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(Mis)-Diagnosis and (Mis)-Management of Prostate Infections

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to describe the clinical classification of prostatitis according to the National Institutes of Health, as well as appropriate management based on NIH category. The participant will be able to select appropriate antibiotic regimens based on clinical scenario and describe when not to treat with antibiotics, as well as explain the prostate microbiome and its role in physiology and pathology. Finally, the participant will be able to recognize non-index cases that may require evaluation for fungal or viral causes.

This AUA Update aligns with the American Board of Urology Modules on Impotence, Infertility, Infection and Andrology and Core/General Urology. Additional information on this topic can be found in the AUA Core Curriculum section on Urologic Infections.

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OVERVIEW

Introduction. The term "prostatitis" represents a constellation of conditions encompassing both inflammation and infection of the prostate in both symptomatic and asymptomatic states. The broad and often misused application of this umbrella term leads to significant confusion among providers regarding classification, diagnosis and management. From an epidemiological perspective, over 8% of all middle-aged men in the ambulatory setting will endorse prostatitis-like symptoms,[1] and the lifetime prevalence in some studies approaches 1 in 6.[2] Indeed, prostatitis symptoms account for 1% of all male visits to primary care physicians and 8% of all visits to urologists.[1] Despite 2 million outpatient visits per year, there exists limited high quality evidence to support management decisions, which vary widely between providers. In particular, the overuse of antibiotics in symptomatic men without objective evidence of infection often causes unnecessary morbidity and delays evidence-based treatments that may provide meaningful improvement. On the other hand, true prostatic infections are often managed inadequately, either in duration of therapy or in choice of antibiotic. The goals of this Update are to focus on the different prostatitis syndromes, and review when and how antibiotics should be used or avoided.

National Institutes of Health (NIH) prostatitis classification scheme. The late 1990s witnessed a revision in the terminology of prostatitis with the development of the NIH prostatitis classification system,[3] which categorizes men based on their presenting syndrome and laboratory workup (fig. 1). Category I (acute bacterial prostatitis) is defined as an acute urinary infection involving the prostate, usually associated with systemic symptoms. Category II (chronic bacterial prostatitis) is defined as recurrent urinary tract infection, usually with the same organism, in a man whose prostate cultures grow the same organism between symptomatic periods. Category III (chronic prostatitis/chronic pelvic pain syndrome) is characterized by symptoms in the absence of demonstrable infection and is further categorized into IIIa (inflammation present) and IIIb (no inflammation present), depending on the presence or absence of leukocytes in prostatic fluid (although admittedly this a/b subclassification has rarely been shown to impact care). Finally, category IV (asymptomatic prostatitis) represents those men without symptoms with either bacteria or inflammation typically identified on a semen analysis or prostate biopsy.

ACUTE BACTERIAL PROSTATITIS AND PROSTATIC ABSCESS

Epidemiology and etiology. While ambulatory evaluation for prostatitis symptoms is relatively common, only 4% of these visits are for ABP (NIH category I).[4] ABP represents a dramatic phenotype characterized by acute onset of both local and systemic symptoms and requiring prompt treatment to prevent clinical decompensation and severe sepsis. ***Escherichia coli* dominates as the most common organism causing acute bacterial prostatitis and accounts for over 50% of all cases.**[5,6] These particular strains carry high rates (up to 100%) of expression of virulence factors, such as the mannose-binding FimH gene,[7] which allow these pathogens to escape host defense mechanisms and generate a clinical infection even in the absence of host risk factors. Other causal agents include *Proteus, Enterococcus, Pseudomonas* and *Staphylococcus aureus*. In contrast to reports from over a century ago, sexually transmitted diseases now constitute a very small (1%) proportion of cases.[8]

Risk factors for ABP. Risk factors for the development of ABP can be broadly categorized into 3 main groups. First, an immunocompromised state due to immunosuppression for organ transplant[9] or AIDS[10] can predispose men to prostatitis. Second, structural or functional issues such as urinary reten-

