<tr>
<td><em>Candida</em> <em>spp.</em></td>
<td></td>
</tr>
<tr>
<td><em>Saccaromices</em> <em>spp.</em></td>
<td></td>
</tr>
<tr>
<td><em>Trichomonas</em> <em>vaginalis</em></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 3.**
The figure shows the prevalence of the major classes isolated microorganisms on 1,686 samples.
shift. To these concepts we have to add the fact that all these microbes are able to form biofilms—especially Staphylococci, Enterococci—and they have the capacity to infect cells intracellularly—Ureaplasma, Enterococci. It is this essential fact that gives rise to the importance of using inside therapeutic regimen antibiotics with a high capacity to pass cell membranes and act inside cells preferentially, which means very little molecule and high affinity with cell membranes.

These data additionally provide evidence that, in this modified M&S test, TE was the most positive sample: excluding the possibility of contamination (see sampling protocol), this means that, once and for all, "prostatitis" has to be considered as a syndrome involving more than one upper genital tract organ, as proved by symptoms in these patients and by microbiological diagnosis; in a wider and more actual access we have to rename all prostatitis as "pelvic pain syndrome", even if it is only bacterial (25).

ACKNOWLEDGEMENTS

We are grateful to all Santa Maria Annunziata Hospital STDs members for their technical laboratory assistance, to dr. Tommaso Cai for his help in study design and support and to Professor John Denton for manuscript language revision.

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INTRODUCTION
Recognising the early stages of prostatitis/chronic pelvic pain syndrome (CPPS) has always been, and still is, arduous because of the wide range of different symptoms that are involved. If diagnosing prostatitis was difficult in the past, it is even more so in the present. Moreover, chaos reigns when we come to consider therapeutic approaches. When chronic prostatitis is diagnosed very often the only therapy seems to be prolonged cycles of high dose antibiotics. Even though this approach is sometimes supported by results of bacteriological tests, in many instances it is prescribed almost automatically because there are no specific guidelines. Data from recent studies do not support the tenets which, for the past three decades, underlie diagnosis and treatment of prostatitis (1). Histopathological studies (2) in 368 biopsies from 97 patients with the chronic prostatitis/CPPS indicated inflammation was present in only 33% of 97 patients. However, histological findings of chronic prostatitis usually derive from biopsies in patients who, from the age of sexual maturity onwards, undergo surgery for other reasons. No research has been conducted in the pre-puberty age group even though symptoms are most common in the young. Let us bear in mind the sickness impact profile quality life score of patients with the chronic prostatitis/CPPS falls within the range for patients with myocardial infarction, angina or Crohn's disease.

Paradoxically prostatitis/CPPS attracts relatively little attention among urologists and the medical world at large (3). In 1998 Nickel wrote: “Most urologists acknowledge that they would be happy never to see another patient with prostatitis in their office again; others simply refuse to see these patients” (4) Nine years have passed since then, but nothing seems to have changed.

This article does not attempt to establish the causes of, and most suitable therapy for, chronic prostatitis/CPPS. It merely presents a critical analysis of present opinions.

HYPOTHESES ON PATHOGENESIS
The aetiologies of chronic prostatitis/CPPS include urogenital infection, autoimmunity, voiding dysfunction, neuropathic pain, prostate stone disease, increased prostate blood flow, psychological dysfunction.

1) Bacteria and prostatitis
As characteristic symptoms of pelvic pain and voiding dysfunction in CPPS resemble a true bacterial infection, it is not surprising that occult infection is one of the most common theories used to account for CPPS aetiology. Seventy per cent of the prostate is glandular tissue i.e. approximately 20 relatively simple tubuloalveolar glands lined with simple cuboidal or columnar epithelium which branch out into the fibromuscular stroma constituting the other 30% of prostate tissue. Prostate secretion enters the urethra after passing through what appear to be two-way ducts.

Prostate secretion's highly nutritive content together with this anatomic configuration might explain how an infection that is ascending the urethra colonises the prostate so easily in retrograde. Despite this evidence which can-
not be refuted, many authoritative voices have denied the hypothesis that infection could be the aetiological agent of prostatitis.

In the Journal of Urology, Shoskes (5), concluded “Bacteria cultured from transperineal prostatic biopsies do not differ between men with and without chronic pelvic pain syndrome. Prostatic bacteria obtained by biopsy are probably not etiologically related to the symptoms in the majority of men with chronic pelvic pain syndrome”.

Schaeffer concurred in the Emerging Concepts in the Management of Prostatitis/Chronic Pelvic Pain Syndrome (6) which concludes: “It is well recognized that even if pathogenic bacteria are present in the prostate, as in men with established chronic bacterial prostatitis, they do not cause chronic pelvic pain unless acute urinary tract infection develops. Taken together, these data suggest that bacteria do not have a significant role in the development of the CPSS. The clinical observation that antimicrobial therapy reduces symptomatology in men with chronic pelvic pain syndrome is being tested in a double-blinded NIH controlled study. Because antimicrobials may have anti-inflammatory activity, it is possible that these drugs may benefit the patient by reducing inflammation rather than eradicating bacteria”.

In a very elegant paper on prostate biopsy cultures Lee JC stated in 2003 that “Bacteria cultures do not differ between men with and without chronic pelvic pain syndrome. Prostatic bacteria obtained by biopsy are probably not etiologically related to the symptoms in the majority of men with chronic pelvic pain syndrome. In his report on “Treatment of chronic prostatitis” (2004) Alexander observed that a large case-control study comparing results of the four-glass test in the 488 patients with CP/CPPS with those of 121 simultaneously-recruited, age-matched, asymptomatic men failed to detect a difference between the two groups. Localization of Escherichia coli and other Enterobacteriaceae did not differ in symptomatic and asymptomatic men. In addition, skin organisms, such as Staphylococcus and Streptococcus, were detected in the prostates of the same proportion of men in each group (70%). This indicates that these bacteria alone do not cause CP/CPPS (1).

The 2004 EAU Guidelines On Chronic Prostatitis (7) hold the same view: “In only 5 to 10% of cases, prostatitis is shown to have a bacterial aetiology. In the remaining proportion the symptoms have been attributed to “Chronic non-bacterial prostatitis”, “Prostatodynia” or “Chronic prostatitis associated with chronic pain syndrome”. Furthermore, in 2005 Hua (8) confirmed that clinicians using the Meares-Stamey criteria identified uropathogens localized to the prostate in only 6% to 8% of CP/CPPS patients. This suggests that bacteria may play a role in under 10% of men with CP/CPPS. That some patients respond to antimicrobials could suggest that eradication of bacteria reduces symptoms. However, the beneficial effect of antimicrobial drugs may not be due to their antibacterial action, but to their anti-inflammatory action.

Why are the pathogenic causes the subject of such a heated debate? Why should chronic prostatitis be labelled as abacterial? Although prostatic fluid and semen have intrinsic antibacterial properties and may hamper bacterial growth in vitro (3) an answer to these questions may be found in an analysis of the pathogenic micro-organisms that were investigated and the laboratory techniques that were used to detect them because some fastidious organisms that do not grow in standard culture media may be the cause of the CPSS symptom complex.

In 2000 Shoskes (9) suggested that increasing culture time from 2 to 5 days yields 7.5% more positive cultures. These cultures correlate with inflammation secondary to gram-positive bacteria. Longer culture time seemed to make the biggest difference in cultures of semen and expressed prostatic secretions (EPS), indicating that there may be local environmental factors in these fluids that could initially inhibit their growth.

Krieger threw some light, not upon the bacterial agents of infection, but upon the response of different organisms to the same bacteria. In 2002 he explained that “bacterial virulence appears to be crucial for overcoming normal host defences. This is the paradigm of uncomplicated UTI. Conversely, in compromised hosts bacterial virulence is much less important. In this situation the host factors appear to be critical. This is the paradigm of complicated UTI” (10).

In fact extreme conditions (supercooling, trauma, radiation, intoxication) non-pathogenic and conditionally pathogenic flora becomes pathogenic and triggers an inflammatory process.

None of these studies (5-9) focused on germs that are hard to culture i.e. Chlamydia trachomatus, Neisseria gonorrhoeae, Ureaplasma urealyticum and Mycoplasma genitalium. The evidence that Mycoplasma genitalium is a sexually transmitted pathogen can hardly be challenged since it is based on concordance rates among partners and on DNA typing which shows the same sequence type among partners in contrast to unrelated M genitalium positive patients. The highest prevalence of M genitalium appears in men who are negative for Chlamydia trachomatis. Several studies have found that M genitalium positive men are symptomatic as least as often as men with Chlamydia infection (11). Despite having non-bacterial prostatitis according to the standard definition, these patients improve with an appropriate course of antibiotics. More recent studies have also increasingly used molecular techniques to try to answer the question of infection in these patients.

In a 1999 Workshop, Mazzoli showed that 129/820 patients (15.7%) with chronic abacterial prostatitis who were screened for Chlamydia t. and Neisseria g. DNA in semen in the previous 2 years, resulted positive for Chlamydia, Gonococcus and Mycoplasma (12).

Krieger suggested in 2002 (13) that in a proper investigation of uropathogens routine culture techniques should be flanked by molecular techniques including PCR-DNA. In his paper “Bacteria in the chronic prostatitis-chronic pelvic pain syndrome: Molecular approaches to critical research questions” he concluded: “Various lines of inquiry have coalesced to make today an opportune time to determine definitively the role of infection in the chronic prostatitis-chronic pelvic pain syndrome cases. We developed powerful methods for evaluating potential pathogens, validated these methods and showed that patients with the chronic prostatitis-chronic pelvic pain syndrome were more likely to have prostatic bacterial DNA than the controls examined.”
Our group (14) reached the same conclusion in 2003 and showed DNA infected with *Chlamydia Trachomatis* was detected in 19/56 patients with abacterial prostatitis (34%).

Recent studies have identified a new class of micro-organisms termed nanobacteria which might be co-responsible for chronic prostatitis-CPPS. Nanobacteria are microorganisms characterized by small size (0.2 to 0.5 μm), slow growth and ability to form calcium phosphate crystals at neutral pH, and at physiological calcium and phosphate concentrations. They are gram-negative, have a unique structure and apparent nucleic acid, and their growth in vitro is best inhibited by tetracycline. Shoskes (2005) found indirect evidence of nanobacteria on ELISA in 60% of blood and 40% of urine samples in patients with CPPS (15). In a Finnish paper the incidence of nanobacteria in the serum of healthy adults in Finland was 5% (Kajander, unpublished data).

2) Tissue auto immunity

Auto immunity has more recently been hypothesized to be the pathogenic mechanism underlying prostatitis and CPPS. It is no less hotly debated than any other proposal.

In search of markers to define CPPS more clearly, Nadler compared the levels of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumour necrosis factor-α (TNF-α) in EPS from men with CPPS, from healthy men and from men with Benign Prostatic Hyperplasia (BPH). He concluded: “Cytokines are frequently present and elevated in the EPS from men with CPPS IIIA and provide a novel means for identification, characterization and potential management of men with CPPS that differs from traditional methods based on WBC” (16).

