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Chronic bacterial prostatitis. Clinical and microbiological study of 332 cases☆

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ABSTRACT

Background and objective: Chronic bacterial prostatitis (CBP) is characterized by long-lasting symptoms, frequently associated with psychosomatic disorders. The objective of the study was to study PCB in our environment clinically and microbiologically.
Methods: Between January 2013 and December 2014 761 patients with suspected CBP were studied. Of these patients 332 (43.6%) underwent a complete microbiological study and the major clinical signs and symptoms were collected.
Results: Eighteen point four percent of patients were diagnosed microbiologically with CBP, *Enterococcus faecalis* being the main aetiologic agent (37.7%), followed by *Escherichia coli* (22.2%). Ninety-six point seven percent of the CBP had positive semen cultures, while only 22.9% had positive urine post-semen cultures. Data of sensitivity, specificity, positive predictive value and negative predictive value of semen were 96.7%, 95.9%, 84.3% and 99.3%, respectively and urine post-semen 22.9%, 99.3%, 87.5% and 85.1%, respectively. Testicular perineum pain (44.3%), ejaculatory discomfort (27.9%) and haemospermia (26.2%) were highlighted as the patients' main clinical manifestations.
Conclusions: Fractionated culture for the microbiological diagnosis of CBP could be simplified by the culture of urine pre-semen and semen, without the need for the culture of urine post-semen. The main aetiologic agent of CBP in our media was *E. faecalis*, followed by *E. coli*.

Prostatitis crónica bacteriana. Estudio clínico y microbiológico de 332 casos

Palabras clave:
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RESUMEN

Fundamento y objetivos: La prostatitis crónica bacteriana (PCB) se caracteriza por una clínica de larga duración, frecuentemente asociada a trastornos psicosomáticos. El objetivo del estudio fue estudiar clínica y microbiológicamente la PCB en nuestro medio.
Métodos: Entre enero de 2013 y diciembre de 2014 se estudiaron 761 pacientes con sospecha de PCB. De ellos, 332 (43,6%) fueron sometidos a un estudio microbiológico completo y se recogieron los principales signos y síntomas clínicos.
Resultados: Un 18,4% de los pacientes fueron diagnosticados microbiológicamente de PCB, siendo *Enterococcus faecalis* el principal agente etiológico (37,7%), seguido de *Escherichia coli* (22,2%). El 96,7% de las PCB presentaron cultivos de semen positivos, mientras que tan solo un 22,95% tuvieron cultivos de orina postsemen positivos. Los datos de sensibilidad, especificidad, valor predictivo positivo y valor predictivo negativo del cultivo de semen fueron 96,7; 95,9; 84,3 y 99,3% respectivamente; y del cultivo de la orina postsemen 22,9; 99,3; 87,5 y 85,1% respectivamente. Destacaron el dolor perineotesticular (44,3%) de los pacientes, molestias eyaculatorias (27,9%) y la hemospermia (26,2%) como principales manifestaciones clínicas de los pacientes con estudio microbiológico significativo.

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Conclusiones: El cultivo fraccionado para el diagnóstico microbiológico de PCB podría simplificarse mediante el cultivo de la orina presemen y del semen, sin necesidad del cultivo de la orina postsemen. El principal agente etiológico de PCB en nuestro medio fue *Enterococcus faecalis*, seguido de *Escherichia coli*.

Introduction

Chronic bacterial prostatitis (CBP) is the most common urological disease in men under 50 years of age and the third most frequent after benign prostatic hyperplasia and prostate cancer in men over 50 years of age.[1] It is responsible for 5–10% of non-acute prostatic syndromes.[2,3] It is characterized by its long duration, clinical course with frequent recurrences and high morbidity. Psychosomatic disorders are often associated with it as a result of the persistence of symptoms, along with nonspecific clinical manifestations, with significant alteration of the quality of life. Along with antibiotic and anti-inflammatory treatment,[4] psychotherapy has also been offered to help these patients, which also supports the clinical significance of this process.

