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# Chronic Bacterial Prostatitis: Theoretical and Experimental Considerations

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**Summary.** The results of the treatment of chronic bacterial prostatitis are disappointing. The current status of antimicrobial and immunological research is described. While both a local and systemic antibody response is demonstrated in acute bacterial prostatis, only a local antibody production is found in chronic bacterial prostatitis. This response as reflected in the expressed prostatic secretion is specific for the infecting organism and immunoglobulin A is the major antibody class involved. Drug penetration into the prostate has mainly been studied in dogs and the ideal drug appears to be a lipid-soluble base which will concentrate in the slightly acidic prostatic secretion because of ion-trapping. However, these results are not directly applicable to humans because of the slight alkalinity of human prostatic secretion, the localization of the chronic inflammatory process in the interstitium, and the evidence of an active secretory mechanism for trimethoprim. The clinical consequences of these findings are discussed in relation to several recent studies and the treatment with lipid-soluble bases with a low plasma protein binding over extended periods is recommended.

**Key words:** Chronic bacterial prostatitis, Immunology, Drug therapy.

## Introduction

Chronic bacterial prostatitis occasionally causes recurring urinary tract infections in males and although great efforts have been invested in postatitis treatment, results have been rather disappointing. The cure rates have varied from 32% to 71% in the most promising series employing trimethoprim-sulfamethoxazole, possibly because of poor drug penetration into the prostate [1]. In order to account for these poor results of treatment, studies have been performed to elucidate the immunological mechanisms combating bacterial colonization of the prostate and to describe the principles responsible for drug penetration into the various prostatic compartments. While the immunological research has been performed mainly in humans, most of the experimental drug studies have been conducted in dogs because no human experimental model has yet been available. The results should therefore be interpreted with caution, mainly because of differences in the pH of prostatic secretion of humans and dogs [2]. In the following we will briefly review the current theories concerning immunology in bacterial prostatitis and drug penetration into the prostate gland.

## *Immunological Considerations*

As in infections of other organ systems, both local and systemic immunological responses may be elicited in genitourinary infections. Using an immunofluorescent test for antibody-coated bacteria in urine, Thomas et al. [3] and Jones et al. [4] found positive results in patients with pyelonephritis. In several patients, however, no corresponding circulating antibody response was demonstrated, suggesting a local antibody production in the kidneys.

Only a few immunological studies have been carried out in patients with bacterial prostatitis, some determining the total amount of immunoglobulin in prostatic secretion [5, 6] and others measuring serum agglutination titres [7, 8]. Recently, Shortliffe et al. demonstrated both a local prostatic and systemic antigen-specific antibody response [9, 10].

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In 1971 Ablin et al. [11] demonstrated the existence of production sites of immunoglobulin G and A in the prostate, and later Jones demonstrated immunoglobulin specific for the infecting *E. coli* in the expressed prostatic secretion (EPS) from two patients with bacterial prostatitis [12]. Gray et al. found significant elevations of total immunoglobulin G, A and M in the prostatic secretion of patients with chronic bacterial prostatitis, but did not identify the relevant antigens [5]. The drawback in determining total immunoglobulin is that the levels are variable from day to day in secretory fluids [9], making interpretation difficult. Some authors have studied ejaculates from patients with prostatitis and found increased levels especially of immunoglobulin A [13, 14]. The significance of these findings is unclear, however, because the ejaculate represents a mixture of fluids from several locations and because increased immunoglobulin A levels also have been proven in benign prostatic hyperplasia and prostatic adenocarcinoma [15]. Using a bacterial agglutination test reflecting mainly the activity of serum immunoglobulin M, Meares reported that patients with chronic bacterial prostatitis generally had increased serum antibody titres, while patients with *E. coli* urethritis did not elicit any systemic antibody response [7]. The same author later demonstrated a decrease in antibody titres to normal levels in patients with bacterial prostatitis following relevant antibiotic therapy [8].