Richard (17) observed cytokine concentrations are high in the seminal fluid of men with chronic prostatitis compared with controls which suggests genital tract inflammation. Auto-immunity might be triggered by an abnormal immune response directed against physiologically secreted antigens in the genital tract (epithelial secretory antigens). Besides increased cytokine concentrations, men with chronic prostatitis also present with high bacterial 16S ribosomal DNA which supports the view that an initial bacterial infection could have triggered an auto immune process. In the course of the disease the role of the bacterial agent becomes blurred. Several groups of researchers have measured the levels of inflammatory mediators in the EPS of men with chronic prostatitis. Hochreiter reported that levels of IL-8 and epithelial neutrophil activating factor-78 were significantly elevated in patients with categories IIIa, IV, and I disease over controls and patients with category IIIb disease. Pausil (18) in 2005 evaluated the presence and role of the cytokines in genital secretion and concluded that IL-6 and IL-8 levels are significantly higher in genital secretions from patients with prostate inflammation and may prove to be excellent markers of chronic prostatitis.

For Jang and Schaeffer (19) there is substantiating evidence to support the role of the immune system in the pathogenesis of chronic prostatitis-CPPS. Inflammation of the prostate is mediated through cytokine-induced expression of several factors such as chemokines, inducible nitric oxide synthase, and cyclooxygenase-2. The balance between the effects of pro- and anti-inflammatory cytokines determines the outcome of the inflammatory process.

Li (20) concluded that interleukin-10 and interleukin-8 played a very important role in the aetiology of CP, and could be detected in VB3 as well as in routine semen and EPS.

Khadra (21) also concluded that semen interleukin-8 levels correlate with subjective symptoms in men with CP/CPPS. IL-8 might contribute to the pathophysiology of CP/CPPS, and high IL-8 levels might be a useful marker of CP/CPPS.

According to Bach (22) infectious agents induce autoimmune diseases in several experimental settings, some of which have clinical counterparts. A variety of mechanisms have been invoked to explain the observations, including molecular mimicry and an inflammation-induced increase in autoantigen immunogenicity in the target organ. Interleukin-10, which is produced by Th2 cells, monocytes and macrophages, slows the progression of autoimmune and allergic diseases in experimental models. Production of Interleukin-10 is increased in several infectious diseases and it probably helps suppress immunopathological complications. Two groups of investigators found considerably less interleukin-10 in the lungs of patients with asthma than in control subjects, although there is also a contradictory report.

In a paper Mazzoli (23) concluded that the results of her trial clearly highlight the role of immune system activation in the pathophysiology of CP/CPPS and that seminal IL-8 and mucosal IgA levels specific to *Chlamydia T. antigens appear to be the best immunologic markers of chronic Chlamydial prostatitis status.

Pontari (24) holds an opposing opinion and questioned the ultimate role that cytokines play in causing pain because they were unable to document increased cytokine levels in patients with IIIb disease, and there is no conclusive evidence on the timing of cytokine release. Does it occur after leukocyte activation or does it precede activation and serve to stimulate leukocyte arrival. Evidence in support of this hypothesis comes from our 2004 therapeutic trial (25). We prescribed in a group of CP/CPPS patients thalidomide as an inhibitor of cytokines delivery but we observed no improvement in symptoms.

3) Bladder neck sclerosis and urethro-prostatic reflux

Prostate infection may occur via ascending urethral infection or reflux of infected urine into the prostatic ducts. Urine reflux may occur in urethral stricture or in bladder neck sclerosis. Refluxing urine, even when sterile, may cause chemical irritation and initiate tubule fibrosis and prostatic stone formation, which then lead to intra-duct obstruction and secretion stagnation. If infected material is trapped in ducts, it may serve as a source of relapsing infections, causing symptoms of prostatitis. This pathogenic mechanism cannot apparently be refuted but little is known about how it concurs in triggering or maintaining chronic prostatitis. Even when physiological urine flow is restored by administration of alpha blockers or TUIP, often symptoms of CPPS do not disappear as might have been expected. Failure of therapy might be related...
to the length of time the high urinary pressure had acted upon the urethra, causing prostatic symptoms. If prolonged, perineal muscle antalgic spasms, that were triggered initially as a reaction to irritative urethral symptoms, could autonomously maintain the disease state.

4) Neuropathic and myofascial pelvic floor pain
The pelvic floor has three functions; support, contraction and relaxation (8). Underactive pelvic floor muscles result in urinary and faecal incontinence and pelvic organ prolapse. Pelvic floor overactivity usually starts with increased muscle tension which may arise from several causes. Overactive muscles may result in high outflow resistance producing low urinary flow rates, obstructed defaecation, dyspareunia. Pain in turn causes anxiety and distress that aggravate and perpetuate muscle contraction. Pudendal nerve entrapment leading to chronic compression of the pudendal nerve arises pelvic floor abnormalities and can cause perineal pain located either anteriorly in the scrotal, penile and vesical region, or posteriorly in the anorectal region. A one-sided, burning sensation is exacerbated by unilateral rectal palpation which may be associated with delayed pudendal motor latency on the painful side. Magnetic resonance imaging (MRI) is the investigation of choice to show both neural tissue and surrounding structures. The examination should include scrutiny of the anatomy along the course of the pudendal nerve. Development of active trigger points can be associated with mechanical, physical, systemic, and psychologic stressors. However, very often, no injury can be identified. Dysfunction of the sacroiliac joints and sacrocccygeal articulation may be aggravating sources of trigger points. Some physicians (26) have implicated voiding dysfunction in the pediatric population as the beginning of a long process that results in pelvic floor dysfunction in adults. It has been suggested and observed that chronic pelvic floor and voiding dysfunction leads to bladder irritation and inflammatory changes damaging the bladder and causing a chronic pelvic pain complex.

Doggweiler-Wiygul (27) reported that more than 50% of patients with interstitial cystitis refer voiding dysfunction in childhood (eg, enuresis, urgency/frequency syndrome, or recurrent urinary tract infections) (28, 29). Few studies have studied pelvic and abdominal muscle function in men with CP/PPS and compared their muscular examination with pain-free men.

Segura in 1979 (30) suggested that patients with symptoms of prostatitis or prostatosis who do not have pathogenic bacteria in the prostatic secretions may not have prostatic problems. Pelvic floor tension myalgia should be considered in these patients.

Zerman in 1999 (31) analyzed clinical and urodynamic findings to evaluate the role of pelvic floor dysfunction in patients with pelvic pain. He concluded that since activity is a reflection of neural control, the apparent association of pelvic floor dysfunction with pelvic pain raises the probability of a primary or secondary central nervous system breakdown in the regulation of pelvic floor function. This hypothesis is supported by the improvement in symptoms caused by therapy aimed at modulating the pelvic floor, such as biofeedback, medication and sacral anterior root stimulation.

Hetrick in 2003 (32) hypothesized that musculoskeletal examinations of men with CP/PPS types IIIA and IIIB would show more spasm, tenderness and dysfunction than men without CP/PPS and concluded that men with CP/PPS have more abnormal pelvic floor muscular findings than men without pain. Pelvic muscle abnormalities may contribute to the pain syndrome.

5) Prostatic Stones
The role of prostatic stones in producing symptoms and disease is controversial (17), particularly because of the high prevalence in older, asymptomatic men. There is a clear correlation between age and the incidence of prostatic stones (33) although their presence in younger men is often associated with inflammation (34) and prostatic symptoms (35). Prostatic stones are presumably formed by precipitation of prostatic secretions and corpora amylacea calcification. Crystallographic analysis has shown a core of apatite in 98% of cases. Interestingly apatite is the mineral formed by nanobacteria, a microorganism mentioned above which is implicated in biomineralization in the kidney (36) and blood vessels (37).

6) Psychological dysfunction
Psychiatric disorders (8) may be involved in some cases of chronic pelvic pain including somatisation and somatoform disorders. Somatisation is an avoidance coping strategy. Childhood physical and sexual abuse are strongly associated with later somatisation, including chronic pelvic pain. When no reasons for chronic pelvic pain can be identified it is important to ask about physical and sexual abuse when taking the history because of the consequences for therapy. Depression is a state of significantly decreased emotional, psychological and social functioning with neurovegetative symptoms lasting at least two weeks. Subclinical depression is often overlooked in men and women and can worsen or prolong chronic pelvic pain. Many physicians also overlook the association of sleep disorders and depression with such pain. In 1992 Nolan (38) examined these linkages in his chronic pelvic pain clinic, using a questionnaire that assists in diagnosis and management of these cases. 51/ 72 patients (72%) with pelvic pain evaluated at date reported sleep disorders, and 37 (51%) had clinical depression, as determined by the Beck Depression Inventory.

In our unpublished report on 720 patients with prostatitis symptoms investi gated by the Beck Depression Inventory, 60% presented a depressive situation and 28% a very depressive situation (BDI score over 20). These findings need to be carefully interpreted. As stated above, the quality of life for patients with chronic prostatitis/CP/PPS is similar to that enjoyed by patients with myocardial infraction, anigra or Crohn’s disease and this alone could cause a depressive syndrome. It is also true that a patient who is depression-prone will emphasise disease symptoms and suffer more than a patient who does not tend to become depressed.

**Therapy**
As in any other disease, therapy for CP/PPS may resolve either the underlying pathogenic cause or merely the
symptoms. As both may be caused by many factors, innumerable types of therapy are available. In our experience of more than 10 years in this field we have developed some new approaches and definitely tried everything. Unfortunately no strategy is successful in every single patient, which is probably Solomon-like proof that all hypotheses on pathogenesis are valid. In any case approaches include medical or surgical therapy; transcutaneous electrical nerve stimulation (TENS), sacral neuromodulation. Medical therapy is based on administration of antibiotics, alpha blockers, myorelaxing agents, antidepressives and neuropsychotropic agents. Surgery treatments include TUIP (to re-establish urethral neck patency), intra-prostatic infiltrations and apply thermotherapy.

