Treatment of Bacterial Prostatitis

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Prostatitis is characterized by voiding symptoms and genitourinary pain and is sometimes associated with sexual dysfunction. Up to 25% of men receive a diagnosis of prostatitis in their lifetime, but <10% have a proven bacterial infection. The causes and treatment of nonbacterial prostatitis are largely unknown, but bacterial prostatitis is caused by infection with uropathogens, especially gram-negative bacilli, although infection is sometimes due to gram-positive and atypical microorganisms. Acute bacterial prostatitis is easily diagnosed (by abrupt urogential and often systemic symptoms, along with bacteriuria) and treated (by systemic antibiotic therapy). Chronic bacterial prostatitis is characterized by prolonged or recurrent symptoms and relapsing bacteriuria; diagnosis traditionally requires comparing urinary specimens obtained before with specimens obtained after prostatic massage. Treating chronic bacterial prostatitis requires prolonged therapy with an antibiotic that penetrates the prostate (ie, one with high lipid solubility, a low degree of ionization, high dissociation constant, low protein binding, and small molecular size). We review recent pharmacological and clinical data on treating bacterial prostatitis.

Prostatitis is a common syndrome that usually presents with voiding symptoms (irritative or obstructive) and pain (genitourinary, pelvic, or rectal) and is sometimes associated with sexual dysfunction (eg, ejaculatory discomfort and hematospermia). Characteristic features include a high prevalence, substantially impaired quality of life, and frequent recurrences [1]. Although some cases are clearly infectious, most men who receive a diagnosis of prostatitis have no evidence of a genitourinary bacterial infection and the cause is usually unknown [2]. Disagreement persists over how to define prostatitis, including debates over the relative importance of various clinical, microbiological, and histopathological findings [3]. Advances in the past decade, however, have spurred better-designed clinical trials and generated more robust evidence regarding treatment.

One major change was the development of a National Institutes of Health (NIH) consensus definition and classification system (Table 1) [4, 5]. This scheme, although limited by the lack of a reliable comparison standard, clarified that a small minority of men with prostatitis have bacterial infection (ie, acute bacterial prostatitis [ABP; category I] or chronic bacterial prostatitis [CBP; category II]) [6]. The rest have nonbacterial prostatitis. If symptomatic, they have chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)—either IIIA, which is an inflammatory condition defined by leukocytes in the semen or postprostatic massage specimens, or IIIB, which is a noninflammatory disorder. A new syndrome, asymptomatic inflammatory prostatitis (category IV), is defined by an abnormal semen analysis, elevated prostate-specific antigen (PSA), or incidental findings of prostatitis on examination of a biopsy specimen. The second advance was developing and validating an NIH–Chronic Prostatitis Symptom Index (NIH-CPSI) [7]. This questionnaire scores disorders relating to pain, voiding, and quality of life. The maximum total score is 43, and a decrease of 4–6 points (or 25%) correlates with clinically significant improvement [8]. The NIH-CPSI has proved to be useful for epidemiological studies and for assessment of patients over time [9].

The greatest area of uncertainty in treating prostatitis concerns the approach to nonbacterial prostatitis. This review, however, will focus on treatment of bacterial prostatitis and will only briefly discuss nontreatment issues or nonbacterial disorders. Because of the familiarity of the prostatitis categories, we will generally refer to them by their classical (rather than NIH) designations. Our recommendations are derived from a comprehensive review of the literature and our combined clinical experience.

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Table 1. Classification of Prostatitis According to Classical and Newer National Institutes of Health (NIH) Categories Based on Prostatic Localization Studies for White Blood Cells (WBC) and Bacteria

Classical classification (NIH category)	Prostatitis cases, %	Mid-stream urine specimen (VB2)		Prostatic specimen (EPS or VB3)	
		WBC	Culture	WBC	Culture
ABP (I)	<1	++	+	++	+
CBP (II)	5–10	+	+	+	+
CP/CPPS (III)	80–90				
Inflammatory (IIIA)		−	−	+	−
Noninflammatory (IIIB)		−	−	−	−
AIP (IV)	10	+	−	−	−

NOTE. Adapted from Doble [4]. +, present or positive; ++, present in large numbers or strongly positive; −, negative; ABP, acute bacterial prostatitis; AIP, asymptomatic inflammatory prostatitis; CBP, chronic bacterial prostatitis; CP/CPPS, chronic prostatitis/chronic pelvic pain syndrome; EPS, expressed prostatic secretions; VB2, voided bladder second specimen (a clean-catch mid-stream urine specimen); VB3, voided bladder third specimen (a post–prostatic massage urine specimen).

EPIDEMIOLOGY

Prostatitis is the most common urological diagnosis in men <50 years of age and is the third most common diagnosis among those >50 years of age [10]. Approximately 10% of men have chronic prostatitis-like symptoms; of these men, ~60% have sought medical help [1, 11]. The lifetime probability of a man receiving a diagnosis of prostatitis is >25% [12, 13], and prostatitis accounts for ~25% of men's office visits for genitourinary complaints [14]. Reported rates of prostatitis are similar in North America, Europe, and Asia [15]. In addition to discomfort, prostatitis syndromes are responsible for substantial physical and emotional distress [16, 17] and financial costs [14].