Although these studies indicate both local and systemic immunological responses to prostatic infection, these responses were not described thoroughly until the publications by Shortliffe et al. [9, 10]. Because of the small amounts of prostatic secretion generally obtained and the low concentrations of antigen-specific antibodies (A-SA), these authors selected a highly sensitive solid-phase radioimmunoassay (SPRIA) and formalin-fixed whole bacterial antigens. In one patient with acute bacterial prostatitis caused by *E. coli* the levels of immunoglobulin G A-SA in both EPS and serum were equally elevated, suggesting transudation of immunoglobulin into the infected prostate gland. The duration of the response was 4–5 months. Total immunoglobulin levels in the same fluids were relatively constant and higher in serum than in EPS. The elevation of immunoglobulin A A-SA was much more pronounced in EPS than in serum, demonstrating a local immune response independent of the systemic response. In contrast, another patient with chronic bacterial prostatitis developed neither an immunoglobulin G A-SA nor an immunoglobulin A A-SA response in serum, but only in EPS, indicating local prostatic production of both immunoglobulin G and A. It was also shown that this local A-SA response is specific for the infecting organism and that immunoglobulin A is the major antibody-class involved in the local response to prostatic infection. Measurements of total serum or EPS immunoglobulin and serum A-SA consequently do not reflect the prostatic immune response as well as do A-SA of EPS, which now can be expressed more conveniently in weight/volume units instead of dilutional titres [16]. Employing the same SPRIA technique, Fowler and Mariano [17] confirmed that the local prostatic immunoglobulin A A-SA production is independent of the systemic immune response.

### *Drug Therapy*

*Theoretical Considerations.* Drug penetration into the prostate gland is governed by the same principles that determine drug passage across biological, lipid-containing membranes in general. The original studies in dogs carried out by Stamey et al. [18, 19] especially stressed the role of non-ionic diffusion of drugs across membranes with different pH values. The ideal physico-chemical properties for a drug to appear in the prostatic secretion (PS) were also described. The process of drug penetration is supposed to be passive and consists of diffusion and concentration. Basically, the antimicrobial drug should be a lipophilic and uncharged substance because biological membranes do not allow the passage of lipophobic or charged substances; that is, the drug should have a high lipid/water partition coefficient and not be ionized at plasma pH 7.4. The degree of protein-binding is also important in determining the fraction of drug available for diffusion. Furthermore, the size and shape of the molecule might be significant because small water-soluble molecules can cross biological membranes as part of the free water diffusion. Most antimicrobials are weak bases or weak acids; consequently, differences in the hydrogen ion concentration in plasma and PS are crucial in introducing the phenomenon of ion-trapping. This implies that when equilibrium has occurred the greatest drug concentration (sum of charged and uncharged fractions) is on the side of the membrane which has the greatest degree of ionization. In dogs with prostatic secretion pH of 6.4, weak acids (low pKa) will concentrate on the plasma side and weak bases (high pKa) in the PS, the degree of ion-trapping being dependent on the pKa of the antimicrobial. In the dog model the concentration of a base in PS might exceed the corresponding plasma concentration: the higher the pKa, the higher the concentration of the drug. Contrarily, the concentration in PS for an antimicrobial acid will only approach the plasma concentration, the PS concentration increasing with increasing pKa. Among antimicrobials fulfilling these requirements are trimethoprim (lipid-soluble base of pKa 7.3) and the basic macrolides (lipid-soluble bases with pKa 8.5 [oleandomycin] and 8.8 [erythromycin]), in contrast to the penicillins, sulfonamides and tetracyclines. Regarding the relevance of measuring drug concentration in PS, the site of infection in chronic bacterial prostatitis must be considered. As shown by Blacklock [20], the inflammation is focal and mostly localized to the peripheral zone of the prostate, while in experimental chronic prostatitis in dogs we found the inflammatory changes mainly in the interstitial tissue and not in the acini as in acute prostatitis [21]. Consequently, a comparison of plasma concentrations to both PS and prostatic interstitial fluid (PIF) concentrations might be of interest in evaluating the therapeutic possibilities of a given antimicrobial substance.