Most authors agree that the most common causative agent is *Escherichia coli* (*E. coli*), accounting for 65–80% of these diseases.[2,5] Other gram-negative bacilli involved are *Pseudomonas aeruginosa*, *Serratia* spp., *Klebsiella* spp. and *Enterobacter* spp. Except *Enterococcus* spp., which is considered a potential etiologic agent, the pathogenic role of the other gram-positive cocci described is uncertain. There is generally much controversy over the participation of *Chlamydia trachomatis* (*C. trachomatis*), *Ureaplasma* spp., *Mycoplasma* spp. and *Corynebacterium* spp. The role of anaerobic bacteria is still unknown.[5] Establishing the microbiological cause of CBP is a complex and difficult process, still, the gold standard continues to be the Meares and Stamey test.[5–9] The value of sperm culture in the diagnosis of this disease is difficult to establish because its sensitivity varies widely in the literature.[7] Because there are few published studies on the etiology of CBPs in the Spanish population,[10,11] we propose in this paper a clinical-microbiological study in our healthcare environment on the population with suspected CBP.

Materials and methods

761 patients who presented with pain at the level of the pelvic region for at least 3 months, with or without sexual or urinary manifestations, compatible with CBP, were studied in the Urology Services of the University Hospital of Granada (Hospital Virgen de las Nieves) between January 2013 and December 2014.[12] This hospital is a reference center in Andalusia, serving a population of 440,000 inhabitants. A complete microbiological study was conducted in 332 (43.6%) patients by means of fractionated sample cultures. This consisted of a modification of fractionated culture of Meares and Stamey,[10] which included the collection and processing, sequentially, of samples of clean catch urine, semen and post-semen urine, under strict aseptic conditions. The clean catch urine sample was processed by the previously described procedure.[6] The post-semen urine sample was inoculated in the same chromogenic medium and a Columbia blood agar was added (Becton Dickinson, USA) incubated in CO_2. In the case of semen samples, the inoculation in Martin-Lewis agar (Becton Dickinson, USA) medium was added to the previous procedure) incubated in CO_2 to recover *Neisseria gonorrhoeae*. The cultures were quantified using 10 μl calibrated loop samples and 48 h incubation at 37 °C. The genital mycoplasmas study was performed by inoculation in the Mycoplasma IST 2 equipment (bioMérieux, Marcy l'Etoile, France), which allows the identification, counting and determination of sensitivity to different antibiotics, and in the A7 Mycoplasma agar (bioMérieux, Marcy-l'Etolie, France).

The fractionated culture was considered indicative of CBP, as gold standard, in any of the following situations: (1) presence of one or more microorganisms only in semen or post-semen urine with a count >1000 CFU/ml; or (2) presence of a bacterial microorganism count, in semen or post-semen urine, at least 10 times higher than in clean catch urine. The presence of urinary pathogens with significant count (>10^5 CFU/ml) in the pre-ejaculatory urine culture was considered indicative of urinary tract infection, and ruled out the presence of CBP. In the case of gram-positive microorganisms, it was necessary to obtain more than one positive fractionated culture by the same microorganism, defined by antibiotype (MicroScan, Barcelona, Beckman Coulter, MicroScan, Beckman Coulter, Brea, California, United States), to consider their involvement in CBP. Genital mycoplasmas were assessed with a count >10^4 CFU/ml and absence of any other possible pathogen of rapid growth.[10] Finally, the main urological signs and symptoms of patients with suspected CBP were also collected. The presence of *C. trachomatis* was not studied as there were no epidemiological and clinical data to justify it.

Statistical analysis

Data were analyzed with the SPSS statistical software package by MS Windows, version 17.0 (Chicago, IL, USA). Quantitative variables are described as the distribution frequency of each of the categories. Sensitivity, specificity, positive predictive value and negative predictive value were calculated separately for semen and post-semen urine analysis, with a confidence interval of 95%.

Ethical considerations

The study protocol was carried out in accordance with the Declaration of Helsinki and the "Comisión de Ética e Investigación Sanitaria de los Centros Hospitalarios y Distritos de Atención Sanitaria" (Ethics and Health Research Committee of Hospital Centers and Helthcare Districts). This was a non-interventional study, with no additional research to routine procedures. The biological material was used only for the standard diagnosis of urinary tract infections, following the prescriptions of doctors. No additional sampling or routine protocol modification was made. Data analyses were done using an anonymous database. Therefore, approval was considered unnecessary according to our country's regulations. The entity which granted permission to access and use the data was the "Clinical Management Unit of Infectious Diseases and Clinical Microbiology, University Hospital of Granada, Spain."