PATHOPHYSIOLOGY

The prostate gland has several natural defenses against infection, including the production of antibacterial substances and mechanical flushing of the prostatic urethra by voiding and ejaculation [18]. However, poor drainage of secretions from peripheral ducts or reflux of urine into prostatic tissue may lead to inflammation, fibrosis, or stones. Most bacterial prostatitis probably follows a urinary tract infection (UTI), especially with uropathogens that demonstrate special virulence factors [19]. Risk factors for developing prostate infection include urinary tract instrumentation, having a urethral stricture, or urethritis (usually due to sexually transmitted pathogens).

ABP, which accounts for <1% of cases of prostatitis, is likely caused by infected urine ascending the urethra to intraprostatic ducts. The 10% of cases that follow genitourinary instrumentation generally occur in older patients, have a higher risk of recurrence or prostatic abscess, and are more often caused by non–*Escherichia coli* species [20]. Despite antibiotic prophylaxis, ~2% of men develop ABP after transrectal prostate biopsy, especially after repeat procedures [21]. CBP complicates a minority of cases of ABP and often occurs without a previous acute infection. The formation of either bacterial biofilm or prostatic calculi favors chronic, treatment-resistant infection [22]. Histopathological findings in bacterial prostatitis are poorly defined, with infection primarily in the acinar rather than the interstitial spaces [22] and primarily luminal rather than parenchymal.

CLINICAL PRESENTATION AND DIAGNOSTIC EVALUATION

ABP typically presents abruptly with voiding symptoms and distressing but poorly localized pain and is often associated with systemic findings (eg, malaise and fever) [5]. Clinicians should enquire about urogenital disorders, recent genitourinary instrumentation, and new sexual contacts. Only ~5% of men with ABP develop CBP, and ~2% develop a prostatic abscess. CBP usually presents with more-prolonged (⩾3 months) urogenital symptoms. The hallmark is relapsing UTI (ie, UTIs due to the same organism), but <50% of patients with CBP have this history [23]. Between symptomatic UTIs, patients may be asymptomatic, despite ongoing prostatic infection.

Physical examination should include obtaining vital signs and examining the lower abdomen (seeking a distended bladder), back (seeking costovertebral-angle tenderness), genitalia, and rectum. Digital prostate palpation in ABP can cause discomfort and can potentially induce bacteremia but is safe if done gently. In ABP, the gland is typically tender, swollen, and warm, whereas in CBP, there may be some tenderness, softening ("boggyness"), firm induration, or nodularity.

Few laboratory tests are diagnostically useful in evaluating

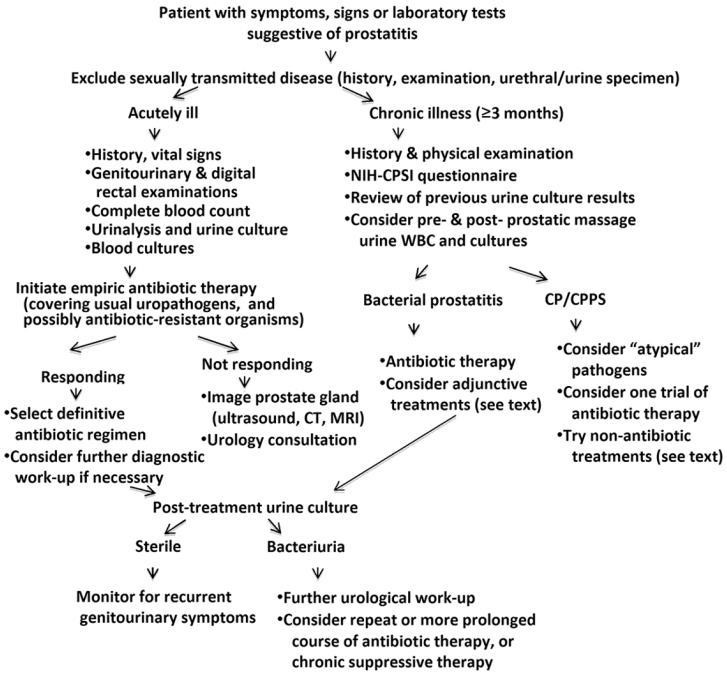

Figure 1. Diagnostic algorithm for evaluating patient with possible prostatitis. CP/CPPS, chronic prostatitis/chronic pelvic pain syndrome; CT, computed tomography; MRI, magnetic resonance imaging; NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index.