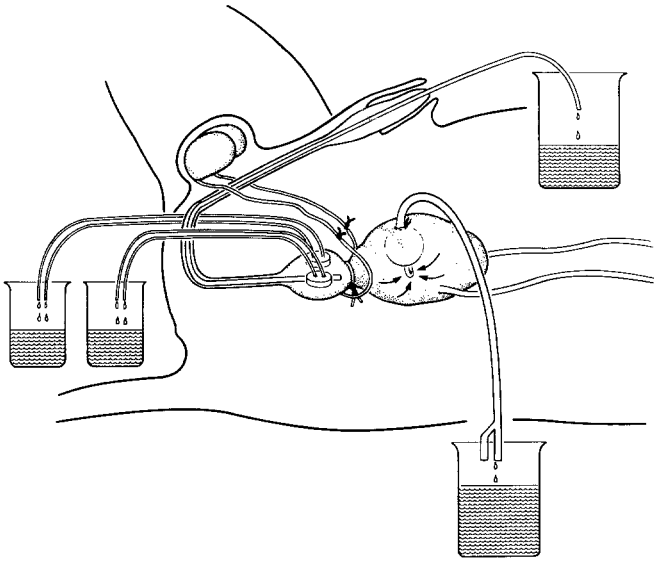

Fig. 1. Schematic drawing of the dog model during drug study

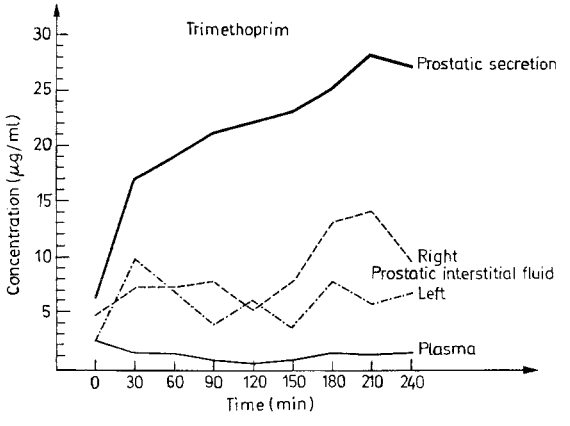


Fig. 2. Trimethoprim concentrations in dog plasma, prostatic interstitial fluid and secretion during drug study (from Baumueller and Madsen 1982)

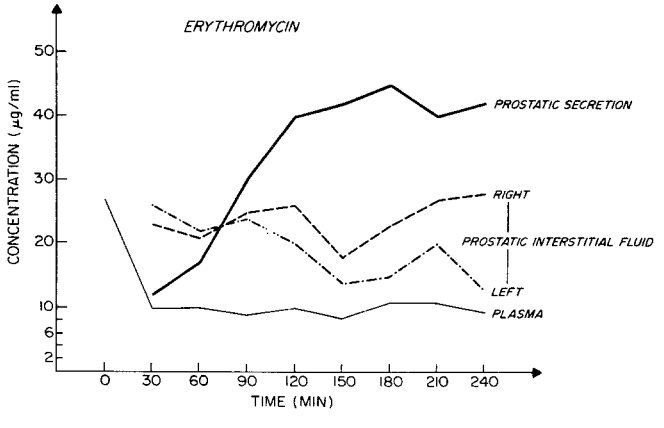


Fig. 3. Erythromycin concentrations in dog plasma, prostatic interstitial fluid and secretion during drug study (from Baumueller and Madsen 1982)

*Experimental Data*

Employing sexually mature male mongrel dogs we developed a two-stage model for testing antimicrobials in the prostate [22]. The dogs were anaesthetized with sodium thiopenthal intravenously and a 10 x 6 mm multiperforated polyethylene tissue chamber with two connective tubings was implanted in each lateral lobe of the prostate. The tubings were sealed with heparin and placed subcutaneously for collection of PIF during the drug study.