Results

Of the 332 patients studied with clinical suspicion of CBPs, 271 (81.6%) did not meet the microbiological criteria for CBP. The remaining 61 patients (18.4%) with a mean age of 48 years and a range of 23–66 years, showed a positive microbiological study of fractionated samples. The isolation in monomicrobial culture of *Enterococcus faecalis* (*E. faecalis*) (Table 1) in 23 patients (37.7%) is worth mentioning, followed by *E. coli*, in 16 (22.2%). *Enterobacter* spp., *Klebsiella* spp., *Streptococcus agalactiae* and *Ureaplasma urealyticum* were isolated in 3 cases each (4.9%), *Morganella morganii*

Table 1
Etiologic agents isolated in patients with chronic bacterial prostatitis.

Microorganisms	Isolations (%)
Monomicrobial cultures	56 (91.8)
Gram-negative	27 (44.3)
E. coli	16 (22.2)
Enterobacter spp.	3 (4.9)
Klebsiella spp.	3 (4.9)
Citrobacter spp.	2 (3.3)
M. morganii	2 (3.3)
Proteus mirabilis	1 (1.6)
Gram-positive	26 (42.6)
E. faecalis	23 (37.7)
Streptococcus agalactiae	3 (4.9)
Ureaplasma urealyticum	3 (4.9)
Polymicrobial cultures	5 (8.2)
E. coli + *E. faecalis*	4 (6.55)
M. morganii + *E. faecalis*	1 (1.65)

Table 2
Distribution of fractionated cultures.

Cultures of	CBP (+)	CBP (−)	Total
Semen (+)	59	11	70
Semen (−)	2	260	262
Post-semen urine (+)	14	2	16
Post-semen urine (−)	47	269	316
Total	61	271	332

CBP: chronic bacterial prostatitis.

and *Citrobacter* spp. in 2 (3.3%) and *Proteus mirabilis* in one (1.65%) case. Of the 5 (8.2%) polymicrobial cultures, *E. coli* and *E. faecalis* were isolated in 4 cases (6.5%), and *Morganella morgannii* and *E. faecalis* in one (1.6%).

Of the 61 patients with positive fractionated samples microbiological study, the semen cultures were positive in 59 of them (96.7%) (in 47 cases it was positive only in the case of semen and 12 also in post-semen urine). The post-semen urine culture was positive in 2 patients (3.3%), semen being nonsignificant, so, in total, 14 cases were confirmed for CBP (22.9%) with post-semen urine (Table 2). Sensitivity, specificity, positive predictive value and negative predictive value for semen were 96.7% (91–100%); 95.9% (93–98%); 84.3% (75–93%) and 99.3% (98–100%), respectively; post-semen and urine were 22.9% (11–34%); 99.3% (98–100%); 87.5% (68–100%) and 85.1% (81–89%), respectively (Table 2).

Analysing the symptoms shown (Table 3), the patients mostly showed concomitant symptoms. Notably perineum/testicular pain (44.3%), ejaculatory discomfort (27.9%) and hematospermia (26.2%). Non-specific symptoms, such as urinary discomfort, appeared in around 15% of patients. Finally, sterility was present in 3 (3.4%) patients.

Discussion

The limitations for the diagnosis and classification of CBPs led the USA's *National Institute of Health* to organize a consensus meeting on prostatitis in December 1995; the result of this meeting was the creation of a specific system of classification of prostate syndromes in 4 categories: acute bacterial prostatitis (I), CBP (II), Chronic pelvic pain syndrome (III), this one subdividing into inflammatory (IIIA) and noninflammatory (IIIB), and asymptomatic inflammatory prostatitis (IV).[12]

Table 3
Signs and symptoms of patients with chronic bacterial prostatitis.

Symptoms	Frequency (%)
Perineum/testicular pain	44.26
Discomfort in ejaculation	27.87
Hematospermia	26.23
Micturition discomfort	22.95
Hypogastric pain	9.84
Suprapubic pain	4.92
Penile pain	4.92
Sterility	4.92