1) Antibacterial Agents

Administering antibiotics is the most common and most discussed approach. Debate rages on the choice of antibiotics and their real efficacy. The main limitation of these studies (5) is generalization of their findings to patients in the community setting. Men with long-standing and refractory symptoms are more likely to be referred to tertiary medical centres, and therefore enrolled in clinical trials. Indeed, many CP/PPS studies enrol patients in this category. They may be end-stage prostatitis patients whom the study drugs, which are commonly prescribed in the community setting failed to treat. But men with less severe symptoms that are cured by medical therapy may in fact be more representative of the CP/PPS population as a whole. This issue still needs clarification. The proportions of these subpopulations referred to urologists, compared with primary care providers or internists, could also differ significantly. Until treatment patterns for CP/PPS change, it will be difficult to test antimicrobials in naive men with symptoms of more than 3 months duration. An important observation regarding drug therapy is that the blood barrier limits penetration of many substances into the prostate. The existence of the barrier had been suspected for several years but was thought to apply mainly to poor penetration of antibiotics from plasma into prostatic secretion. Clinical experiences had shown that trimethoprim has the most favourable pharmacokinetics, followed by the quinolones and some macrolides and tetracyclines; beta-lactams and aminoglycosides show poor penetration in the prostatic tissues (39). There is consensus that antibiotic treatment has to be prolonged. Development of antibiotic resistance also has to be borne in mind. Krieger (11) recommended re-evaluating traditional antibiotic treatment in light of the recent dramatic changes in antimicrobial susceptibility. In many USA areas, for example, the increasing probability of resistance (including quinolone resistance in some parts of the world) supports the need for continued monitoring of urinary tract isolates with quantitative cultures and susceptibility testing, especially for patients with recurrent or complicated infections. Resistance has also increased dramatically in gram-positive bacteria. Vancomycin resistant enterococci are among the best known antibiotic resistant bacteria. These organisms are commonly recovered from patients who have received multiple courses of antibiotics, particularly those who have been hospitalized for prolonged periods. Enterococcus faecium is the most common of the vancomycin resistant enterococci. These organisms are often resistant to ampicillin. Furthermore, strains resistant to gentamycin and streptomycin are also often resistant to fluoroquinolones, rifampicin and the tetracyclines. Conjugation can rapidly spread resistance to other bacteria. For example vancomycin resistant enterococci have been isolated from many healthy Europeans, including 28% of outpatients studied in Belgium. This high rate of resistance has been associated with the use of antibiotics in animal feed. There are currently some prospects for new antimicrobial agents. For example the oxazolidinones are the first new antimicrobial class for treatment of gram-positive bacteria in 30 years.

For gram-positive bacteria (eg Staphylococcus, Corynebacteria) Shoskes prefers a "second generation" quinolone because of their extended gram-positive coverage. Incidentally, while Staphylococcus often shows up as sensitive to sulpha drugs on the lab test, sulphas have no activity against these bacteria in vivo. Shoskes, like Yasuda (40) uses erythromycins as second choice because there is evidence they may penetrate in a bacterial biofilm. Use of amoxicillin and Cephalosporins is questionable because of poor penetration into the prostatic tissue. Bundrick (41) compared the effects of levofloxacin and ciprofloxacin and concluded that levofloxacin is as effective as ciprofloxacin for 28 days for the treatment of chronic bacterial prostatitis. Isolation of a high proportion of gram-positive organisms, as well as gram-negative pathogens, underscores the need to choose an antimicrobial agent with broad-spectrum activity.

Shoskes (16) eradicated nanobacteria with daily 500 mg tetracycline, a proprietary nutraceutical and an EDTA suppository. Therapy designed to eliminate nanobacteria resulted in significant improvement in the symptoms of recalcitrant CPSS in the majority of men. Whether this was due to the treatment of stone producing nanobacteria or some other mechanism is not clear.

For Bradshaw (42) the specific treatment for Mycoplasma genitalium is appropriate in asymptomatic patients in whom the organism has been detected; current evidence suggest that first line therapy with a 5 day course of azithromycin would be most appropriate. Single doses of azithromycin may be less effective in men with urethritis and occasionally macrolide resistance has been encountered. Patients with treatment failure after azithromycin have been successfully treated with moxifloxacin 400 mg daily for 10 days but because of the risk of development of resistance this treatment should be considered second line.

But many Authors are definitively not convinced by antibiotic treatment. In 2001 Nickel (43) concluded that culture, leukocyte and antibody status of prostate specific specimens does not predict antibiotic response in patients with the chronic prostatitis/chronic pelvic pain syndrome. The perceived beneficial effect of antibiotics needs to be evaluated in a randomized placebo controlled trial. In 2003 his pilot study on levofloxacin versus placebo confirmed that 6 weeks of levofloxacin therapy in men diagnosed with CP/PPS resulted in symptom improvement that was not significantly different from placebo at end of treatment or follow-up (44). In 2004 in a year-long study Nickel (45) confirmed that a treatment strategy based on sequential application of monotherapies for patients with a long history of severe CP/PPS remains relatively poor.
In a randomized, prospective, placebo-controlled trial, Alexander (46) tested ciprofloxacin, the alpha blocker tamsulosin and the two drugs in combination in men with long-standing, refractory CP/CPPS. The study showed no difference in NIH-CPSI scores or response rate after 6 weeks of treatment. This indicates that ciprofloxacin and tamsulosin do not substantially relieve symptoms in men with long-standing, refractory CP/CPPS.

2) **Alpha-blockers**

The rationale for the use of alpha blockers as therapy for CP/CPPS derives from the hypothesis that CP/CPPS is wholly or partly due to high pressure urinary flow which causes first ureter-prostate reflux and then chronic bacterial or abacterial inflammation. An improvement in uroflow is to be expected in patients with reduced uroflow. Other symptoms improved even in patients who had a non-obstructed voiding pattern (40). In this field opinions really are discordant. Two recent studies conducted outside North America indicate that longer treatment with the alpha blockers terazosin (47) and alfuzosin (48) was very efficacious in men who had not previously been treated with alpha blockers. On the other hand Nickel reports (49, 50) that alpha-blockers improve lower urinary tract symptoms, including pain, in patients who are diagnosed with both prostatitis and benign prostatic hyperplasia. Evidence has proven there is definitely a role for alpha-blockers in the management of the prostatitis syndromes, particularly in those with more severe symptoms. Lee (51) observed that treatment-naive and/or newly diagnosed patients appear more likely to respond than long-term, chronic refractory patients. Long courses of treatment (12 weeks to 6 months) appear better than short courses, and less selective agents appear more efficacious than more selective α-1 blockers. In a meta-analysis, Yang (52) showed a significant reduction of total NIH-CPSI or IPSS in patients with treatment duration of more than 3 months. There were also valuable results in alleviation of urinary symptoms. Alpha-adrenergic antagonists did not show benefit in pain relief. The Editorial Comment on Yang’s paper stated that there are conflicting results on the role of α-blockers in the treatment of CP/CPPS. This meta-analysis of several α-blocking drugs shows an improvement in voiding symptoms but not in pain. There is hope that some of the α-blocking drugs could also have a central nervous system effect on a sympathetic component of pain. More studies are needed on individual drugs before the data are definitive but this trend might be what is expected from a drug used mainly for voiding symptoms. For Mehik (49) six months of alfuzosin therapy for CP/CPPS is safe and well tolerated and results in a modest, but statistically significant, improvement in the NIH-CPSI, particularly in the pain domain, compared with placebo and standard/traditional treatment. The beneficial effect is only apparent after several months of treatment and disappears when treatment is discontinued. And (47) as reported above concludes that tamsulosin do not substantially relieve symptoms in men with long-standing, refractory CP/CPPS. In a systematic review, Mishra (53) reports that evidence from current publications is insufficient to conclude with certainty that α-blockers are effective for type III prostatitis. Future studies should incorporate uniformity in data collection and reporting with improved health-related quality of life as the end-point of therapy.

3) **Other drugs**

Many other drugs have been used to treat CP/CPPS, including myorelaxants such as diazepam and baclofen, and cytokines modulators as thalidomide (54) and antidepressants like amitriptyline, herbal extracts (55). Phosphodiesterase 5 inhibitors are now the new entry (56). In our experience the most effective treatments are with myorelaxant and antidepressant drugs. Our unpublished data show baclofen combined with diazepam and a physical tool named Dilatan® is very effective in relaxing perinea wall muscles. In presence of pudendal nerve inflammation we successfully use amitriptyline from 5 to 75 mg/daily, depending on response and severity of symptoms, confirming results achieved in the field of Intestinal Cystitis.

4) **Intraprostatic injections**

Although this approach was proposed at least 30 years ago (57), it has recently returned to vogue with the use of ultrasound guiding techniques. Few reports are available, showing urologists are generally not very interested in this approach. In 1988 Baert (58) demonstrated that remission periods of at least 6 months were obtained in 71% of 24 selected patients with chronic bacterial prostatitis after 1 or 2 infiltrations, while 6/24 (25%) required several procedures to achieve long-term remission and therapy failed in 1 (4%). In 1996 Yamamoto (59) reported results of direct transrectal infiltration of the prostate with antibiotics in 25 selected patients with refractory chronic prostatitis, suggesting that local antibiotic treatment of chronic bacterial prostatitis is useful, although careful randomized studies with long follow-up are required to evaluate the merits of the method. In our experience (60) the technique is associated with good efficacy. This therapy is aimed at overcoming all prostatic barriers and storing therapeutical agents directly in the prostate parenchyma. Our therapy is based on a cocktail of antibiotics with an acid pH, powerful anti-bacterial agents and a strong anti-inflammatory agent like cortisone. At the same time a long-lasting anaesthetic is injected into the pelvic floor to stop spasm of the elevator anus muscles. This approach is indicated for many patients but mainly for two groups: 1) patients with large intra-parenchymal fibro-calcified areas which prevent drug diffusion in whom cultures over the years have shown high bacterial concentrations. We have to keep in mind that administration of 1 g of antibiotic directly into the prostatic capsule, is the equivalent of a systemic dose 2000-2500 times higher; 2) patients with major pain symptoms in whom local cortisone infiltration will reduce oedema in the canaliculi and acini, re-establish normal flow of prostatic secretions and inhibit any auto-immune process which may have been triggered. The only adverse side effect we have observed in a large cohort of patients is hemosperma in 70% of cases.

**Conclusions**

This review has attempted to describe the large number of hypotheses of pathogenesis and the vast number of treat-
ments have been proposed over the years as therapy for CP/CPPS. Most of these approaches have been tested in heterogeneous groups of patients who were never or rarely treated naive. In assessing results one should bear in mind that the psychological factor plays a large role in patients with CP/CPPS and so results with placebo may be even better than results with active drugs. These studies have generated divergent results which probably cannot be compared and led to the conclusion that guidelines to therapy for CP/CPPS are not feasible. At present many eminent researchers as well as we ourselves are of the view that no single drug or approach is valid (46) and that CP/CPPS needs a multi-tasking approach. We are of the opinion the optimal therapeutical combination is antibiotics (if infection is clearly present) and myorelaxants while physiological intra-anal pressure is re-established and inflammation disappears from pudendal nerves. In 2003 Shoskes (61) proposed a good example of this type of approach. He treated 53 patients with presence of chronic prostatitis (minimum follow-up of 6 months) with antibiotics, prostatic massage, anti-inflammatory phyotherapy, alpha-blockers and neuromuscular agents. At the final assessment based on a global subjective assessment, 43 of the patients (80%) were better, 8 were the same and 3 were worse. An approach using stepwise therapy with antibiotics, anti-inflammatory agents and neuromuscular agents may be successful in the majority of patients with long-standing chronic prostatitis. Magri (62) subjected 137 patients with chronic bacterial prostatitis (CBP) to a combination of pharmacological therapy with antibacterial agents (ciprofloxacin/azithromycin), alpha-blockers (alfuzosin) and Serenoa repens extracts. Clinical remission was extended throughout a follow-up period of 30 months for 94% of patients, whereas seven patients relapsed.