Approximately 4 weeks later the dogs were anaesthetized again and a low paramedian abdominal incision was made as before. The urethra was ligated at the bladder neck to prevent urine contamination of the PS obtained from a 14F urethral catheter. The vasa deferentia were also ligated. Urine was obtained from a cystostomy and PIF from the tubings of the prostatic tissue chambers (Fig. 1). To maintain a constant plasma drug concentration an intravenous bolus injection of the drug was followed by constant intravenous infusion for 4 h. To stimulate prostatic secretion, pilocarpin (0.25 mg/kg) was given intravenously initially and when needed during the experiment. PS, PIF, plasma and eventually urine were collected at 30 min intervals during the study. In order to examine drug concentrations in dogs with bacterial prostatitis the prostate in these dogs was freed from the surrounding fat and a suspension of $10^6$ *E. coli* in 0.5 ml saline was injected into a branch of the prostatic artery. To limit infection to the prostate the surrounding tissue was washed with ampicillin solution before closure [21].

After the experiments the dogs were sacrificed, tissue from various organs was removed, and the drug concentration in the tissues and various prostatic fluids was determined by bioassay employing a disk diffusion method. Sulfamethoxazole was determined by the Bratton-Marshall method [23].

Generally, the implanted tissue chambers healed in without infection and during the drug study yielded 0.03 to 0.1 ml of a clear yellowish fluid every 30 min. Culture of *E. coli* from PIF and PS in the prostatitis dogs confirmed the establishment of an experimental bacterial prostatitis.

The concentration of the bases trimethoprim (Fig. 2) and erythromycin (Fig. 3) in both PS and PIF exceeded the plasma level; the highest concentrations were found in the PS. The concentration pattern of acids such as sulfamethoxazole (Fig. 4), and amplicillin and amphoteric substances such as doxycycline (Fig. 5), differed in that the plasma concentrations were highest and the PS concentrations lowest. The separation of the concentration graphs for doxycycline, which is a lipid-soluble amphoteric tetracycline with three pKa's, was the least pronounced. However, no statistically significant differences were found between the PIF/plasma ratios and the PS/plasma ratios for any of the drugs studied, which is important clinically because PIF usually cannot be obtained from humans. Comparison of PIF/plasma ratios for dogs with normal and infected prostates revealed significant differences for erythromycin ($p < 0.001$) but not for trimethoprim, sulfamethoxazole, doxycyclin or ampicillin.

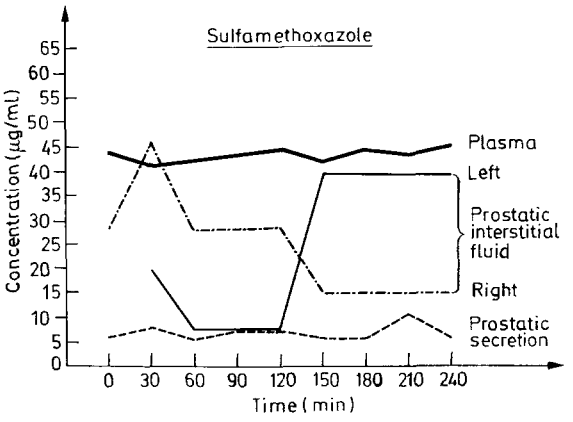


**Fig. 4.** Sulfamethoxazole concentrations in dog plasma, prostatic interstitial fluid and secretion during drug study (from Baumueller and Madsen 1982)