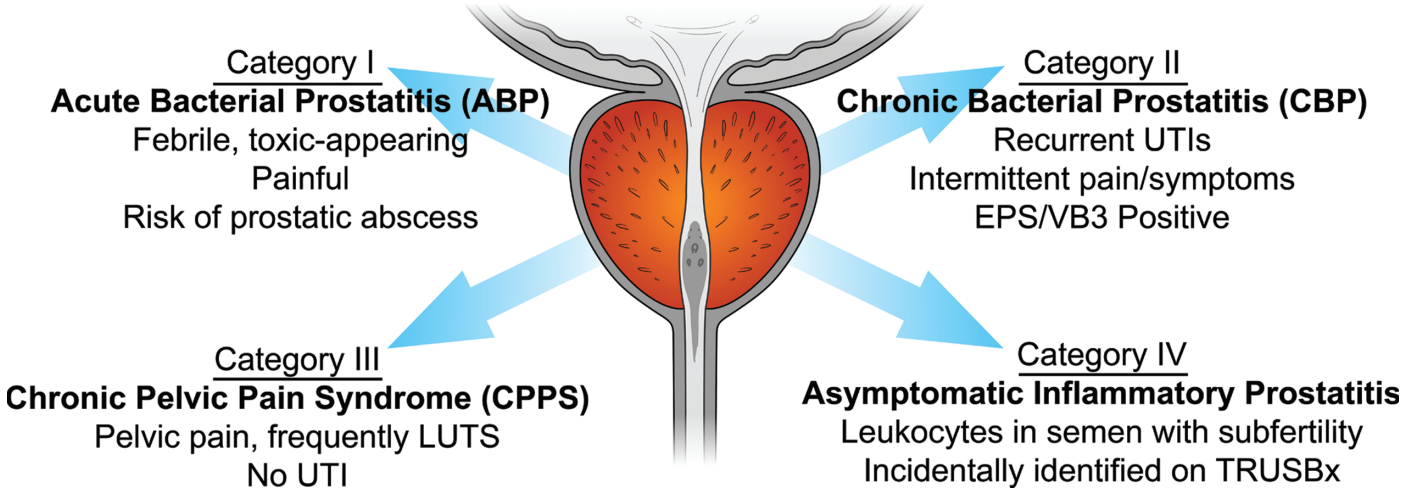

Figure 1. Brief description of each NIH category of prostatitis. *TRUSBx*, transrectal ultrasound-guided prostate biopsy.

ABBREVIATIONS: ABP=acute bacterial prostatitis, AIDS=acquired immunodeficiency syndrome, CBP=chronic bacterial prostatitis, CP=chronic prostatitis, CPPS=chronic pelvic pain syndrome, EPS=expressed prostatic secretions, HIV=human immunodeficiency virus, LUTS=lower urinary tract symptoms, MRI=magnetic resonance imaging, NIH=National Institutes of Health, UTI=urinary tract infection

tion or stasis are also a significant risk factor. Finally, men who have undergone recent urinary tract instrumentation are at increased risk for prostatitis and accompanying sepsis. Perhaps the best described form of post-procedural genitourinary infection is iatrogenic ABP following transrectal ultrasound-guided prostate biopsy. Over 1 million biopsies are performed annually in the U.S. alone,[11] and transient bacteremia has been shown to occur in 100% of men without antibiotic prophylaxis and 50% of men with antibiotic prophylaxis.[12] Driven largely by the rising rates of fluoroquinolone resistance,[13] the rate of clinically relevant infectious complications is increasing and is currently approaching 5%.[14] A thorough discussion of post-prostate biopsy infection is beyond the scope of this Update, and readers are referred to the recent White Paper by American Urological Association/Society of Urologic Nurses and Associates on this topic for further information.[15] Other procedures shown to be associated with post-procedural ABP and abscess formation include SpaceOAR™ hydrogel rectal spacer placement (Boston Scientific, Marlborough, Massachusetts)[16] and prostate artery embolization.[17]

Presentation. Most men who develop ABP are in the 5th to 7th decade of life and report perineal pain, dysuria, difficulty urinating with or without acute urinary retention (50%–96%) and systemic signs such as malaise or fever (34%–92%).[5,8,18] Examination will reveal a painful prostate on digital rectal examination in the majority (60%–90%) of men with ABP[8,18] and should be performed gently (ie without massage) to minimize risk of bacterial translocation and bacteremia.