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Reduction of PSA values by combination pharmacological therapy in patients with chronic prostatitis: Implications for prostate cancer detection.

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We identified from our clinical database a total of 471 patients affected by cat. II chronic bacterial prostatitis (CBP), cat. III (IIIa and IIIb) chronic pelvic pain syndrome (CP/CPPS), or cat. IV asymptomatic inflammatory prostatitis (AIP), according to NIH criteria. 132 intent-to-treat patients, showing levels of PSA ≥4 ng/mL, were subjected to a 6-week course of combination pharmacological therapy with 500 mg/day ciprofloxacin, 500 mg/day azithromycin (3 days/week), 10 mg/day alfuzosin and 320 mg b.i.d. Serenoa repens extract. At the end of treatment, 111 per-protocol patients belonging to all categories of prostatitis showed a total 32.5% reduction of PSA levels. In the same group, 66 patients (59.4%) showed “normalization” of PSA values under the 4 ng/mL limit. Patients affected by cat. IIIb CP/CPPS showed the highest PSA reduction and normalization rates (40% and 68.4%, respectively). Follow-up data show that, after a marked, significant reduction at completion of therapy, PSA levels, urine peak flow rates and NIH-CPSI symptom scores remained constant or decreased throughout a period of 18 months in patients showing normalization of PSA values.

Prostatic biopsy was proposed to 45 patients showing persistently high PSA values (≥4 ng/mL) at the end of treatment. Fourteen patients rejected biopsy; of the remaining 31, 10 were diagnosed with prostate cancer. Four months after a first biopsy, a second biopsy was proposed to the 21 patients with a negative first diagnosis and persistently elevated PSA levels. Three patients rejected the procedure; of the remaining 18, four were diagnosed with prostatic carcinoma.

In summary, combination pharmacological therapy decreased the number of patients undergoing prostatic biopsy from 111 to 45. Normalization of PSA values in 59.4% of patients - not subjected to biopsy - increased the prostate cancer detection rate from 12.6% (14/111) to 31.1% (14/45). The reduction of PSA after a 6-week course of therapy was calculated in patients affected by cat. II, IIIa, IIIb and IV prostatitis after stratification with respect to the concomitant presence or absence of benign prostatic hyperplasia (BPH). PSA was reduced by 41% in cat. II CBP patients without BPH, compared to a 12.7% reduction in patients affected by BPH. Cat. IIIa CP/CPPS patients without BPH showed a 38.3% reduction of PSA levels, compared to a 20.7% reduction observed in CPPS/BPH patients. These data show that the presence of BPH may prevent the reduction of PSA induced by combination pharmacological therapy, and suggest that care has to be taken in the adoption of PSA as a marker of therapeutic efficacy in the presence of confounding factors like BPH. PSA should in our opinion be used as a significant component of a strategy integrating multiple diagnostic approaches.

KEY WORDS: Chronic Bacterial Prostatitis; Prostate Specific Antigen; Prostate Cancer; Azithromycin; Ciprofloxacin; Alfuzosin; Serenoa repens; NIH-CPSI.
Reduction of PSA by pharmacological therapy in patients with chronic prostatitis: Implications for prostate cancer detection

**INTRODUCTION**

The adoption of the prostate specific antigen (PSA) has greatly improved the detection of patients with prostate cancer. PSA is a useful marker for screening individuals at risk for prostatic neoplasia, for following disease progression and relapse, and for monitoring the response of patients to therapy. However, PSA is not specific for prostate cancer, and enhanced PSA serum levels frequently characterize a variety of prostatic conditions, including prostatitis and BPH. Although a number of strategies have been adopted to improve the cancer-sensitivity of PSA (1, 2), conditions like BPH and prostatitis continue to be factors accounting for a high proportion of negative, unnecessary biopsies, or – on the contrary – masking an actual association between cancer and elevated levels of the marker.

An increasing number of studies are confirming that prostatitis syndromes are major causes of elevated PSA, and that treatment of prostatitis may decrease PSA and improve its specificity as a prostate cancer marker by reducing the number of patients with a continuing indication for prostatic biopsy. In a retrospective subset analysis performed on 137 patients characterized by elevated PSA levels (>4 ng/mL) and chronic prostatitis evidenced by white blood cell counts in EPS specimens, Bozeman et al. showed that 4-week combination therapy with antibacterial agents (fluoroquinolones/co-trimoxazole/doxycycline) and ibuprofen caused a 36.4% reduction of PSA. Forty-seven percent of patients showed PSA values below 4 ng/mL after treatment and were not subjected to prostate biopsy, thus increasing the positive biopsy detection rate from 13.7% to 25.5% (3).

From a cohort 187 asymptomatic men, Potts identified a subset of 51 patients with signs of cat. IV AIP (4). It was shown that four-week treatment with co-trimoxazole or fluoroquinolones normalized the PSA levels (<4 ng/mL) in 42% of patients, thus decreasing the number of biopsies by 18%. Schaeffer et al. have performed a subset analysis of a randomized, double blind control trial, focusing on patients with cat. II CBP. 377 ITT patients were subjected for four weeks to therapy with ciprofloxacin/levofloxacin - with or without NSAIDs (5). Therapy caused a 32% reduction of PSA levels. Moreover, 42% of patients with increased PSA at baseline had normalized PSA (<4 ng/mL) after fluoroquinolone treatment. Interestingly, 90.9% of levofloxacin-treated patients (or 93.3% of ciprofloxacin-treated patients) showing PSA normalization had responded to therapy with eradication of causative pathogens. The proportion of eradicated patients was markedly lower (levofloxacin group, 69.2%; ciprofloxacin group, 61.5%) if post-therapy PSA levels remained increased.

Other reports directly or indirectly support the view that pharmacological treatment of prostatitis or other lower urinary tract conditions can improve specificity and sensitivity of PSA as a marker of neoplastic conditions at the prostatic level (6-9). The present study was aimed at assessing the effect of a course of pharmacological therapy based on a combination of antibacterial agents, alpha-adrenoceptor blockers and S. repens extracts on patients belonging to all categories of chronic prostatitis (cat. II CBP, cat. IIIa CP/CPPS, cat. IIIb CP/CPPS, cat. IV AIP), to investigate whether the reduction of PSA levels might decrease the number of patients with continuing indication for prostatic biopsy and enhance the rate of cancer detection in prostatic specimens.

**PATIENTS AND METHODS**

**Study design and diagnostic procedures**

The data presented in this study are the result of retrospective observations performed on patients which underwent diagnostic and therapeutic protocols routinely adopted in our clinical setting; these protocols were based on recommended, validated and approved algorithms, protocols and therapeutic agents. An informed consent has been signed by all patients after adequate information on the “aims, methods, benefits and hazards” (Declaration of Helsinki, 1964, and successive emendations) of the diagnostic procedures and pharmacological treatment adopted in our clinical practice.

A total of 471 consecutive patients were identified from our clinical databases (years 2001-2004). The mean age of patients is shown in Table 1. Patients were diagnosed and treated in a single urology/sonography outpatient clinic at the Istituti Clinici di Perfezionamento, Milano, Italy.

Patients were affected by cat. II chronic bacterial prostatitis, cat. IIIa (inflammatory) and IIIb (non-inflammatory) chronic prostatitis/chronic pelvic pain syndrome, or other conditions.

**Table 1.**

<table>
<thead>
<tr>
<th>Prostatitis, category</th>
<th>Age (mean)</th>
<th>Age (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBP II</td>
<td>44.39</td>
<td>22-79</td>
</tr>
<tr>
<td>CP/CPPS, IIIa</td>
<td>50.40</td>
<td>22-78</td>
</tr>
<tr>
<td>CP/CPPS, IIIb</td>
<td>48.57</td>
<td>22-75</td>
</tr>
<tr>
<td>AIP IV</td>
<td>60.82</td>
<td>29-79</td>
</tr>
<tr>
<td>Total</td>
<td>48.84</td>
<td>29-79</td>
</tr>
</tbody>
</table>

**Abbreviations:** AIP, Asymptomatic Inflammatory Prostatitis; BPH, Benign Prostatic Hyperplasia; CBP, Chronic Bacterial Prostatitis; CP/CPPS, Chronic Prostatitis/Chronic Pelvic Pain Syndrome; DRE, Digital Rectal Examination; EPS,Expressed Prostatic Secretions; ITT, intent-to-treat; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health; NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; PIN, Prostatic Intraepithelial Neoplasia; PSA, Prostate-Specific Antigen; Qmax, urine peak flow rate.
cat. IV asymptomatic inflammatory prostatitis, according to NIH criteria (National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health [NIDDK], Chronic Prostatitis Workshop, 1995).

Patients were not included in this study in the presence of any of the following conditions: acute prostatitis or urinary tract infections; therapy with antibiotics/antibacterials at the prostatic level within a 90-day period prior to entering the study; renal/hepatic failure; indwelling catheters; cystostomy; ureterostomy; prostate surgery; hypersensitivity to quinolones/macrolides; renal/hypotension.

At timepoint T0, after complete clinical and microbiological assessments, a 6-week course of pharmacological therapy was initiated. At diagnosis (T0) and at the completion of the 6-week course of treatment (timepoint T1) patients were subjected to a complete diagnostic protocol, including microbiological and clinical evaluations. At timepoints T2, T3 and T4 - 6, 12 and 18 months after timepoint T1, respectively - patients were subjected to complete clinical evaluation.

Published recommendations were followed (10) for evaluation of patients. Anamnesis included a review of past and present symptoms, focusing on previous and concurrent urinary diseases and infections, on genitourinary surgery and on past and present medications. The severity of CBP symptoms was scored at all timepoints (T0-T4) by means of an Italian translation of the NIH Chronic Prostatitis Symptom Index (NIH-CPSI) (11) - rating pain and voiding symptoms, and the impact of the disease on the quality of life of the patients (12). The clinical exam included thorough examination of the abdomen and external genitalia and perineum. Consistency and irregularity of the prostate gland were evaluated by digital rectal examination (DRE). Total serum Prostate Specific Antigen (PSA) levels were determined in each patient at timepoints T0 and T1, at first or second biopsy, and at follow-up timepoints T2, T3 and T4. Complete low urinary tract diagnostic imaging was performed by pelvic and transrectal ultrasound. Urine peak flow rate measurements (Qmax) were performed at all timepoints (T0-T4). Microbiological tests included (i) pre-VB2 urethral swab analysis and culture, (ii) a segmented localization test according to Meares-Stamey, with slight modifications, as previously described (13), and (iii) post-VB3 semen analysis and culture. Bacterial loads were calculated in all microbiological tests. For diagnosis of chronic bacterial infection of the prostate (cat. II CBP), colony counts in EPS/VB3 were required to be at least tenfold greater than those assessed on VB2.