possible prostatitis. Any patient at risk should be screened for sexually transmitted infections. All patients with possible prostatitis need a urinalysis and urine culture. Urine dipstick testing (for nitrites and leukocytes) in ABP has a positive predictive value of ~95%, but a negative predictive value of only ~70% [24]. Blood cultures and a complete blood count are useful in ABP. For patients with possible CBP, the 4-glass test is considered to be the diagnostic criterion standard. Diagnosis is based on finding substantially lower leukocyte and bacterial counts in voided bladder urine specimens from the urethra (VB1) and bladder (VB2), compared with counts in post–prostatic massage voided urine (VB3) or expressed prostatic secretions (EPS). Adding a culture of ejaculated semen improves the diagnostic utility of the 4-glass test [25, 26], but semen cultures are positive more often than are cultures of VB3 or EPS in men with nonbacterial prostatitis [27]. The 4-glass test is cumbersome, inadequately validated, and rarely performed, even by urologists [28, 29]. It may be diagnostically helpful on first presentation, but its value is limited in previously treated patients with chronic symptoms. A simpler 2-glass test (comparing pre– with post–prostatic massage urine specimens) provides similar results [30]. Leukocyte counts in expressed prostatic secretions do not correlate with the severity of symptoms in men with CP/CPPS [31].

Evaluating patients with chronic prostatitis should usually include administering the NIH-CPSI and perhaps measuring urinary flow rate and post-void residual urine; only selected patients need further urodynamic or imaging studies [32]. Culturing prostatic tissue obtained by biopsy is neither sensitive (because infection is focal) nor specific (because ~25% of prostatectomy specimens are culture positive) [33]. PSA levels are elevated in ~60% of men with ABP, 20% of men with CBP, and 10% of men with nonbacterial prostatitis [34]; a decrease after antibiotic therapy (which occurs in ~40% of patients) correlates with clinical and microbiological improvement [35]. Various imaging studies can detect a suspected prostatic abscess. Figure 1 shows our approach to evaluating a patient with possible prostatitis.

CAUSATIVE PATHOGENS IN PROSTATITIS

Aerobic gram-negative bacilli are the predominant pathogens in bacterial prostatitis. *E. coli* cause 50%–80% of cases; other pathogens include Enterobacteriaceae (eg, *Klebsiella* and *Proteus*, which account for 10%–30% of cases), *Enterococcus* species (5%–10% of cases), and nonfermenting gram-negative bacilli (eg, *Pseudomonas* species; <5% of cases). Some debate the role of gram-positive organisms other than enterococci [36, 37], but most accept *Staphylococcus* and *Streptococcus* species as pathogens [37–39]. The increasing prevalence of gram-positive pathogens may represent changing disease epidemiology (perhaps related to fluoroquinolone therapy) or acceptance of their pathogenicity by health care providers. Limited data suggest that obligate anaerobes may rarely cause chronic prostatitis [40].

Some cases of prostatitis are caused by atypical pathogens [34]. A large prospective study of men with chronic prostatitis

found that 74% had an infectious etiology; the most common isolates were *Chlamydia trachomatis* (37% of cases) and *Trichomonas vaginalis* (11%), whereas 5% of patients had infection due to *Ureaplasma urealyticum* [41]. Classical bacterial uropathogens were found in 20% of patients, and more patients with these pathogens, compared with patients with nonbacterial pathogens, had prostatic specimens with leukocytes [41]. Other possible prostatitis pathogens include *Mycoplasma genitalium, Neisseria gonorrhoeae, Mycobacterium tuberculosis*, various fungi, and several viruses [34].

TREATMENT OF BACTERIAL PROSTATITIS

The approach to treating bacterial infection of the prostate largely centers on appropriately selected antibiotic therapy. The best approach to treating nonbacterial prostatitis (NIH categories III and IV) is less clear.

Overview of antibiotic therapy. Treatment of bacterial prostatitis is hampered by the lack of an active antibiotic transport mechanism and the relatively poor penetration of most antibiotics into infected prostate tissue and fluids. Most antibiotics are either weak acids or bases that ionize in biological fluids, which inhibits their crossing prostatic epithelium (Figure 2) [23]. Only free, non–protein-bound antibiotic molecules enter tissues. Ordinarily, substances with molecular weights of <1000 pass through openings (fenestrae) between capillary endothelial cells, but prostate capillaries are nonporous. Passage of a drug through prostatic capillary endothelium and prostatic epithelium is enhanced by a high concentration gradient, high lipid solubility, low degree of ionization, high dissociation constant (pKa; allowing diffusion of the unionized component into the prostate), low protein binding, and small molecular size [42]. A pH gradient allows electrically neutral molecules to pass through membranes, become ionized, and be trapped. Although ion trapping may increase prostatic drug concentration, the charged fraction has an unclear antimicrobial role. Fluoroquinolones are zwitterions that have a different pKa in an acidic versus an alkaline milieu, allowing concentrations in the prostate to be 10%–50% of concentrations in serum [43].