Since the clinical presentation of category II is usually indistinguishable from category III (in fact, in the consensus, category III is clinically defined as the presence of discomfort or pain in the pelvic region for at least 3 months with associated micturition syndrome and/or sexual dysfunction without evidence of infection) it is important to study this subject more deeply for a better management of patients. In our series, clinical criteria were not sufficient to define the disease, since the microbiological study for CBP was not significant in 81.6% of our patients. This fact could have indicated the presence of a different syndrome, such as prostatic hyperplasia, prostate cancer or a one of the previously mentioned syndromes. It is therefore essential to carry out a complete microbiological study to allow the application of strict inclusion criteria, such as Meares and Stamey, in order to confirm the clinical diagnosis of CBP, as they can determine the origin of the infection process by assessing the fractionated culture.[5,7,10] Thus, the isolated presence of a uropathogenic agent in a sample of semen or prostatic fluid will not be enough to confirm a case of CBP, but requires a joint and quantified analysis of urine samples pre- and post-semen/prostate massage to avoid bias caused by urogenital microbiota or cases of true urinary tract infection. Some authors have compared the fractionated culture versus semen culture as the only sample in the diagnosis of CBP, but the results show that the fractionated culture yield is much higher than semen, especially due to the low specificity of this if not compared with the pre-semen urine. Therefore, the isolated semen/prostatic fluid culture is insufficient to confirm the CBP.[8] Also, studies have been conducted comparing the cost-effectiveness rate of Meares and Stamey fractionated culture against a simplified fractionated culture based on pre and post-semen urine culture, getting good correlations in the results,[9] even recommending the simplified fractionated culture.[13] Other authors consider that only pre-semen and semen urine samples are necessary.[10] Furthermore, studies that compare the sensitivity of semen against prostatic fluid within the whole fractionated culture have reported that the first one presents greater sensitivity, especially in terms of recovery of gram-positive microorganisms.[10] This could be relevant given the complexity of obtaining the prostatic fluid, which would certainly be the best sample if it wasn't for this complexity.

In our study, comparing the sensitivity data obtained, the semen sample seems more appropriate than post-semen urine as more than 95% of the CBP in our series were diagnosed with this (59 of the 61 cases of CBP were confirmed by semen, while only 14 of 61 with post-semen urine), meaning that the microbiological diagnosis of CBP could be simplified by just doing pre-semen urine and semen cultures, making post-semen urine culture unnecessary. Finally, we must not forget how awkward the taking of this sample can be for the patient. Despite the above, in our specialized hospital care population, the diagnostic yield of sperm and urine culture was very low (about 20%) and culture interpretation was often complex, requiring significant laboratory time and effort to avoid misinterpretations. The poor performance may be due to the large number of tests requested to the microbiology laboratory before any clinical suspicion and before implementing other specific treatments.

Traditionally it has been said that *E. coli* is the main pathogen involved in CBP, responsible for up to 70–80% of these.[2,10] There are studies in which the incidence of this pathogen in CBP is not so prevalent,[14] and some studies point to gram-positive microorganisms such as *E. faecalis*[15] or *Staphylococcus* spp.[16] as the main etiologic agents. In our area, the incidence of gram-negative

microorganisms CBP is only slightly higher than that of gram-positive, however, the isolation of *E. faecalis* affected almost 40% of cases, followed by *E. coli* (22.2%) as the main gram-negative bacillus isolated. In this connection we have described the significant presence of *E. faecalis* as uropathogenic agent[17] and, since our work is subject to significant performance controls in the collection and processing of samples, these should be considered, in principle, as potential etiologic agents of urinary tract infections. The continued presence of these agents is a major risk factor for CBP. In addition, the empirical over-use of ciprofloxacin in these patients may have determined a greater presence of this bacteria, which is less sensitive to this drug. Finally, its ability to produce biofilm has been described as a virulence factor for CBP,[18] similarly to *E. coli*. Other authors, however, have highlighted the prevalence of *Ureaplasma* spp., *Mycoplasma* spp. and *C. trachomatis* as primarily responsible for CBP,[19] despite their dubious and controversial pathogenic role in this location. However, because the pathogenic role of gram-positive cocci is unclear, these microorganisms were evaluated in our series only when there was a repeated positive fractionated culture for the same microorganism. Therefore, there is great heterogeneity regarding the etiology of this disease, although there seems to be a tendency to highlight the pathogenic role of gram-negative microorganisms and *E. faecalis*.

Finally, we have attached great importance to PMN count in urine and semen as it provides information about the inflammation/infection site, being its study complementary to the culture result. It was not used as a screening test in our work because the variability of its presence in the clinical sample has been demonstrated, motivated by the conditions in the collection of the same or the underlying disease of the patient. A comparison of clinical signs and symptoms between patients with positive cultures (Table 3) and patients with negative cultures has not been carried out, something which could be considered a study limitation.

This study has shown that the microbiological analysis of the CBP could be simplified by conducting the pre-semen urine and semen culture in the same procedure, obtaining excellent results compared to a fractionated microbiological study; and that, in our environment, there is a significant incidence of *E. faecalis*, followed by *E. coli*.

Conflict of interests

The authors declare no conflict of interest.

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