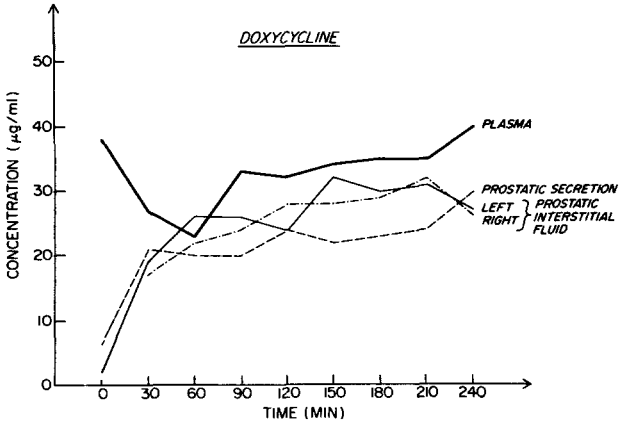


**Fig. 5.** Doxycycline concentrations in dog plasma, prostatic interstitial fluid and secretion during drug study (from Baumueller and Madsen 1982)

Only minor differences in pH were found, with a slight increase in some dogs with prostatitis and a slight decrease in others [24].

Most penicillanic acid derivatives tested appeared in relatively high concentrations in the PIF; generally the concentrations in PIF were 5 to 10 times higher than in the PS, but never exceeded the corresponding plasma values. Both carbenicillin and carbenicillin indanyl sodium had significantly higher PIF/plasma ratios than the other penicillins, while the ratios for mecillinam were significantly lower. Carbenicillin and carbenicillin indanyl ester were not detectable in PS [25].

*Clinical Application.* As illustrated, the concentration of bases in PS clearly exceeds the corresponding plasma levels under steady state conditions, while the PIF/plasma and PS/plasma ratio for acids only approaches 1.0, confirming the theories presented by Stamey et al. [18, 19]. However, there is a significant difference between the hydrogen ion concentration in dogs and humans, the pH of PS being approximately 6.4 in both normal and infected dogs opposed to pH values of 7.3 and 8.3 in the PS of normal and infected humans, respectively [2]. This implies that acids rather than bases will be charged in the alkaline human PS and therefore concentrated because of ion-trapping, assuming that the diffusion-concentration process is entirely passive. But, in fact, this is not true for trimethoprim. In a patient with urinary diversion (bilateral cutaneous ureterostomy) we found trimethoprim concentrations in PS more than 40 times greater than in plasma, while the PS/plasma ratio according to Stamey et al. [26] should be only 20:1, assuming the pH in PS is 6 and the pKa of trimethoprim is 7.4. The pH of the patient's PS was 7 and the ratio therefore far exceeds the theoretical ratio, if only passive secretion is postulated. These data imply the existence of an active concentration mechanism [27]. As previously mentioned, clinical application of results obtained in the laboratory has been disappointing. Several reasons must be considered, including the described significance of the pH and the involvement of an active secretion mechanism, perhaps regulated hormonally. In general, antimicrobial concentrations have been measured in the PS rather than in the PIF, despite the evidence that the interstitium is the site of infection in chronic bacterial prostatitis [21]. Considering bases, the PIF concentration will be lower than the PS concentrations and vice versa for acids, resulting in too optimistic estimates for basic substances and too pessimistic estimates for acidic substances. In cases of marginal plasma levels the drug concentration in PIF might not exceed the minimum inhibiting concentration (MIC) for a sufficient period.

The high failure rates of the trimethoprim-sulfonamide combination might be explained by the trimethoprim-sulfa ratio in the PIF which we previously found to be only 1:6.8, whereas the ideal ratio for maximum synergism is 1:20 [28, 29]. The existence of a prostatic factor inhibiting the antibacterial effect of trimethoprim on *E. coli* strains, and thereby increasing the MIC enormously, might also contribute to the poor clinical results [30]. Anatomical factors, which result in poor drainage of the infectious process, and the presence of prostatic calculi may be important in some cases of chronic bacterial prostatitis [20, 31].