Normal human prostatic fluid has a pH of ~7.3; in individuals with CBP, the prostatic fluid may become markedly alkaline (mean pH, 8.34) [44]. Many early studies of prostatic antibiotic penetration used dogs, which generally have acidic prostatic fluid. Human studies have mostly used adenoma tissue derived from prostate resection. These uninfected samples of mixed tissues and fluids with varied pH levels generally have antibiotic concentrations that exceed those in plasma. In humans, alkaline drugs (eg, trimethoprim and clindamycin) undergo ion trapping, which leads to high prostatic concentrations. Acidic drugs, such as beta-lactams, achieve lower levels, but more drug is in the active unionized state.

Fluoroquinolones have emerged as the preferred antibiotics for treating bacterial prostatitis, and several have been approved by the US Food and Drug Administration (FDA) for this indication. Compared with concentrations in plasma, drug levels are generally higher in urine, similar in seminal fluid and prostatic tissue, and lower (albeit therapeutic) in prostatic fluid [43, 44]. One concern with these agents is the growing problem of fluoroquinolone resistance, which generally requires treat-

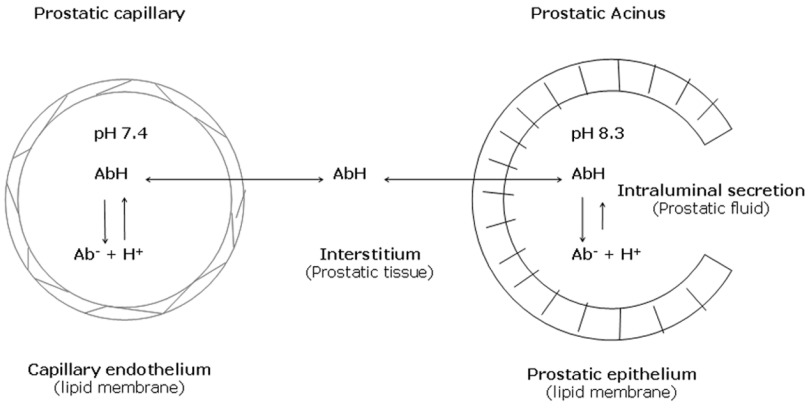

Figure 2. Illustration of ion trapping of antibiotics within prostatic tissue. Prostatic fluid is separated from capillary blood by the lipid-containing biologic membranes of the capillary endothelium and the cuboidal prostatic epithelial cells. Prostatic capillary endothelial cells lack secretory and active transport mechanisms, and they form tight intracellular junctions, preventing the passive diffusion of small molecules through intercellular gaps. Most antibiotics are either weak acids or bases that ionize in biological fluids. Lipid-soluble, uncharged antibiotics (AbH) can passively diffuse across these membranes and the prostatic interstitium, thus tending toward equal concentrations in each compartment. Acidic or basic drugs are also in equilibrium with their electrically charged dissociated forms (Ab^-), but the charged forms are unable to pass through the membranes. The extent of dissociation of a drug is governed by its pKa and the pH of its local environment. Weakly acidic antibiotics dissociate to a greater degree in the alkaline environment of the chronically infected prostatic fluid (pH 8.3) than in the plasma (pH 7.4), leading to an increased total drug concentration ($AbH + Ab^-$) within prostatic fluid relative to the plasma.

Table 2. Antibiotics with Pharmacological Data, Clinical Case Report(s), or a License to Support Their Use for Treatment of Bacterial Prostatitis

Drug(s)[a]	Prostate tissue or fluid concentration	FDA approval	Reference(s)
Amoxicillin-clavulanate	Tissue, 3.8–7.2 μg/g amoxicillin	UTI	[55, 56]
Ampicillin-sulbactam	Tissue, 0.42–548.33 μg/g ampicillin	No	[57]
Piperacillin	Tissue, 70.7 μg/g	UTI	[42, 58]
Piperacillin-tazobactam		No	
Cephalexin	Tissue, 0.5–10 μg/g	UTI, ABP	[42, 59, 60]
Cefazolin	Fluid, <10 μg/mL	UTI, BP	[42, 60]
Cefaclor	Tissue, 0.74 μg/g	C-UTI, UC-UTI	[42, 61]
Cefuroxime	Tissue, 7.6–29.2 μg/g	UTI	[62–64]
Cefotetan	Tissue, 36 μg/g; Fluid, 0.8 μg/mL	UTI	[42, 65]
Cefotaxime	Tissue, 6.8–22.5 μg/g	UTI	[42, 66–68]
Ceftriaxone	Tissue, 12.9–73.7 μg/g	UTI	[42, 69]
Ceftazidime	Tissue, 23.4 μg/g	UTI	[70]
Cefepime		C-UTI, UC-UTI	
Cefixime	Tissue, 1.08 μg/g	UC-UTI	[71]
Cefpodoxime	Tissue, 0.5 μg/g	UC-UTI	[72]
Aztreonam	Tissue, 6–10 μg/g	C-UTI, UC-UTI	[73, 74]
Imipenem[b]	Tissue, 5.3 μg/g	C-UTI, UC-UTI	[21, 42]
Doripenem		C-UTI	
Ertapenem[b]		C-UTI	[75]
Vancomycin[b]		No	[76, 77]
Trimethoprim-sulfamethoxazole	Tissue, 7.1 μg/g for trimethoprim, 24 μg/g for sulfamethoxazole	UTI	[78]
Nitrofurantoin		UTI	
Ciprofloxacin	Tissue, 0.6–4.18 μg/g	UTI, CBP	[79]
Gatifloxacin	Fluid, 1.72–3.1 μg/mL	UTI	[80]
Levofloxacin	Tissue level greater than corresponding plasma level	C-UTI, UC-UTI	[81]
Moxifloxacin	Fluid, 3.8–8.5 μg/mL	No	[82, 83]
Ofloxacin	Tissue, 4.1 μg/g; fluid, 4.0 μg/mL	C-UTI, UC-UTI, BP	[84]
Prulifloxacin	Tissue, 1.9–5.5 μg/g	No	[85]
Clindamycin	Tissue level greater than corresponding plasma level	No	[42]
Azithromycin	Fluid, 2.54 μg/mL	No	[86]
Clarithromycin	Tissue, 3.08–3.22 μg/g	No	[87]