**Therapeutic protocol and data analysis**

Starting from timepoint T0, patients received an oral once-daily dose of 500 mg of the fluoroquinolone ciprofloxacin. The quinolone was associated with a 15-membered macrolide (14), as previously described (13): a single daily dose of 500 mg azithromycin was administered only during the first three consecutive days at the beginning of each week of treatment with ciprofloxacin (15). Combination therapy included a daily dose of the alpha-adrenoceptor blocker alfuzosin (10 mg) (16) and a lipido-sterolic extract of *Serenoa repens* (640 mg/day), showing anti-inflammatory properties at the prostatic level (17, 18). This therapeutic regimen was administered for 6 weeks to all patients (time frame: T0-T1). In agreement with an algorithm suggested by Wagenlehner and Naber (19), for the first 6 months of the follow-up period (time frame: T1-T2) patients were treated with the alpha-blocker, to which the *S. repens* extract was associated.

Adverse effects caused by drugs used in the present protocol were spontaneously reported by patients or recorded during periodical visits and controls. NIH-CPSI scores and Qmax were analysed by the Wilcoxon Signed Rank test (analysis of intra-group differences) or by the Wilcoxon Rank Sum test (analysis of inter-group differences). The differences between PSA levels were measured by parametric (two-tailed t-test) or nonparametric tests (Wilcoxon Signed Rank/Wilcoxon Rank Sum tests), depending on the population size. Variance was analyzed by the Kruskal-Wallis test. The XLStatistics 5.71 program (© Rodney Carr 1997-2006) was used for statistical analysis of data.

### Table 2.

PSA values in 339 patients with PSA levels at timepoint T0 <4 ng/ml (Group 2); reduction after combination pharmacological therapy in cat. II and IIIa prostatitis.

<table>
<thead>
<tr>
<th>Prostatitis category</th>
<th>Patients (N)</th>
<th>PSA at T0 (ng/mL; mean±SD)</th>
<th>PSA at T1 (ng/mL; mean±SD)</th>
<th>PSA reduction (%)</th>
<th>p, (T1 vs. T0)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>120</td>
<td>1.16±0.85</td>
<td>0.94±0.69</td>
<td>19</td>
<td>0.023</td>
</tr>
<tr>
<td>IIIa</td>
<td>96</td>
<td>1.72±1.11</td>
<td>1.15±0.60</td>
<td>33.13</td>
<td>0.0022</td>
</tr>
<tr>
<td>IIIb</td>
<td>120</td>
<td>1.15±0.77</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IVb</td>
<td>3</td>
<td>0.76±0.39</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>339</td>
<td>1.31±0.93</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

a, Wilcoxon Signed Rank test.
b, patients diagnosed with cat. IIIb CP/CPPS and cat. IV AIP, showing PSA <4 ng/ml, were not subjected to a 6-week course of therapy.
RESULTS AND DISCUSSION

A total of 471 patients were retrospectively evaluated from our clinical databases (years 2001-2004) according to the inclusion/exclusion criteria described in the Methods section. At diagnosis (timepoint T0), 132 patients (28% of a total of 471 patients; group 1) were characterized by levels of PSA ≥ 4 ng/mL. The remaining 339 patients, showing PSA levels inferior to 4 ng/mL (1.31±0.93, Table 2), were assigned to group 2.

Two patients developed Chlamydial prostatitis - which in our practice is treated with antibacterial agents different than the ones used in this study – and were excluded from group 1. Moreover, one patient suspended voluntarily the assumption of antibacterial agents after the emergence of side effects (diarrhea), and 18 patients were excluded because non-compliant or because rejected a prospective biopsy. The remaining 111 patients belonging to group 1 (average PSA: 7.09±3.82 ng/mL, Table 3) were subjected to combination therapy for a period of 6 weeks. Among patients belonging to group 2, only individuals diagnosed with cat. II CBP and cat. IIIa CP/CPPS were subjected to combination therapy (N=216): in our clinical practice, patients affected by cat. IIIb CP/CPPS - showing levels of PSA <4 ng/mL - are treated with a combination of alpha-blockers and S. repens extracts, whereas patients with cat. IV AIP are not subjected to pharmacological treatment. In group 1, administration of antibacterial agents to patients affected by cat. IIIb or cat. IV prostatitis was suggested by the evidence – mentioned by several experts (e.g., 20, 21) – that antimicrobial treatment can improve signs and symptoms of prostatic syndromes that appear to be of non-bacterial etiology. This may be due to the presence of undetected pathogens at the prostatic level (22), or to the intrinsic anti-inflammatory activity displayed by quinolones or macrolides (23).

The chart in Figure 1 shows the overall reduction of PSA values in a total of 327 patients belonging to group 1 (all categories) and group 2 (cat. II CBP and cat. IIIa CP/CPPS), at the completion of a 6-week course of combination therapy. T1 vs. T0: p<0.0001; paired t-test. The combination treatment was well tolerated and adverse effects – including the emergence of sexual dysfunction – were neither observed at periodical controls nor reported by patients; as mentioned above, only in one case, therapy was voluntarily suspended due to the appearance of side effects (diarrhea).

Table 2 shows the PSA levels of patients belonging to group 2. Cat. II and IIIa patients underwent 19% and 33.13% reductions of PSA levels, respectively. The small number of cat. IV patients shown in this record is due to the fact that asymptomatic subjects exhibiting low PSA levels at periodical check-ups rarely undergo further clinical controls. Although reductions of PSA values shown by cat. II and IIIa patients are statistically signifi-

**Table 3.**

PSA reduction and normalization in 111 patients with PSA levels at timepoint T0 >4ng/ml (Group 1), after combination pharmacological therapy.

<table>
<thead>
<tr>
<th>Prostatitis category</th>
<th>Patients (N)</th>
<th>PSA at T0 (ng/mL; mean±SD)</th>
<th>PSA at T1 (ng/mL; mean±SD)</th>
<th>PSA reduction (%)</th>
<th>p, (T1 vs. T0)*</th>
<th>Patients with PSA &lt;4ng/ml at T1 [N; (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>18</td>
<td>7.06±2.42</td>
<td>5.25±2.47</td>
<td>25.5</td>
<td>0.037</td>
<td>9 (50.0%)</td>
</tr>
<tr>
<td>IIIa</td>
<td>37</td>
<td>6.83±2.38</td>
<td>4.83±2.63</td>
<td>29.3</td>
<td>&lt;0.0001</td>
<td>23 (62.1%)</td>
</tr>
<tr>
<td>IIIb</td>
<td>19</td>
<td>7.51±4.81</td>
<td>4.51±3.97</td>
<td>40.0</td>
<td>0.003</td>
<td>13 (68.4%)</td>
</tr>
<tr>
<td>IV</td>
<td>37</td>
<td>7.13±4.94</td>
<td>4.66±2.31</td>
<td>34.6</td>
<td>0.0002</td>
<td>21 (56.7%)</td>
</tr>
<tr>
<td>Total</td>
<td>111</td>
<td>7.09±3.82</td>
<td>4.78±2.76</td>
<td>32.5</td>
<td>&lt;0.0001</td>
<td>66 (59.4%)</td>
</tr>
</tbody>
</table>

*Wilcoxon Signed Rank test.
PSA levels in 66 patients belonging to group 1 (PSA at timepoint T0 ≥ 4 ng/mL) showing normalization of PSA (<4 ng/mL) at the end of a 6-week course of combination therapy (T1). Patients were analyzed every six months during an 18-month follow-up period (time frame: T1-T4). a, p<0.0001 vs. T0; b, p=0.0007 vs. T0; c, p=0.0079 vs. T1; d, p=0.00077 vs. T1; e, p=0.12 vs. T1; f, p=0.18 vs. T1. Wilcoxon Signed Rank test.

Figure 3.

Urine peak flow rate (Qmax) in 66 patients belonging to group 1 (PSA at T0 ≥ 4 ng/mL) showing normalization of PSA levels (<4 ng/mL) at the end of a 6-week course of combination therapy (T1). Patients were analyzed every six months during an 18-month follow-up period (T1-T4). a, p<0.0001 vs. T0; b, p=0.01 vs. T0; c, p=0.025 vs. T0; d, p=0.0009 vs. T0; e, p=0.016 vs. T1; f, p=0.04 vs. T0; g, p<0.0001 vs. T0 and p=0.05 vs. T1; h, p=0.0014 vs. T0 and p=0.25 vs. T1; i, p=0.003 vs. T0. Wilcoxon Signed Rank test.
NIH-CPSI scores of the same group of patients are shown in Figure 4. Scores relative to pain, voiding symptoms and the impact of the disease on patients' quality of life decreased significantly in patients belonging to all prostatitis categories at the end of a 6-week course of combination therapy. At later timepoints further significant decreases were observed (for statistical details and p values, see figure legend). Inter-group differences were observed. At diagnosis (T0), patients affected by cat. II CBP showed significantly higher pain, voiding symptoms and life quality impact scores, when compared to cat. IIIa and IIIb CP/CPPS patients (p<0.05 vs. IIIa or IIIb [all symptoms], Wilcoxon Rank Sum test; p=0.03 [pain], p=0.04 [voiding symptoms], p=0.03 [impact on life quality, Kruskal-Wallis analysis]).

At timepoint T1, inter-group differences with regard to pain scores were no longer statistically significant (p>0.05 vs. IIIa or IIIb, Wilcoxon; p=0.08, Kruskal-Wallis). Similarly, the differences between voiding symptom scores were no longer significant at T1, when cat. II patients were compared to cat. IIIb patients (p>0.05, Wilcoxon; p=0.16 [all prostatitis categories, Kruskal-Wallis]). The difference between cat. II and IIIa patients, still significant at T1 (p=0.02, Wilcoxon), lost significance at later timepoints (p=0.13 at T2 for all prostatitis categories, Kruskal-Wallis). In a similar fashion, significant inter-group differences were observed with regards to the impact of the disease on patients' quality of life at T0 (cat. II CBP: p<0.05 vs. cat. IIIa or IIIb, Wilcoxon Rank Sum test; p=0.03, Kruskal-Wallis). The II-IIIb difference lost significance at T1 (p=0.05, Wilcoxon; p=0.04 [all prostatitis categories, Kruskal-Wallis]), whereas the II-IIIa difference lost significance at timepoint T2 (p=0.5 [all prostatitis categories, Kruskal-Wallis]). Taken together, these data show that combination therapy could level the scores of patients belonging to prostatitis categories by reducing the symptoms of cat. II CBP patients to values non-statistically different from those observed in patients affected by CP/CPPS. The observed marked reduction of all tested parameters persisted throughout an 18-month follow-up period.