Although neither carbenicillin nor the carbenicillin indanyl ester appeared in PS but only in PIF in dog experiments [25], some clinical studies [32, 33] report the ester to be effective in treatment of chronic bacterial prostatitis. In a recent clinical study, trimethoprim-sulfamethoxazole and minocycline were found equally effective [34], while Ristuccia and Cunha chose doxycycline for the treatment of chronic bacterial prostatis because of its ability to penetrate the prostate, its broad antibacterial spectrum including chlamydia and its few side effects [35]. The synergistic combination of rifampicin and trimethoprim is also notable. Giamarellou et al. found these combined drugs to have a clinical and bacteriological cure rate of as high as 89% [36]. However, most of the patients in Giamarellou et al.'s series suffered from the rather unusual *Staphylococcus aureus* prostatitis. Since gram-negative pathogens are the major cause

of chronic prostatitis, it is difficult from this report to evaluate the effectiveness of the rifampicin-trimethoprim combination.

## Conclusion

The local prostatic immunological response described might be valuable in differentiating between bacterial and nonbacterial prostatitis in cases where localization studies are unclear. However, much research still remains to be performed before immune-stimulating drugs perhaps can be applied clinically. When conventional antibacterial therapy is considered, data obtained in dog studies should be interpreted with caution. It is suggested that, depending on the bacterial sensitivity pattern, the drug of choice in the treatment of chronic bacterial prostatitis should be a lipid-soluble base with a low binding to plasma proteins or perhaps a combination of two such drugs which act synergistically. To obtain relevant concentrations in the PIF and prevent relapsing urinary tract infections, high dosages over extended periods are recommended.