NOTE. ABP, acute bacterial prostatitis; BP, bacterial prostatitis; CBP, chronic bacterial prostatitis; C-UTI, complicated urinary tract infection; FDA, US Food and Drug Administration; UC-UTI, uncomplicated urinary tract infection; UTI, urinary tract infection.

[a] Drugs administered by various routes at varying dosages.

[b] Drugs for which there are clinical reports of use in treating bacterial prostatitis.

ment with a third-generation cephalosporin (eg, ceftazidime or ceftriaxone) or a carbapenem (eg, imipenem or ertapenem) [45]. Table 2 provides information on other antibiotics that may be useful for treating bacterial prostatitis, based on pharmacodynamic data, case reports, or FDA approval for treating UTIs.

Although penicillin G achieves poor prostatic concentrations, piperacillin has good levels and has been used successfully to treat CBP. Cephalosporins, despite being weak acids with low lipid solubility, can attain therapeutic levels in prostatic fluid or tissue (Table 2). Aztreonam, imipenem, and some aminoglycosides can attain levels in prostatic tissue that exceed the minimum inhibitory concentrations of most Enterobacteriaceae. Prostatic concentrations of minocycline and doxycycline are at least 40% of the corresponding serum concentrations. Erythromycin—and probably other macrolides, as well—can develop high prostate concentrations. Clindamycin and trimethoprim readily enter prostatic fluid, and levels of these drugs in prostatic fluid may exceed levels in plasma. The prostatic concentration of sulfamethoxazole is much lower, raising doubts that it synergizes with trimethoprim. Nitrofurantoin prostatic levels are likely nontherapeutic. Table 3 outlines the advantages and disadvantages of commonly used antimicrobial agents for the treatment of CBP.

Antibiotic therapy for ABP. For systemically ill patients with ABP, parenteral antibiotic therapy is preferable, at least initially. Most antibiotic agents penetrate the acutely inflamed prostate, but experience favors empirical treatment with a

Table 3. Selecting an Antibiotic for Treatment of Chronic Bacterial Prostatitis

Antimicrobial agent	Advantages	Disadvantages
Fluoroquinolones	Good oral bioavailability; oral and IV formulations; good prostate penetration; activity against most usual bacterial pathogens; activity against most atypical pathogens; may be active against organisms in biofilm; most extensively studied	Potential for interactions with other drugs; relatively high risk of *Clostridium difficile* infection; various known toxicities; some relatively expensive
Trimethoprim (alone or combined with sulfamethoxazole)	Fair oral bioavailablility; oral and intravenous formulations; penetrates prostate; relatively inexpensive; activity against common gram- negative pathogens	No activity against *Pseudomonas*; relatively little activity against enterococci; resistance among some Enterobacteriaceae; synergy with sulfamethoxazole in prostate unclear; not active against atypical pathogens
Tetracyclines	Fair oral bioavailability; oral and intravenous formulations; inexpensive; activity against many atypical pathogens and MRSA strains	No activity against *Pseudomonas*; limited activity for many Enterobacteriaceae; unreliable for enterococci; caution required with renal or liver disease; risk of photosensitivity
Macrolides	Fair oral bioavailability; active against gram-positive bacteria but not most MRSA strains; good prostate penetration; some activity against atypical pathogens; most relatively inexpensive; relatively safe; may be active against organisms in biofilm	Only azithromycin available intravenously; minimal clinical evidence of efficacy; not active against gram-negative bacteria; gastrointestinal upset relatively common

NOTE. Adapted from Grabe et al [88]. MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 4. Antibiotic Treatment Trials of Chronic Prostatitis, 1999–2009