Prostatic biopsy was proposed to 45 patients showing PSA values ≥4 ng/mL at the end of a 6-week combination treatment. 14 patients rejected biopsy; of the remaining 31, 10 were diagnosed with prostate cancer (Gleason score: 2+3, 4 patients; 2+4, one patient; 3+3, 3 patients; 3+4, one patient; 4+3, one patient). Among the remaining 21 patients, two were diagnosed with high-grade prostatic intraepithelial neoplasia (PIN). Table 4 shows the mean PSA of patients showing a positive or negative biopsy measured at T0 and T1 timepoints; total PSA levels (8.07±3.77 ng/mL) were unchanged after pharmacological therapy (8.17±2.74 ng/mL). Patients diagnosed with prostatic carcinoma at first biopsy showed a modest increase of PSA levels at T1 (8.03±3.03 ng/mL) vs. T0 (6.96±2.61 ng/mL) (Table 4); the difference is not statistically significant.

Four months after a first biopsy, a second biopsy was proposed to the 21 patients with a negative first diagnosis and persistently elevated PSA levels. Three patients rejected the procedure; of the remaining 18, four – including the two patients with high-grade PIN detected
at first biopsy - were diagnosed with prostatic carcinoma (Gleason score: 3+4, three patients; 4+5, one patient). Thus, a second biopsy was useful to increase the cancer detection rate in patients characterized by elevated PSA levels after combination therapy. Table 5 shows the PSA levels of patients at T0 and at a first or second biopsy. PSA values are unchanged at the three different time-points both in patients with negative biopsies and in patients diagnosed with prostate cancer. Inter-group differences are also not significant at the statistical level. These data show that PSA values displayed by patients showing a first or second negative biopsy were not significantly decreased by combination therapy: due to the low statistical power of data we could not ascertain which additional factors were interfering with reduction/normalization of PSA in these patients. Thus, although the vast majority of patients analyzed in this study responded to combination therapy with significant decreases of PSA, care has to be taken in considering the absolute predictive value of this marker in the management of prostatitis syndromes.

Figure 5 shows the pattern of PSA levels measured at T0 and at cancer diagnosis (following a first or second biopsy) in total 14 patients. The difference between PSA levels is not statistically significant (p=0.31, Wilcoxon Signed Rank test).

In conclusion, our study shows that combination pharmacological therapy decreased the number of patients undergoing prostatic biopsy from 111 to 45. Normalization of PSA values in 59.4% of patients – not subjected to biopsy - increased the prostate cancer detection rate from 12.6% (14/111) to 31.1% (14/45). Our data are in line with the findings of Bozeman et al. (3) on...
prostatitis patients (13.7% positive biopsies increasing to 25.5% after a combination of antibacterial drugs and Ibuprofen/Celecoxib), of Guercio et al. (6) on asymptomatic patients showing histological evidence of prostatitis (19% positive second biopsies raising to 26% after Levofloxacin), and of Potts (4) on cat. IV AIP patients (17% positive biopsies increasing to 31% after quinolones or co-trimoxazole), and extend to other categories of chronic prostatitis the evidence that medical therapy can reduce PSA and decrease the number of negative biopsies, raising the effectiveness and specificity of prostate cancer screening.

We are aware that since a significant number of patients refused to be subjected to biopsy, our data can only indicate a possible increased efficiency of cancer detection. Nevertheless, we believe that combination therapy can contribute to the removal of confounding factors that may decrease the specificity of PSA, when this marker is used to detect neoplastic alterations of the prostate. By discussing the Bozeman study, Nickel criticizes the assumption that patients showing PSA levels decreased under the 4 ng/mL concentration may not be at significant risk for prostate cancer (3, 24). In our observational study, based on ‘real life’ medical practice, we have used the widely adopted serum concentration of 4 ng/mL as a cutoff value to define “normalization” of PSA. However, we are aware that this is a controversial issue, that some experts have proposed other PSA thresholds (e.g. 2.5 ng/mL), and that a general consensus on diagnostically and prognostically significant levels of the marker is still lacking. We also agree that cases of prostate cancer might be disregarded within patients showing PSA values reduced under the 4 ng/mL limit. However, our patients were excluded from biopsy only in the presence of convincing clinical evidence (DRE, transrectal sonography) of the absence of suspect neoplastic lesions, and were subsequently subjected to frequent, accurate follow-up visits.

In the Italian context, a prostatic biopsy is felt by patients as a rather traumatic, invasive procedure. Moreover, morbidity - occasionally caused by the procedure (25) - can further deter patients from accepting prostatic biopsy. This is demonstrated by the significant number of individuals (first biopsy: 31%; second biopsy: 14%) rejecting biopsy in the presence of suspect levels of PSA. In the present study, all patients showing PSA levels equal or superior to 4 ng/mL were willing to accept the relative discomfort and the cost of a 6-week course of pharmacological treatment as a possible option aimed at decreasing the likelihood of a prospective biopsy.

It is known that benign prostatic hyperplasia (BPH) is frequently associated with elevated PSA levels (26). The mean age of patients in the Bozeman, Potts and Schaeffer studies was 63 (3-5), and 65 in the Guercio study (6), suggesting that a significant proportion of patients might be affected by BPH. To ascertain the influence of BPH on PSA reduction in prostatitis patients, we have stratified patients subjected to combination therapy with respect to the concomitant presence/absence of BPH (Figure 6). The most striking differences were shown by a 41% decrease of PSA in cat. II CBP patients without BPH, compared to a 12.7% reduction observed in patients affected by BPH. Cat. IIIa CP/CPPS patients without BPH showed a 58.3% reduction of PSA levels, compared to a 20.7% reduction in CPPS/BPH patients. The reduction of PSA levels in BPH patients belonging to all categories of prostatitis retained statistical significance (p<0.05, Wilcoxon Signed Rank test). Because cat. IV patients show a higher mean age when compared to other prostatitis groups (Table 1), the low PSA reduction observed in AIP subjects not affected by BPH might be due to age-related factors. Research is in progress to ascertain the nature of such effect in a larger patient population. In summary, these data show that the presence of BPH may prevent the reduction of PSA induced by combination pharmacological therapy, thus hindering the efficacy of this approach in decreasing the number of patients subjected to prostatic biopsy. Thus, we believe that care has to be taken in the adoption of PSA as a marker of therapeutic efficacy in the presence of confounding factors like BPH. PSA should in our opinion be used as a significant component of a strategy integrating multiple diagnostic approaches.

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INTRODUCTION

Chronic Prostatitis includes a group of diseases of bacterial or non-bacterial etiology, characterized by pelvic pain, voiding dysfunction and a number of additional signs and symptoms (1). The adoption of the NIH-CPSI as an internationally-acknowledged formal symptom inventory, the use of low urinary tract segmented diagnostic tests, the application of a novel classification system (NIDDK Chronic Prostatitis Workshop, 1995) and the administration of fluoroquinolones as first-line antibacterial agents (2) have been major landmarks in the scientific understanding and clinical management of chronic prostatitis. Due to the complexity of the disease, the body of knowledge about the etiology, diagnosis and treatment of the chronic prostatitis syndrome is continuously revised and discussed. In particular, the role of specific infecting microorganisms as causative agents of chronic prostatitis is recurrently debated, and a major challenge for scientists is the assessment of “the significance of uropathogenic, pre...

Original Paper

Eradication of unusual pathogens by combination pharmacological therapy is paralleled by improvement of signs and symptoms of chronic prostatitis syndrome.

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We performed a comparative analysis of microbiological and clinical responses to combination therapy in 104 symptomatic patients showing evidence of infection by traditional uropathogens (TU) or by unusual pathogens (UP) at the prostatic level. Eighty-two pathogens out of a total of 104 isolated microorganisms were eradicated at the end of a 6-week course of combination therapy with ciprofloxacin, azithromycin, alfuzosin and a S. repens extract. The TU and UP groups showed eradication rates of 75.5% and 82.3%, and clinical success rates of 78.8% and 85.7%, respectively. Thus, a similar response to therapy was observed in patients infected by TU or by UP. Intergroup differences were not significantly different, with the exception of higher scores relative to the impact of the disease on quality of life in TU-patients. Long-term improvement of signs and symptoms of prostatitis indicates that combination therapy is beneficial for symptomatic patients showing evidence of infection by unusual pathogens at the prostatic level. Our data support the hypothesis that organisms other than the traditionally recognized uropathogens may play a role in the onset of prostatitis.

KEY WORDS: Chronic Bacterial Prostatitis; Uropathogens; Azythromycin; Ciprofloxacin; Alfuzosin; Serenoa repens; NIH-CPSI.

Abbreviations: CBP, chronic bacterial prostatitis; CP, chronic prostatitis; CPPS, Chronic Pelvic Pain Syndrome; EPS, Expressed Prostatic Secretions; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health; NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; Qmax, urine peak flow rate; TU, traditional uropathogens; UP, unusual pathogens.

Summary

We performed a comparative analysis of microbiological and clinical responses to combination therapy in 104 symptomatic patients showing evidence of infection by traditional uropathogens (TU) or by unusual pathogens (UP) at the prostatic level. Eighty-two pathogens out of a total of 104 isolated microorganisms were eradicated at the end of a 6-week course of combination therapy with ciprofloxacin, azithromycin, alfuzosin and a S. repens extract. The TU and UP groups showed eradication rates of 75.5% and 82.3%, and clinical success rates of 78.8% and 85.7%, respectively. Thus, a similar response to therapy was observed in patients infected by TU or by UP. Intergroup differences were not significantly different, with the exception of higher scores relative to the impact of the disease on quality of life in TU-patients. Long-term improvement of signs and symptoms of prostatitis indicates that combination therapy is beneficial for symptomatic patients showing evidence of infection by unusual pathogens at the prostatic level. Our data support the hypothesis that organisms other than the traditionally recognized uropathogens may play a role in the onset of prostatitis.
were excluded, possibly uropathogenic and acknowledged non-uropathogenic microorganisms in prostate specimens” (3). Whereas there is a general consensus on the role of bacteria like Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae or Pseudomonas aeruginosa in the pathogenesis of type II Chronic Bacterial Prostatitis (CBP)(4), the classification of other microorganisms as prostate-specific uropathogens (e.g. Gram-positive bacteria, Ureaplasma, fungi and protozoa) is still controversial. Recent studies have investigated the role of “unusual pathogens” (5), “non-traditional uropathogens” (6), or “uncommon organisms” (7) in the pathogenesis of chronic prostatitis. By reviewing previous studies aimed at characterizing the role of “controversial organisms” like staphylococci, coryneforms, Chlamydia trachomatis and Ureaplasma urealyticum, Domingue and Hellstrom suggested that chronic idiopathic prostatitis (or prostatodynia) may indeed in most cases be of bacterial etiology, as demonstrated by molecular and cultural evidences, and that inadequate diagnostic techniques may preclude the detection of controversial microorganisms, thus leading to the classification of the disease as “abacterial” (8). Other authors adopt a more conservative approach, and tend to exclude that organisms different from traditional uropathogens (TU) may play an etiological role in CBP (reviewed in: 9). The present study was aimed at assessing a possible association between pharmacological eradication of unusual pathogens and clinical remission in patients affected by signs and symptoms of chronic prostatitis.