Diagnosis. Initial evaluation of the man with suspected acute bacterial prostatitis should include a complete blood chemistry to assess for leukocytosis, urinalysis to assess for pyuria and bacteriuria, and urine and blood culture collection prior to initiation of antibiotics. Nucleic acid amplification tests for gonorrhea and chlamydia can be performed in the presence of risk factors. **There is no role for measurement of prostate specific antigen in the setting of suspected acute infection, as it is uniformly elevated and takes approximately 1 month to normalize following acute infection.[19]** Imaging to establish the diagnosis of ABP in an index patient may not be necessary. In patients who do not rapidly improve with therapy or where abscess is suspected, transrectal ultrasound, computerized tomography or magnetic resonance imaging may provide the diagnosis.

Initial management. Hospitalization is indicated in patients who appear toxic, are immunosuppressed or are at high risk for decompensation. Despite the relatively high incidence, there exists a significant heterogeneity in management.[8] A recent descriptive study by Etienne et al demonstrated significant heterogeneity among providers (particularly across different clinical specialties, including urology, internal medicine, infectious diseases and geriatrics) in the diagnosis and management of ABP in the inpatient setting.[8] They showed that age, history of urinary catheter, *Pseudomonas* infection and inadequate empirical antibiotic coverage were all associated with incomplete clearance on follow-up cultures. Assessment of urinary retention or residual is required, and bladder drainage should be strongly considered in acutely ill patients. While traditional teaching has advocated for up-front placement of a suprapubic catheter, there is minimal evidence to support the superiority of this strategy over placement of a urethral catheter if technically feasible and well-tolerated. Initiation of an alpha blocker may provide symptomatic relief as well as improved emptying.

Antibiotic selection. The choice of initial empirical broad-spectrum coverage and subsequent culture-directed therapy should be guided by 1) historical data suggesting *E. coli* as the most common pathogen, 2) local antibiograms, 3) patient-specific factors such as recent antibiotics treatment or allergies, and 4) the need for sufficient prostatic penetration (table 1). Prostatic penetration is multifactorial and correlates with increased lipid solubility, a high acid dissociation constant (pKa) and a small molecular weight.[20] Driven by these factors, the most commonly prescribed empirical regimen is often oral or parenteral fluoroquinolones (table 2).[8] Aminoglycosides and/or 3rd generation cephalosporins are also commonly used. Roughly 1 in 6 empirical regimens are proven to be inappropriate based on culture and sensitivity results,[8] supporting the need for vigilance in collection of initial urine culture and monitoring culture results in the early treatment period. Tempering enthusiasm for the class, fluoroquinolones now hold a black box warning for tendonitis. Fluoroquinolone resistance remains a significant problem in the modern era, although it appears that the rate of fluoroquinolone resistance in spontaneous ABP may be lower than cases of post-prostate biopsy infection.[21] Case reports have also demonstrated efficacy of tigecycline in multidrug-resistant *E. coli* prostatitis.[22] **Preliminary data have also suggested that fosfomycin may provide sufficient coverage and prostatic penetration for treatment of both acute and chronic prostatitis.[23]** Interestingly, this medication has shown good coverage against even difficult-to-treat organisms such as methicillin-resistant *S. aureus* and gram-negative organisms with extended-beta-lactamase activity.[24] **Duration of treatment (either oral or parenteral) should be at least 2 weeks and up to 4 weeks pending clinical course[25] to allow for sufficient prostatic penetration.**