Publication	Year	Country, clinical setting	No. of patients, trial design	Criteria for enrolment (extrapolated)	Agent(s) (no. of patients)	Outcome measure (response)	Follow up after treatment completed, weeks	Principle conclusion(s)
Cai et al [89]	2009	Italy, single center	143, Randomized open label	CBP	Prulifloxacin plus phytotherapy[a] (106); prulifloxacin alone (37)	CPSI (Y), IPSS (Y), microbiological (Y)	26	Response increased with added phtyotherapy.
Jeong et al [90]	2008	Korea, single center	81, Randomized open label	CP/CPPS	Levofloxacin (26); doxazosin (26); both (29)	CPSI (Y) (Korean version)	0	Response greatest with levofloxacin
Naber et al [38]	2008	EU, multicenter	117, Open label, no comparator	Clinical, microbiological (CBP)	Levofloxacin (117)	Clinical (Y), microbiological (Y)	26	Most responded
Giannarini et al [91]	2007	Italy, single center	96, Randomized, consecutive, double blind	CBP	Prulifloxacin (48); levofloxacin (48)	CPSI (Y), microbiological (Y)	26	No difference
Magri et al [92]								
Trial 1	2007	Italy, single center	104, Open label, no comparator	CBP	Ciprofloaxcin plus alfuzosin plus azithromycin plus *Serenoa repens* (104)	CPSI (Y), microbiological (Y)	130	Most responded
Trial 2	2007	Italy, single center	137, Open label, no comparator	CBP	Ciprofloaxcin plus alfuzosin plus azithromycin plus *S. repens* (137)	CPSI (Y), microbiological (Y)	130	Most responded; second cycle increased response
Chen et al [93]	2006	Taiwan, single center	14, not stated	CBP, CP/CPPS (IIIA)	Ciprofloxacin plus doxazosin plus allopurinol plus massage (14)	CPSI (Y), microbiological (Y)	26	Most responded
Ziaee et al [94]	2006	Iran, single center	56, Randomized, double blind	CP/CPPS	Ofloxacin (27); ofloxacin plus allopurinol (29)	CPSI (Y)	12	No difference
Alexander et al [95]	2004	US, multicenter urology	196, Randomized, double blind	CP/CPPS CPSI >15	Ciprofloxacin (48); tamsulosin (48); both (49); placebo (49)	CPSI (N)	6	No difference
Nickel et al [96]	2003	Canada, multicenter	80, Randomized, double blind	CP/CPPS	Levofloxacin (45); placebo (35)	CPSI (N)	12	No difference
Bundrick et al [97]	2003	USA multicenter	377, Randomized, double blind	Clinical, microbiological (CBP)	Levofloxacin (199); ciprofloxacin (184)	Clinical (Y), microbiological (Y)	26	No difference
Naber et al [98]	2002	Germany/UK, multicenter	182 Randomized, open label	Clinical, microbiological (CBP)	Lomefloxacin (93); ciprofloxacin (89)	Clinical (Y), microbiological (Y)	26	No difference
Hu et al [99]	2002	China, single center	50, Randomized, open label	Clinical, microbiological (CBP)	Amikacin local (30) vs systemic (20)	CPSI (Y), microbiological (Y)	13	Response better with local injection than with systemic therapy

NOTE. CBP, chronic bacterial prostatitis (category II); clinical, clinical criteria other than NIH criteria that were assessed as reasonable by the authors; CP/CPPS, chronic prostatitis/chronic pelvic pain syndrome (category III); CPSI, NIH Chronic Prostatitis Symptom Index; EU, European Union; IPSS, International Prostatic Symptom Score; microbiological, microbiological criteria other than NIH criteria that were assessed as reasonable by the authors; N, author assessment that study reported no effect as judged by CPSI, IPSS, clinical, or microbiological criteria; NIH, National Institutes of Health; Y, author assessment that study reported improvement as judged by CPSI, IPSS, clinical, or microbiological criteria.

[a] Comprised of ProstaMEV and FlogMEV (which contains *Serenoa repens*, *Urtica dioica*, quercitin, curcumin).

broad-spectrum beta-lactam drug—either a penicillin (eg, piperacillin-tazobactam) or a cephalosporin (eg, cefotaxime or ceftazidime)—perhaps combined with an aminoglycoside for patients who are severely ill or who have recently received antibiotic therapy. Clinicians should consider local drug-resistance patterns in choosing antibiotics, especially with the emergence of extended-spectrum beta-lactamase–producing strains in complicated UTIs [21], and should adjust therapy on the basis of culture results. Clinically stable patients may be treated with oral therapy (usually a fluoroquinolone). Duration of therapy for ABP is usually 2 weeks, although it can be continued for up to 4 weeks for severe illness or treatment of patients with concomitant bacteremia.