**Patients and Methods**

The data presented in this study are the results of observations performed on databases of patients which underwent diagnostic and therapeutic protocols routinely adopted in our clinical setting; these protocols were based on recommended, validated and approved algorithms, protocols and therapeutic agents. An informed consent was signed by all patients after counseling and adequate information on the “aims, methods, benefits and hazards” of the diagnostic procedure and pharmacological treatment adopted in our clinical practice (Declaration of Helsinki, 1975, and subsequent revisions). Patients provided as well a written consent to the publication of personal data for research purposes.

**Diagnosis of prostatitis**

Table 1 shows the demographic data of 104 patients included in the present study. Patients were affected by symptomatic chronic bacterial prostatitis (N=53) – category II, according to NIH criteria (NIH Chronic Prostatitis Workshop, 1995), or by chronic prostatitis signs and symptoms, associated with positive cultures of unusual pathogens (N=51; in the present paper we adopt the definition of “unusual pathogens” (UP) suggested by Skerk et al. (5). Patients were diagnosed and subjected to pharmacological treatment in a single urology/sonography outpatient clinic specialized in the diagnosis and treatment of prostatitis at the Istituti Clinici di Perfezionamento, Milano, Italy. Patients were randomly identified through a computerized database of diagnoses that indicated a combination of signs/symptoms of CP and positive cultures for a single TU or UP. Patients were not included in this study in the presence of one or more of the following conditions: acute prostatitis, acute urinary tract infection, therapy with antibiotics known to be effective on bacterial prostatitis within a 90-day period prior to entering the study, renal or hepatic failure, hypersensitivity to macrolides or quinolones; indwelling catheters; cystostomy; ureteroscopy; prostate surgery; presence of massive calcifications (macrolithiasis) or fibrosis in extended areas of the gland (>30% of the total gland volume).

Patients infected by *Chlamydia trachomatis* were excluded from the present study, because in our clinical practice chlamydial infections are treated with antimicrobial agents different than those described in this paper. At time T0, drug therapy was initiated. At diagnosis/start of therapy (T0), and at timepoint T1 (at the end of a therapeutic protocol of 6 weeks) patients were subjected to a complete diagnostic protocol that included microbiological and clinical evaluations. At timepoint, T2, 12 months after assessment of microbiological eradication, patients were subjected to complete clinical and microbiological evaluations. Due to the observational nature of our study, if patients were asymptomatic and had shown uninterrupted remission throughout the whole 12-month follow-up period, microbiological tests were not performed, to avoid discomfort due to the relatively invasive nature of the procedures (urethral swabs, prostatic massage).

For diagnosis (T0), end-treatment (T1) and follow-up (T2) evaluation of patients, published recommendations and internationally acknowledged guidelines were followed (10). History included a review of past and present symptoms, focusing on previous genitourinary diseases and infections, on genitourinary surgery, and on past and present medications. The severity of chronic prostatitis symptoms was scored by means of an Italian translation of the NIH Chronic Prostatitis Symptom Index (NIH-CPSI) (11). The physical exam included complete abdominal examination, focusing on external genitalia and perineum. Consistency and irregularity of the prostate gland were evaluated by digital rectal examination (DRE). Pelvic and transrectal ultrasound was used for prostatic and bladder diagnostic imaging. Urine

<table>
<thead>
<tr>
<th>Total patients</th>
<th>TU</th>
<th>UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>104</td>
<td>53</td>
<td>51</td>
</tr>
<tr>
<td>Age (average ± SE)</td>
<td>43.43±14.52</td>
<td>43.21±13.86</td>
</tr>
</tbody>
</table>

*Patients infected by traditional uropathogens

*Patients infected by unusual pathogens

*p=0.87 vs. UP group; two-tailed t-test
peak flow rate measurements (Qmax) were performed on all patients. Microbiological tests included (i) pre-VB2 urethral swab analysis and culture, (ii) a modified version of the Meares-Stamey segmented localization test (12), previously described (13), and (iii) post-VB3 semen analysis and culture. For diagnosis of bacterial infection of the prostate, colony counts in EPS/VB3 were required to be at least tenfold greater than those assessed on VB2.

**Pharmacological protocol**

At timepoint T0 patients received an oral once-daily dose of 500 mg ciprofloxacin (14) for a period of six weeks. Combination antibacterial therapy included a macrolide, as described by Tsukamoto et al. (15). A 500 mg once-daily dose of azithromycin was orally administered to patients during the first three consecutive days of each week of treatment with ciprofloxacin, as described by the protocol of Skerk et al. (16). Therapy also included an extended-release formulation of the alpha-adrenoceptor blocker alfuzosin (10 mg), administered once-daily (17), and a total dose of 640 mg of a *Serenoa repens* extract (320 mg b.i.d.), adopted for its anti-inflammatory profile at the level of the prostatic gland (18). This therapeutic regimen was administered for 6 weeks to all patients (timepoints T0-T1).

In agreement with a recently published therapeutic algorithm (19), during the follow-up – starting at timepoint T1 - patients were treated for a period of 6 months with the alpha-blocker, to which the *S. repens* extract was associated. Therefore, at timepoint T2 patients had been completely off-therapy for a period of 6 months.

**Evaluation of responses and clinical follow-up**

The bacteriological response to therapy was based on the results of microbiological analyses performed at timepoints T0, T1 and T2 on EPS, VB3 and total ejaculate specimens. Response was graded as follows:

- **Eradication**, defined as causative organism absent (bacterial load: \(<10^3\) CFU/ml) after completion of therapy (T1 timepoint), up to timepoint T2.
- **Persistence**, defined as causative organism present (bacterial load: \(\geq 10^3\) CFU/ml) after completion of therapy (T1 timepoint).

Due to the nature of the present study, multiple infections and reinfection by a different organism after completion of therapy were considered confounding factors for the outcome of our investigation. Therefore, patients showing evidence of reinfection or multiple infections were not included in the present study. The clinical response to combination therapy was assessed at the completion of treatment (T1) and twelve months thereafter (T2), and was scored on the basis of symptoms reported by patients on the NIH-CPSI questionnaire. The sum of NIH-CPSI points defined total symptom scores as follows:

- **Mild symptoms**: points 0-9;
- **Moderate symptoms**: points 10-18;
- **Severe symptoms**: points 19-31.

A successful response to combination therapy was defined, according to Nickel et al. (4), as “clinical success (cure + improvement)”. This term included the “cure” and “improvement” categories, which - in the context of the present study - were defined as follows:

- **Cure**, defined as absence of symptoms at the T2 timepoint (NIH-CPSI=0);
- **Improvement**, defined as transition from “severe” to “moderate”, “severe” to “mild” or “moderate” to “mild” symptoms at the T2 timepoint, compared to the T0 timepoint, with a decrease of at least 5 points.

**Table 2.**

<table>
<thead>
<tr>
<th>Type of infecting organism</th>
<th>Isolated organism (timepoint T0)</th>
<th>Eradication&lt;sup&gt;1&lt;/sup&gt;</th>
<th>%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional Uropathogens (TU)</td>
<td><em>Enterococcus faecalis</em></td>
<td>19</td>
<td>64.3</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td><em>Escherichia coli</em></td>
<td>13</td>
<td>72.2</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td><em>Proteus mirabilis</em></td>
<td>5</td>
<td>100</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td><em>Pseudomonas aeruginosa</em></td>
<td>2</td>
<td>50</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella pneumoniae</em></td>
<td>1</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Total TU</td>
<td>40</td>
<td>75.5</td>
<td>53</td>
</tr>
<tr>
<td>Unusual Pathogens (UP)</td>
<td><em>Gr. B Streptococcus beta-haemolyticus</em></td>
<td>13</td>
<td>76.5</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td><em>Ureaplasma urealyticum</em></td>
<td>10</td>
<td>83.3</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td><em>Haemophilus parainfluenzae</em></td>
<td>5</td>
<td>62.5</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td><em>Corynebacterium seminale</em></td>
<td>6</td>
<td>100</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td><em>Corynebacterium spp.</em></td>
<td>2</td>
<td>100</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td><em>Streptococcus haemolyticus</em></td>
<td>2</td>
<td>100</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td><em>Citrobacter koseri</em></td>
<td>1</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td><em>Gardnerella vaginalis</em></td>
<td>1</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td><em>Streptococcus alpha-haemolyticus</em></td>
<td>1</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td><em>Morganella morganii</em></td>
<td>1</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Total UP</td>
<td>42</td>
<td>82.3</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>Total all pathogens</td>
<td>82</td>
<td>78.8</td>
<td>104</td>
</tr>
</tbody>
</table>

<sup>1</sup>assessed at timepoint T1 and persisting at timepoint T2 without evidence of relapse or reinfection
A secondary endpoint of the present protocol was the assessment of the safety profile and acceptability of the therapeutic agents administered to patients. To this aim, drug-induced adverse effects were recorded during periodic visits and controls, or were spontaneously reported by patients.

Statistical analysis of clinical parameters showing normal distribution (NIH-CPSI scores; Qmax) was performed using a two-tailed t-test. Differences between the proportions expressing bacteriological and clinical outcomes were analyzed by the $\chi^2$ approximation (Table 3).

**Results**

**Microbiological response**
At timepoint T0, in 53 patients - showing symptoms and microbiological evidence of type II CBP - traditional uropathogens (TU) were isolated in EPS/VB3 and/or total ejaculate (Table 1; Table 2). A second group of 51 patients showed signs and symptoms of chronic prostatitis, associated with positive cultures for 10 different unusual pathogens (UP), localized in the same specimens. In all cases infection by either TU or UP was associated with microscopic signs of inflammation and with congestion of the prostate gland.

All patients were evaluated for microbiological and clinical responses to therapy. A total of 104 pathogens were isolated at T0, of which 82 were eradicated at timepoint T1. Table 2 lists the traditional uropathogens and unusual pathogens isolated, and the microbiological response for each microorganism. In the TU group, which showed a total eradication rate of 75.5%, the most common isolates were *Enterococcus faecalis* and *Escherichia coli*. *Pseudomonas aeruginosa* was eradicated in 2 out of 4 TU-patients. A higher total eradication rate (82.3%) was shown by the UP group, which included Group B *Streptococcus beta-haemolyticus* and *U. urealyticum* as the most representative species (Table 2). Three different coryneforms were detected in total 9 patients. *H. parainfluenzae* was the most difficult-to-eradicate UP (eradication rate: 62.5%).

**Clinical response**
Combination pharmacological therapy was characterized by a high safety profile. A total of 104 patients completed with good compliance a 6-week cycle of therapy without signs of toxicity, with the exception of three uncomplicated, transient episodes of diarrhea, which were resolved by reconstitution of the enteric flora with standard probiotics. The graphs shown in Figure 1 show the peak flow rates and NIH-CPSI scores of patients infected with traditional uropathogens (filled bars) or unusual pathogens (hollow bars) at enrolment, at completion of a 6-week cycle of therapy (T1), and at the end of a follow-up period of 12 months (T2). The T2 timepoint was adopted to evaluate the clinical outcome of the present protocol because the effects of the supportive therapy with the alpha-blocker and *S. repens* extract, that was extended for a period of 6 months starting from timepoint T1, could have been confounding factors in the scoring of Qmax and of voiding, pain and life quality symptoms. At timepoint T2, patients had been off-therapy for a period of 6 months, which in our opinion represented a suitable time for an objective, unbiased evaluation of the symptom scenario and sequelae of chronic bacterial prostatitis.