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## References

1. Meares EM Jr (1980) Prostatic syndromes: New perspectives about old woes. J Urol 123:141
2. Fair WR, Cordonnier JJ (1978) The pH of prostatic fluid: A reappraisal and therapeutic implications. J Urol 120:695
3. Thomas V, Shelokov A, Forland M (1974) Antibody-coated bacteria in the urine and the site of urinary-tract infection. New Engl J Med 290:588
4. Jones SR, Smith JW, Sanford JP (1974) Localization of urinary-tract infections by detection of antibody-coated bacteria in urine sediment. New Engl J Med 290:591
5. Gray SP, Billings J, Blacklock NJ (1974) Distribution of the immunoglobulins G, A and M in the prostatic fluid of patients with prostatitis. Clin Chem Acta 75:163
6. Grayhack JT, Wendel EF, Oliver L, Lee C (1979) Analysis of specific proteins in prostatic fluid for detecting prostatic malignancy. J Urol 121:295
7. Meares EM jr (1977) Serum antibody titers in urethritis and chronic bacterial prostatitis. Urology 10:305
8. Meares EM jr (1978) Serum antibody titers in treatment with trimethoprim-sulfamethoxazole for chronic prostatitis. Urology 11:142
9. Shortliffe LMD, Wehner N, Stamey TA (1981) Use of a solid-phase radioimmunoassay and formalin-fixed whole bacterial antigen in the detection of antigen-specific immunoglobulin in prostatic fluid. J Clin Invest 67:790
10. Shortliffe LMD, Wehner N, Stamey TA (1981) The detection of a local prostatic immunoglobulin response to bacterial prostatitis. J Urol 125:509
11. Ablin RJ, Gonder MJ, Soanes WA (1971) Localization of immunoglobulins in human prostatic tissue. J Immunol 107:603
12. Jones SR (1974) Prostatitis as a cause of antibody-coated bacteria in urine. New Engl Med 291:365
13. Nishimura T, Mobley DF, Carlton CE (1977) Immunoglobulin A in split ejaculates of patients with prostatitis. Urology 9:186
14. Riedasch G, Ritz E, Möhring K, Ikinger V (1977) Antibody-coated bacteria in the ejaculate: A possible test for prostatitis. J Urol 118:787
15. Shah N (1976) Diagnostic significance of levels of immunoglobulin A in seminal fluid of patients with prostatic disease. Urology 8:270
16. Wishnow KI, Wehner N, Stamey TA (1982) The diagnostic value of the immunologic response in bacterial and nonbacterial prostatitis. J Urol 127:689
17. Fowler JE Jr, Mariano M (1982) Immunologic response of the prostate to bacteriuria and bacterial prostatitis. II. Antigen specific immunoglobulin in prostatic fluid. J Urol 128:165
18. Stamey TA, Meares EM Jr, Winningham DG (1970) Chronic bacterial prostatitis and the diffusion of drugs into prostatic fluid. J Urol 103:187
19. Stamey TA (1972) Urinary infections in males. In: Urinary infections. The Williams and Wilkins Co, Baltimore, p 161
20. Blacklock NJ (1974) Anatomical factors in prostatitis. Br J Urol 46:47
21. Baumueller A, Madsen PO (1977) Experimental bacterial prostatitis in dogs. Urol Res 5:211
22. Madsen PO, Baumueller A, Hoyme U (1978) Experimental models for determination of antimicrobials in prostatic tissue, interstitial fluid and secretion. Scand J Infect Dis, Suppl 14:145
23. Bratton AC, Marshall EV Jr (1939) A new coupling component for sulfanilamide determination. J Biol Chem 128:537
24. Baumueller A, Madsen PO (1982) Antimicrobial substances in secretion, interstitial fluid, and tissue of normal and infected canine prostate glands. Urol Res 10:31
25. Nielsen OS, Frimodt-Moeller N, Maigaard S, Hoyme U, Baumueller A, Madsen PO (1980) Penicillanic acid derivatives in the canine prostate. The Prostate 1:79
26. Stamey TA, Bushby SRM, Bragonje J (1973) The concentrations of trimethoprim in prostatic fluid: Nonionic diffusion or active transport. J Infect Dis, Suppl 128:S686
27. Madsen PO, Kjaer TB, Baumueller A (1976) Prostatic tissue and fluid concentrations of trimethoprim and sulfamethoxazole. Experimental and clinical studies. Urology 8:129
28. Madsen PO, Baumueller A, Frimodt-Moeller N, Kjaer TB, Naber KG, Nielsen OS, Maigaard S (1981) Trimethoprim/Sulfonamid-Kombinationen bei der Behandlung von Prostatiden. In: Naber KG, Adam D (eds) Chemotherapeutika im Vergleich. Gustav Fischer Verlag, p 99
29. Bushby S, Bushby M (1976) Trimethoprim-sulfonamethoxazole synergy and prostatitis. In: Williams J, Geddes A (eds) Chemotherapy, vol 6. Plenum Press, New York, p 383
30. Madsen PO, Whalen PR (1978) Interaction between antimicrobial agents and prostatic tissue extract and fluid. Infection 6, Suppl 1:S75
31. Meares EM Jr (1974) Infection stones of prostate gland. Urology 4:560
32. Oliveri RA, Sachs RM, Caste PG (1979) Clinical experience with geocillin in the treatment of bacterial prostatitis. Clin Res 25: 415
33. Mobley DF (1981) Bacterial prostatitis: treatment with carbenicillin indanyl sodium. Invest Urol 19:31
34. Paulson DF, White RD (1978) Trimethoprim-sulfamethoxazole and minocycline-hydrochloride in the treatment of culture-proved bacterial prostatitis. J Urol 120:184
35. Ristuccia AM, Cunha BA (1982) Current concepts in antimicrobial therapy of prostatitis. Urology 20:338
36. Giamarellou H, Koshidis J, Leonidas M, Papadakis M, Daikos GK (1982) A study of the effectiveness of rifampicin in chronic prostatitis caused mainly by *Staphylococcus aureus*. J Urol 128: 321

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