Two recent studies provide insights on treating ABP. A multicenter retrospective survey revealed that community -acquired infections were 3 times more common than nosocomial infec-

Table 5. Recommended Antibiotic Therapy for Various Types of Bacterial Prostatitis

Type of bacterial prostatitis, usual microbial etiology	Primary empirical regimen	Alternative agents	Other considerations
Acute			
Uncomplicated (with low risk of STD pathogens)			
Enterobacteriaceae (especially *Escherichia coli*)	Ciprofloxacin 400 mg iv or 500 mg po BID or levofloxacin 500–750 mg iv/po QD	TMP-SMX DS (160 mg TMP) BID	2 weeks duration of therapy of may be sufficient; if patient remains symptomatic, extend to 4 weeks
Enterococcus species[a]	Ampicillin 1–2 g IV every 4 h; vancomycin 15 mg/kg every 12 h	Levofloxacin 750 po QD; linezolid 600 mg every 12 h	Use intravenous therapy if systemically ill; switch to oral therapy when stable
Pseudomonas aeruginosa	Ciprofloxacin 400 mg TID	Piperacillin-tazobactam 4.5 g iv every 6 h	
Uncomplicated (with risk of STD pathogens)			
Neisseria gonorrhoeae or *Chlamydia trachomatis*	Ceftriaxone 250 mg IM or Cefixime 400 mg po × 1 dose plus Doxycycline 100 mg po BID or azithromicin 500 mg po QD	Fluoroquinolones not recommended for gonococcal infection	Treat for 2 weeks in most cases. Obtain urine nucleic-acid amplification test for *N. gonorrhoeae* and *C. trachomatis*
Uncomplicated, with risk of antibiotic resistant pathogen			Consider extending duration of therapy to 4 weeks
Fluoroquinolone-resistant Enterobacteriaceae	Ertapenem 1 g iv QD	Ceftriaxone 1 g iv QD or imipenem 500 mg iv every 6 h or tigecycline 100 mg iv × 1 dose then 50 mg iv every 12 h	
ES or AmpC beta lactamase producing Enterobacteriaceae	Ertapenem 1 g iv QD	Cefipime 2 g iv every 12 h or imipenem 500 mg iv every 6 h or tigecycline 100 mg iv × 1 dose then 50 mg iv every 12 h	
Fluoroquinolone-resistant pseudomonas	Imipenem 500 mg iv every 6 h	Meropenem 500 mg iv every 8 h	
Complicated by bacteremia or suspected prostatic abscess			
Enterobacteriaceae or *Enterococcus* species	Ciprofloxacin 400 mg iv every 12 h or levofloxacin 500 mg iv every 24 h	Ceftriaxone 1–2 g iv every 24 h plus levofloxacin 500–750 mg po QD, or ertapenem 1 g iv every 24 h or piperacillin-tazobactam 3.375 g iv every 6 h	Treat for 4 weeks. Obtain blood cultures. Consider genitourinary imaging. Change iv to po regimen when blood cultures are sterile and abscess drained.
Chronic			Duration of therapy 4–6 weeks. Consider suppressive therapy if relapses occur.
Enterobacteriaceae (*Enterococcus* species)	Ciprofloxacin 400 mg iv every 12 h or levofloxacin 500 mg iv every 24 h	TMP-SMX × 1 dose DS BID	
Staphylococcus species	Azithromycin 500 mg po QD	Doxycyline 100 mg BID	

NOTE. Uncomplicated was defined as no signs, symptoms, or other findings highly suggestive of sepsis or prostatic abscess. AmpC, ampicillin C; BID, twice daily; BL, beta lactamase; DS, double strength (160 mg trimethoprim); ES, extended spectrum; iv, intravenous; po, oral; QD, once daily; STD, sexually transmitted disease; TID, 3 times per day; TMP-SMX, trimethoprim-sulfamethoxazole.

[a] Several recommended agents are not active against strains of *Enterococcus*, especially *Enterococcus faecium.*

tions; *E. coli* remained the predominant pathogen, but nosocomial infections were more often caused by *Pseudomonas aeruginosa*, enterococci, or *Staphylococcus aureus*, and these organisms were associated with higher microbiological and clinical failure rates [46]. A similar study found a high rate of ciprofloxacin-resistant pathogens and that nosocomial acquisition or prior instrumentation were associated with increased antibiotic resistance and higher rates of clinical failure [47]. Ancillary measures for ABP include ensuring adequate fluid intake and urinary drainage.

Antibiotic therapy for CBP (category II) or inflammatory nonbacterial (category IIIA) prostatitis. CBP should be

treated with 4–6 weeks of antibiotic therapy. When persistent infection is caused by infected prostate stones or other types of genitourinary pathology, patients who have shown some response may benefit from more-prolonged antibiotic therapy [48]. In contrast with treatment of ABP, treatment of CBP can usually be delayed until culture and susceptibility results are available. Fluoroquinolones are the preferred drugs, except when resistance to these agents is confirmed or strongly suspected. Overall rates of clinical and microbiological response for CBP treated with fluoroquinolones are 70%–90% at the end of therapy, but only ~60% after 6 months [38]. Clinical and microbiological response rates are similar in those whose prostatic specimens grow either well-accepted uropathogens or coagulase-negative *Staphylococcus* or *Streptococcus* species [39]. Giving repeated courses of antibiotics is generally unwise. Surgically removing infected prostatic stones may help when other measures fail. Some case reports suggest apparent benefit from direct injection of antimicrobials into the prostate, but the evidence is insufficient to recommend this approach. Long-term suppressive therapy with low doses of oral antibiotics (eg, trimethoprim-sufamethoxazole) may reduce symptomatic recurrences, but evidence is lacking.