Table 1. Oral antibiotic options for prostatitis based on spectrum of coverage

Class	Oral Antibiotic	Gram Negatives: Chlamydia	E. coli	Klebsiella	Mycoplasma	Neisseria	Proteus	Pseudomonas	Ureaplasma	Gram Positives: Enterococcus	Staphylococcus	Streptococcus	Side Effects
3rd Gen Cephalosporins	Cefdinir, Cefixime	▨	■	▨	▩	▨	■	▩	▩	▩	▨	■	Poor prostatic penetration
Fluoroquinolones	Ciprofloxacin, Levofloxacin	▨	▨	■	▨	▩	▨	▨	▩	▩	▨	▨	Black box warning tendinitis, risk of aneurysm rupture
Macrolides	Azithromycin	■	▨	▩	■	■	▨	▨	■	▩	▨	■	Arrythmias, diarrhea
Sulfonamides	Trimethoprim-Sulfamethoxazole	▨	▨	■	▩	▨	▨	▩	▩	▩	■	▨	Rash, hyperkalemia
Tetracyclines	Doxycycline	■	▩	▩	■	■	▩	▩	■	▩	■	▨	Sun sensitivity, GI upset
Other	Fosfomycin	▩	■	■	▩	■	■	▨	▩	■	■	■	Diarrhea, headache, rash

■ Adequate coverage ▨ Use with caution ▩ Not recommended

Green cells indicate appropriate coverage, yellow cells indicate increasing levels of resistance or intermediate coverage, and red cells indicate high levels of resistance or intrinsic resistance.

Complications. Once appropriately treated with resuscitation and antibiotics, most men recover uneventfully. Patients with overt bacteremia and sepsis may develop multiorgan system failure and require extensive supportive care in the intensive care unit. Rarely, the infection may spread unexpectedly and cause severe sequelae, such as epidural abscess, which requires aggressive management.[26] If the patient fails to improve, consider imaging to assess for prostatic abscess.[27] **Roughly 1% of men with ABP will progress to category II CBP, and an additional 10% may develop category III inflammatory CPPS.[28]**

Prostate abscess. Prostate abscess occurs in roughly 20% of men with ABP.[29] Risk factors appear to include longer duration of symptoms and urinary retention.[29] Similar to ABP in general, men who develop abscess typically have *E. coli* as their causative agent.[6] Presentation is quite similar to ABP, including pain with digital rectal examination, fevers and leukocytosis. While the diagnostic accuracy of transrectal ultrasound approaches 100%,[30,31] computerized tomography or MRI provides additional anatomical information regarding the periprostatic tissue. MRI may be particularly useful at the early stages. The decision to escalate intervention beyond medical management depends primarily on abscess size, but no guidelines currently exist regarding the optimal management strategy. Prior studies have proposed 1–3 cm cutoffs,[29] but this remains poorly supported by data. Approaches to management include percutaneous drainage and surgical intervention.[32] Percutaneous drainage can be accomplished via transrectal aspiration,[31] which offers familiarity and a success rate of 42%–83%[31,33] but with the added theoretical risks of seeding the cavity with rectal flora and increasing risk of fistula formation. Transperineal[34] and transvesical[35] drainage has also been reported, but long-term success rates are unknown for these approaches. Transurethral surgical drainage can be accomplished using traditional electrosurgical[32] or holmium laser.[36] There is currently scant evidence supporting one of these approaches over the other. A recent systematic review summarized a total of 210 cases and found a higher recurrence rate with aspiration compared to surgery.[32] A recent small prospective randomized study supported these findings.[37] **Taken together, this limited evidence suggests that transurethral intervention offers the highest rate of success but at the cost of increased morbidity.**

CHRONIC BACTERIAL PROSTATITIS

Introduction. Category II (chronic bacterial prostatitis) is characterized by recurrent UTIs of the same organism interspersed with asymptomatic periods or documentation of urinary clearance.[3] Importantly, prostatic secretions during these asymptomatic periods should demonstrate the same causal organism, suggesting a prostatic source. CBP is less common and accounts for less than 10% of all outpatient visits for prostatitis.