For all tested parameters and at all timepoints, intergroup differences were not significantly different, with the exception of the scores relative to the impact of the disease on patients’ quality of life. This was found to be significantly higher at T2 (p<0.001) in patients infected with TU, when compared to patients belonging to the UP group (Figure 1). Concerning the scores relative to pain, voiding symptoms and life quality impact, intragroup differences between timepoints T0 and T1, or T0 and T2 were in all cases statistically significant (Figure 1). Table 3 summarizes the microbiological eradication and clinical success rates in both TU and UP groups, at the end of a follow-up period of 12 months (T).
**DISCUSSION**

In the present study we performed a comparative analysis of the microbiological and clinical response patterns in symptomatic patients showing evidence of localized infection by traditional uropathogens or by unusual pathogens at the level of the prostate gland, in order to investigate the role of non-traditional organisms in the etiology of the chronic prostatitis syndrome. Results show (i) a marked intergroup similarity between sign/symptom values and trends measured in patients infected either with traditional uropathogens or with unusual pathogens (Figure 1), and (ii) a close intragroup similarity between eradication and clinical success rates (Table 3).

A major outcome of the present study is the marked, long-term improvement of CP symptoms in patients subjected to combination therapy after showing evidence of prostatic colonization by unusual pathogens. Interestingly, the peak flow rates measured in both TU and UP groups at the end of a 6-week course combination therapy (T1) were not significantly different from Qmax values assessed at timepoint T0. Conversely, significant increases of Qmax were measured at timepoint T2, at the end of a 12-month post-eradication follow-up period, (p<0.005 vs. T0; Figure 1), and six months after suspension of the alpha-blocker. It therefore seems that the voiding improvement is not exclusively due to the effect of the alpha-blocker. It has been hypothesized that long-term treatment with alpha-blockers may maintain the alpha-blockade effect even though the drug has been discontinued (20). Due to the observational nature of our study, a group of patients treated with the sole alpha-blocker was not available. However, in a previously published study we have included patients showing single or multiple infections by unusual pathogens (13).

This study was characterized by a 30-month follow-up period. Also in this case the positive effect of combination therapy was extended through the entire follow-up period in patients showing infections by UP (data not shown), thus indicating that a clinical benefit may be due not only to the to the short-term effect of combined alpha-blocker and *S. repens* agents, but also to the long-term elimination of infecting UPs by quinolone and macrolide antibacterial agents.

Recently, Skerk et al. have investigated the role of unusual pathogens in 1442 patients showing symptoms of chronic prostatitis (5). Infectious microorganisms were isolated by means of the Meres-Stamey test in 1070 (74.2%) patients, of which 52% showed evidence of prostatic inflammation. The most frequent isolates were *Chlamydia trachomatis* (N=536), *Trichomonas vaginalis* (N=151) and *Ureaplasma urealyticum* (N=72). 15.2% of patients were infected by traditional uropathogens. By discussing the strikingly high proportion of symptomatic patients showing evidence of prostatic infection by either traditional or unusual pathogens, the authors provocatively propose the revision of the current classification of prostatitis syndromes, and in particular of type III CP/CPPS. Interestingly, the Skerk study shows that infection by specific UP (e.g. *U. urealyticum*) is not necessarily associated with evidences of inflammation of the prostatic gland. On one hand, such a finding may simply demonstrate the presence at the prostatic level of a “normal” bacterial flora similar to what colonizes the posterior urethra, as outlined by Nickel in a comment on a work of Krieger et al. focusing on uncommon organisms in prostatitis (7). However, in a previous study our research group has confirmed that microbiological and microscopic findings do not always correlate in symptomatic chronic bacterial prostatitis (21). For this reason, white blood cell counts are cautiously adopted in our practice as inflammatory markers. In the present study, all patients displayed prostatic anomalies detected by DRE and prostatic sonography. Thus, a congested, oedematous gland, with microscopic evidence suggestive of a persistent inflammatory condition, was in our study associated with the presence of infecting microorganisms of both TU and UP groups, and with symptoms of chronic prostatitis.

In the Skerk study (5), all patients showing an infective etiology of the prostatitis syndrome were also symptomatic. It would have been interesting to assess whether eradication of UP in these patients would have been be paralleled by attenuation/remission of CP symptoms. Such an evidence was recently anticipated by a report by Nickel et al., demonstrating a statistically significant correlation between clinical improvement and eradication of non-traditional Gram-positive uropathogens (*Coagulase-negative Staphylococcus* spp.; *Streptococcus* spp.), in a group of 261 patients treated with various quinolones for a period of 4 weeks (6). By discussing these data, the authors suggest the implication of non-traditional uropathogens in the etiology of chronic bacterial prostatitis, and advise that patients with CBP associated with non-traditional uropathogens should be subjected to treatment with first-line antibiotics like fluoroquinolones. Our data are in agreement with these findings, confirm a possible pathogenic role of Gram-positive species like *Streptococci*, and - according to previous data by the Giesen and Yerevan groups - (22, 23), strengthen the hypothesis that a number of unusual pathogens - including *U. urealyticum* and *Haemophilus* spp. - may be implicated in the etiology of chronic bacterial prostatitis. In our study, 9 out of 51 patients showed the presence of high loads (>10^4) of coryneforms localized to the prostate.

**Table 3.**

<table>
<thead>
<tr>
<th></th>
<th>Traditional Uropathogens</th>
<th>Unusual Pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eradication (%) 1</td>
<td>75.5</td>
<td>82.3</td>
</tr>
<tr>
<td>Clinical success (%)</td>
<td>78.8</td>
<td>85.7</td>
</tr>
</tbody>
</table>

χ^2=0.011; P=0.916

*Calculated at timepoint T2*
gland (Table 2). The role of coryneforms in chronic prostatitis is debated: although it is accepted that low counts of these microorganisms may be constitutive of normal urethral microflora (24), an increasing body of evidence implicates coryneforms in the chronic prostatitis syndrome (8). In a study performed on 109 patients, Türk et al. have recently shown that patients with severe leukocytospermia harbored significantly more Corynebacterium group G and Arthrobacter sp. in prostate-specific specimens in comparison with controls, and that high loads (>10^4 CFU/ml) of coryneforms, including C. seminale, are associated with symptomatic, inflammatory chronic prostatitis (24). Further research will focus on the etiological role of coryneforms and Haemophilus spp. in CBP.

In conclusion, our data show that eradication of unusual pathogens localized at the prostatic level is associated with rapid relief of clinical signs and symptoms of the chronic prostatitis syndrome, and with a marked, significant improvement of patients’ life quality. Our results and our clinical experience are in agreement with an increasing number of authors suggesting that antibacterial treatment may be indicated for symptomatic patients showing evidence of infection by unusual pathogens at the prostatic level. Moreover, a marked, significant decrease of the impact of the disease on the quality of life of UP-infected patients, compared to TU-infected patients, justifies treatment of the former with a combination of antibiotics, alpha-blockers and anti-inflammatory agents.

Acknowledgements
We are thankful to Marta Conti for assistance in data analysis, and to paramedics Monica Bertocchi, Teresa Rossioni, Giusi Meli, and Maria Soledad Valle Mena for skilful clinical assistance.

References

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Il ruolo della SIEUN

La SIEUN (Società Italiana di Ecografia Urologica Nefrologica e Andrologica) riunisce diversi medici specialisti e non che si occupano di tutte quelle metodiche in cui gli ultrasuoni vengono utilizzati a scopo diagnostico in ambito nefro-uro-andrologico.

La SIEUN organizza un Congresso Nazionale con periodicità biennale e diverse altre iniziative negli anni in cui non si tiene il Congresso.

Dal 2001 la SIEUN è affiliata all’ESUI (European Society of Urological Imaging) pertanto tutti i soci possono partecipare alle iniziative della Società Europea.

L’Archivio Italiano di Urologia e Andrologia è l’organo ufficiale della SIEUN. Questa pagina permette un’informazione puntuale sulle attività della nostra Società e consente al Consiglio Direttivo della SIEUN di comunicare ai soci ogni nuova iniziativa.

Notizie dalla SIEUN

Milano Check Up – Milano, 6-9 giugno 2007

Si è appena conclusa a Milano la prima edizione di Milano CheckUp, mostra della salute e sanità di Fiera Milano alla quale la SIEUN ha partecipato con uno spazio espositivo. Alla manifestazione hanno partecipato anche altre società scientifiche quali la SIUD e la SIUrO. Sono state circa 8.000 le presenze di operatori (specialisti e personale sanitario, ricercatori e gestori del sistema sanitario) in quattro giorni di lavori, contrassegnati da un intenso programma di congressi e workshop di aggiornamento e formazione.

Gli addetti ai lavori hanno apprezzato molto questo programma che ha reso questa manifestazione un grande forum della ricerca biomedicale e delle più avanzate tecniche di diagnosi e terapia, ma anche un ambito privilegiato di dibattito della politica sanitaria.

Sblocco sponsorizzazioni

La Giunta di Farmindustria ha detto il primo sì alla revoca del blocco delle sponsorizzazioni delle aziende farmaceutiche a congressi e convegni per la formazione continua in medicina e operatori sanitari e ha stabilito delle “nuove regole di auto-regolamentazione” ancora più restrittive delle precedenti. Infatti, le nuove norme limiteranno le sponsorizzazioni agli eventi con i più elevati standard di qualità.

16° Congresso Nazionale SIEUN

A seguito dello sblocco delle sponsorizzazioni da parte di Farmindustria, il Comitato Direttivo della SIEUN si riunirà a breve per decidere le nuove date e il luogo del Congresso Nazionale della SIEUN, che doveva tenersi a Stresa dal 17 al 19 maggio u.s. ma è stato posticipato a causa del blocco delle sponsorizzazioni, che verranno comunicati tempestivamente a tutti gli interessati e anche tramite i prossimi numeri dell’Archivio Italiano di Urologia Andrologia.

PUNTI SIEUN

(una possibilità di incontro tra Soci SIEUN e di contatto con altri specialisti)

Presso i punti SIEUN i nostri soci potranno essere continuamente informati su tutte le attività e le iniziative della Società e rinnovare il pagamento della quota associativa.

PROSSIMI APPUNTAMENTI SIEUN (da non mancare!)

80° Congresso Nazionale SIU (Bari, 27 settembre – 1 ottobre 2007)
Corso SIEUN-SIU dal titolo “Studio ecografico della statica pelvica femminile” (giovvedì 27 settembre dalle 14.00 alle 16.00),

RINNOVO PAGAMENTO QUOTA 2007

I soci sono invitati a versare la quota 2007 al più tardi entro il 30 giugno p.v.