Although <10% of men who receive a diagnosis of prostatitis have a proven bacterial infection, approximately one-half are treated with antibiotic therapy [49]. Clinicians often treat nonbacterial prostatitis because of concern over missing infections that are due to pathogens that are difficult to culture, and because many apparently uninfected patients appear to respond to treatment. Most treatment studies have been poorly designed, but several, including randomized controlled trials, note improved symptoms in ~50% of patients with CP/CPPS treated with a fluoroquinolone [50]. In one study, however, patients with CP/CPPS who had received multiple prior treatments (including treatment with antimicrobials) had similar symptom response rates (20%–30%) after 6 weeks of therapy with either fluoroquinolones or placebo [23]. In the subset of patients who had been symptomatic for a shorter duration and had not recently received antibiotics, the response rate was as high as 75% [23]. One prospective study involving men with CP/CPPS found that the percentage of patients who responded to antibiotic therapy was similar for those with and those without bacterial prostatitis [3]. This may be at least partly related to the fact that some antibiotics (eg, macrolides and tetracyclines) have direct anti-inflammatory effects.

There is no validated test of cure for bacterial prostatitis. If the patient's symptoms resolve after therapy, we would usually not treat asymptomatic bacteriuria, if present. If symptoms that are thought to be related to prostatitis persist, culture-directed antibiotic therapy with a more prolonged course, higher dosage, or different agent should be considered.

To interrogate the literature on the possible value of antibiotic therapy for chronic prostatitis (bacterial or presumed nonbacterial), we identified studies published in the previous decade that reported rates of either symptom improvement or microbiological eradication (Table 4). All but 1 of the studies used an oral fluoroquinolone for treatment of at least some of the patients, and the duration of therapy was typically ~4 weeks; the comparator arms varied. In all 8 trials involving patients with CBP, the patients experienced significant symptomatic and microbiological improvement (usually defined by improved prostate symptom scores and infection eradication) with antibiotic therapy. Of the 5 trials that involved patients with CP/CPPS treated with antibiotics, 2 showed no advantage for fluoroquinolone therapy over placebo. Thus, these studies show clear benefit from fluoroquinolone therapy for CBP but not for CP/CPPS.

Older studies have shown that longer (≥6 weeks) duration of therapy with trimethoprim-sulfamethoxazole for probable CBP is more effective than a shorter duration of therapy. Outcomes in treating CBP with trimethoprim-sulfamethoxazole, however, are not as good as those with fluoroquinolones [51]. Our recommendations for treatment of ABP and CPS are shown in Table 5. A single, limited (<6-week) course of antibiotic therapy may be appropriate for some patients with CP/CPPS patients but repeated courses are not.

Because antibiotics are not helpful for most cases of nonbacterial prostatitis, many nonantibiotic agents and procedures have been recommended, most of which are inadequately studied. Recently published expert recommendations, based on data from prospectively designed, randomized, placebo-controlled trials that enrolled a well-defined population of men with CP/CPPS and employed the NIH-CPSI, offer some guidance [50]. Adding an alpha blocker to antibiotic therapy appears to improve symptomatic outcomes, especially for patients with newly diagnosed disease and patients who are alpha blocker naive [52], but there is no support for 5-alpha reductase inhibitor therapy. Anti-inflammatory drugs are rarely effective alone but may help some patients as part of multi-modal therapy. There is no definitive evidence of efficacy for most other conventional or alternative medications [52]. Few controlled trials support various non-pharmacological treatments, such as repetitive prostatic massage, physical therapy, acupuncture, biofeedback, or local heat [53]. In a well-designed systematic study, no more than one-third of patients with CP/CPPS had even modest improvement during 1 year of follow-up [54]. Finally, no surgical procedure, whether minimally invasive or more extensive, has proven to be effective for treating prostatitis [53].

CONCLUSIONS

Considering the high prevalence of symptoms attributed to prostatitis and the many studies conducted during the past 50 years that have attempted to define its causes and optimal treat-

ments, it is surprising how little we know about this syndrome. Although bacterial prostatitis constitutes a small minority of cases, we now have good data on the causative pathogens and a better understanding of the most appropriate antimicrobial treatment regimens. Fluoroquinolones are currently the major weapon in our therapeutic arsenal, but growing resistance to these agents will require that we find others that adequately penetrate the prostate (and are perhaps active in the presence of biofilm) to effectively treat CBP. Moving this "stuck" field forward will require developing accurate diagnostic tests to differentiate bacterial prostatitis from nonbacterial syndromes and new antimicrobials that demonstrate efficacy in properly designed clinical trials.

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