Etiology. E. coli again dominates the microbiological landscape and is responsible for over 85% of cases in most series.[38] Numerous other potential organisms have been identified including *Enterococcus, Proteus, Klebsiella, Pseudomonas, Staphylococcus, Streptococcus, Mycoplasma, Neisseria, Chlamydia* and *Ureaplasma*, but it remains unclear whether these represent causality or merely innocent bystanders (particularly the gram-positives).[39] Biofilms, which are bacterial communities organized within an adherent polysaccharide matrix, appear to play a significant role. Organisms causing prostatitis appear to be more adept at biofilm creation than those causing cystitis or pyelonephritis,[40] and biofilms are notoriously resistant to antibiotic penetration and treatment.[41] At present, beyond merely extending the duration of antibiotics, this finding remains difficult to directly integrate into clinical management algorithms.[41]

Presentation. Men with CBP typically present with a history of discrete episodes of irritative or to a lesser extent obstructive lower urinary tract symptoms and/or dysuria or perineal/testicular pain punctuated by asymptomatic episodes. Diabetes and recent urinary tract instrumentation appear to be risk factors for this conversion.

Diagnosis. Following a thorough history, a genitourinary examination should be performed to assess for external genital abnormalities such as phimosis or meatal stenosis and assess for epididymo-orchitis. A digital rectal examination should be performed to assess prostate tenderness, size and abnormalities. The pelvic floor should also be assessed to identify men with pelvic floor spasm, who may benefit from pelvic floor physical therapy. There is little role for up-front imaging, cystoscopy and/or urodynamics in men with suspected CBP. Uroflow and/or post-void residual measurement can assess for urinary retention. Traditionally, the Meares-Stamey 4-glass test was considered the diagnostic tool of choice for CBP.[42] The initial urethra-predominant urine (VB1) is collected, followed by a midstream voided urine (VB2). The prostate is then massaged, and expressed prostatic secretions are collected. Finally, a post-massage urine sample is collected (VB3). The diagnosis is made when bacteria is isolated to EPS/VB3 or when colony counts are at least tenfold higher than VB1/VB2. **The simplified 2-glass test consisting of pre- and post-prostatic massage urine specimens has now been shown to yield accurate results for diagnostic purposes.[43]**

Management. Antibiotics represent the backbone of initial treatment for NIH category II CBP. Due to high lipid solubility and acidic conditions, delivery of antibiotics into the prostatic stroma requires an antibiotic with high pKa and lipid solubility. These include quinolones, macrolides, sulfas, tetracyclines and fosfomycin. As with ABP, fluoroquinolones are often first-line treatment, with no major advantage to any specific drug in the class (table 2).[44] **This class, however, remains plagued by concerns regarding increasing levels of resistance, QT prolongation, tendinitis and aneurysm rupture.** If an atypical (eg chlamydial) infection is proven, macrolides such as azithromycin are a better choice.[44] For a thorough discussion of all available agents with good tissue penetration, the reader is referred to the recent article by Lipsky et al.[25] There are no evidence-based guidelines regarding the duration of antibiotic treatment for CBP.[44] Most providers recommend treatment for 4 to 6 weeks with assessment of clearance after therapy, given the modest prostatic penetration, and to treat any biofilm-causing organisms that may be present. Using this duration of treatment, culture-proven "cure" can be demonstrated in up to two-thirds of patients,[45] although relapses are quite common.

Role of alpha blockade. While modest, there is some evidence to suggest that alpha blockade can improve symptoms of CBP.[46] Data from animal literature have suggested that alpha blockade may actually improve the efficacy of antibiotic therapy in ABP via increasing antibiotic concentration in the prostate.[47] Given the minimal morbidity associated with these medications, it seems prudent to either initiate or continue treatment with alpha blockers in conjunction with antibiotics for CBP.

Table 2. Antibiotic regimens for each category of prostatitis

Chronicity	Symptoms	NIH Category	Condition	Indication for Antibiotics	First Line Antibiotic Treatment Regimens	Duration	Adjunct Therapies
Acute	Symptomatic	1	Acute bacterial prostatitis	All patients	Ciprofloxacin/levofloxacin Piperacillin Tazobactam 3rd generation cephalosporin Fosfomycin	2-4 weeks	Abscess drainage Catheterization
Chronic	Symptomatic	2	Chronic Bacterial Prostatitis	Symptomatic patients	Fluoroquinolone Trimethoprim Sulfamethoxazole	4-6 weeks	Alpha blockers Prostate massage Surgery
	Symptomatic	3	Chronic Pelvic Pain Syndrome	Not routinely recommended	n/a	n/a	Multimodal therapy UPOINT
	Asymptomatic	4	Asymptomatic Inflammatory Prostatitis	Subfertility Leukocytospermia	Doxycycline Trimethoprim-sulfamethoxazole	2 weeks	N/a

N/A=not available.

Prostatic massage. In addition to antibiotics, prostatic massage may also be considered. This topic is the subject of one of the few prospective randomized studies in prostatitis.[48] The study enrolled 81 patients with category II or IIIa prostatitis and randomized them into antibiotics plus prostate massage versus antibiotics alone. The investigators found no major differences between groups. Other prospective studies, however, have demonstrated some effects.[49,50] The reader is referred to a systematic review for further discussion of this topic.[51]

Treatment failure. **In cases of refractory infection or as first-line treatment in men with drug-resistant organisms, fosfomycin has been shown to demonstrate adequate prostate penetration[23,52] and is capable of meeting both microbiological clinical end points for cure.**[53] This drug has also been combined parenterally with cefoxitin with reasonable response rates at the cost of requiring intravenous access and continuous outpatient infusion.[54] In cases with relapse, chronic antibiotic suppressive therapy via long-term low-dose antibiotics (eg single pill 2–3 times per week) or alternatively intermittent self-start antibiotics for symptomatic flares has also been employed, although at present the data for this approach are severely limited and this strategy may exacerbate antibiotic resistance patterns. Finally, a recent report has shown that men with CBP and prostatic calcifications experience worse symptom burden than those without calcifications, regardless of bacterial clearance.[55]

Surgical management for refractory CBP. Historical work advocated for the role of transurethral resection of the prostate[56] in men with chronic prostatitis as early as 1973. Subsequent studies have replicated these results in small uncontrolled series using either subjective or validated (via NIH Chronic Prostatitis Symptom Index) end points, with "cure" reported in roughly 70% of these men.[57] Care must be taken in interpreting these results, however, as none of these studies included a control group. Finally, radical prostatectomy is occasionally indicated in highly selected patients with category II CBP and multidrug-resistant infections requiring frequent admission and intravenous antibiotics, and whose infectious source can be definitively localized to the prostate. In our experience, men with incomplete emptying, significant prostatic stone burden and/or recurrent multidrug-resistant infections appear to have the highest rate of success with surgical intervention (fig. 2).

CHRONIC PELVIC PAIN SYNDROME

Chronic pelvic pain syndrome, categorized as NIH category III prostatitis, represents a biologically distinct entity characterized by pelvic symptoms in the absence of objective evidence of infection. For the purposes of this Update, we will focus exclusively on the role of antibiotics in CPPS. Logically, the role of antibiotics in a clinical entity defined by an objective lack of infection would be null, and indeed 2 small randomized controlled trials using ciprofloxacin[58] and levofloxacin[59] failed to show benefit over placebo. Despite these findings, antibiotic usage in this context remains high, and other reports including a network meta-analysis did indeed show a modest benefit to antibiotic therapy.[46] A growing body of literature, however, now supports the indirect effect of antibiotics such as fluoroquinolones as anti-inflammatory agents[60] via downregulation of cytokines such as tumor necrosis factor-alpha in response to inflammatory stimulus.[61] This, coupled with the common finding that men with CPPS treated with antibiotics often report symptoms return rapidly within days of treatment cessation, supports the hypothesis that this benefit is inflammatory and not infectious in nature. **Within the context of shared**

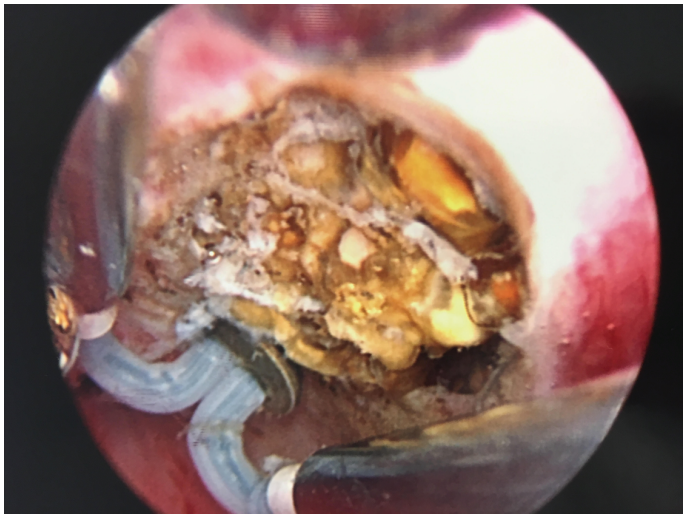

Figure 2. Representative image of young patient with 18 gm prostate, recurrent UTIs and significant prostatic stone burden who underwent transurethral removal with resolution of symptoms.

decision-making, it is reasonable to trial a single course of fluoroquinolone therapy in antibiotic-naïve or diagnostically complex patients, but repeated courses of antibiotics should be avoided. Patients refractory to antibiotics should be managed according to the widely adopted multimodal phenotype-driven UPOINT[62] (urinary symptoms, psychosocial dysfunction, organ-specific findings, infection, neurologic/systemic and tenderness of muscles) treatment approach.

ASYMPTOMATIC INFLAMMATORY PROSTATITIS

In contrast to NIH category I–III prostatitis, category IV represents asymptomatic men incidentally found to have leukocytes on prostate biopsy or semen analysis. Given the high prevalence of leukocytospermia in subfertile men, the role of treatment in this specific subpopulation remains contentious. Prior work has demonstrated that these men have increased bacterial (particularly anaerobic) concentrations compared to controls,[63] but the evidence linking bacteriospermia and leukocytospermia remains mixed.[64] Regardless of underlying etiology, the presence of leukocytes in the ejaculate clearly increases seminal oxidative stress and impairs fertility. There is some evidence that empirical antibiotic treatment (eg doxycycline 100 mg twice daily for 3 weeks) improves semen analysis parameters and paternity[65] but the evidence remains weak[66] and further work in this area is clearly needed.

ROLE OF THE MICROBIOME AND NEXT-GENERATION SEQUENCING

Prostate microbiome. Recent technological advances in the areas of high throughput genomic sequencing and bioinformatics analysis have enabled the identification of the microbiome, which is the resident microbiological community in a specific niche. The urological microbiome has been associated with numerous disease states, including bladder cancer,[67] prostate cancer,[68,69] infertility,[70] LUTS[71] and numerous other conditions. Recent studies have also shown that the urinary microbiome in men with CP/CPPS is more highly diverse, with significant differences at the species level[72] compared to healthy controls. Wu et al sequenced the EPS in 30 men with NIH category III CPPS and 30 healthy men, and found no identifiable pathogenic cause of symptoms.[73] In contrast, work by our group has identified numerous taxonomic differences between men with CP/CPPS and healthy controls.[74] Based on inference of functional pathways via taxonomic inference, this work also identified several pathways, including sporulation, chemotaxis and pyruvate metabolism as future diagnostic and therapeutic targets. A complementary study investigating the role of the gut microbiome in CPPS also showed significant differences.[75] Whether these differences represent correlation or causation remains, however, to be proven. Indeed, follow-up work investigating the microbiome of EPS has failed to localize these differences to the prostate or to identify symptomatic improvement with directed antibiotic therapy.[76] **Taken together, these data suggest that correlation may not imply causation, and support caution regarding the use of next-generation sequencing in clinical decision-making in CP/CPPS until more nuanced mechanistic studies can be performed.** Furthermore, future integration of this evolving area of research within the existing NIH framework must be done in a thoughtful and clinically oriented fashion.

OTHER, LESS COMMON INFECTIONS OF PROSTATE

Granulomatous prostatitis. While the phenomenon has been reported previously, Butel and Ball recently described the high (>80%) prevalence and anatomical distribution of granulomatous changes in the prostate following treatment of bladder cancer with bacillus Calmette-Guérin.[77] Using whole-mount specimens, the group showed preferential localization to the peripheral zone. This finding is consistent with reports describing the striking similarity of bacillus Calmette-Guérin prostatitis to prostate cancer in several imaging modalities including MRI,[78] and underscores the importance of placing imaging results in clinical context prior to procedural or surgical intervention. Treatment for this condition is typically conservative until more aggressive measures are clinically warranted.[79]

L-form bacteria. Numerous bacteria have the capability of forming wall-deficient variants, or L-forms, which may play a role in recurrent or chronic infection. Several recent elegant studies have identified the mechanistic basis behind the rapid cell division seen in L-form bacteria and implicate this entity in recurrent UTIs.[80,81] Further work is needed to understand whether these play a role in the pathogenesis of prostatitis.

Fungal prostatitis. In contrast to bacterial prostatitis, fungal prostatitis appears to be an uncommon entity. Several case reports thus far have described fungal prostatitis due to candida,[82] coccidioides,[83] aspergilla,[84] blastomyces,[85] cryptococcus[86] and paracoccidioidodes.[87] The largest published series to date by Epstein et al collected 15 cases across 3 institutions.[88] The majority of patients were symptomatic with LUTS, and nearly all had favorable outcomes with prolonged treatment (typically fluconazole for several months). Fungal infection should be considered in men refractory to initial therapy and in endemic areas corresponding to each of the above organisms, and should be treated with assistance from an infectious disease expert.

Viral prostatitis. Similarly, viral prostatitis appears to be rare. Infection has been reported with cytomegalovirus almost uniformly in immunosuppressed patients (eg HIV/AIDS,[89,90] solid organ transplant[91] or malignancy[92]). Adenoviral prostatitis has been reported in an AIDS patient as well.[93] Zika virus, responsible for a 2016 outbreak and causing developmental defects including microcephaly, appears to cause histological prostatitis in rodent and non-human primate models[94] and can be transmitted via intercourse. Zika appears to replicate in human prostate stromal cells,[95] but it is unknown whether this causes a clinical prostatitis phenotype in men.

Prostatitis and SARS-CoV-2. The role of the SARS-CoV-2 virus, which is responsible for the COVID-19 pandemic, in the setting of the human prostate remains poorly understood. It is known that male sex is a risk factor for complications from the disease, and evolving data suggest that differences in androgen signaling may be partially responsible for this phenotype.[96] Early work has failed to identify a linkage between acute SARS-CoV-2 infection and male LUTS as measured by International Prostate Symptom Scale score.[97] The possibility of genitourinary transmission of SARS-CoV-2 remains contentious. A contemporary study by Ruan et al evaluated

urine, semen and EPS from men who had recovered from mild to moderate disease at a median of 80 days prior to specimen collection.[98] **None of the participants reported symptoms characteristic of prostatitis, and none of the genitourinary samples tested positive for SARS-CoV-2 by RT-PCR.** Further work is undoubtedly ongoing and will hopefully shed light on the role of the genitourinary system in this deadly disease.

CONCLUSIONS

Prostatitis is a family of 4 distinct and usually unrelated syndromes, ranging from asymptomatic to critical illness, and from sterile to florid infection. While the field has made tremendous advances in the past several decades, there is still much work to be done to better understand this disease process and develop data-driven treatment approaches. When a true infection is identified, antibiotic therapy needs to be driven by cultures, sensitivities and biological features of the antibiotic. In the absence of infection, antibiotics may give temporary symptomatic relief, but there is no evidence that prolonged antibiotic therapy in category III is effective.

DID YOU KNOW?

- The NIH prostatitis classification system provides a reproducible evidence-based approach to characterize men with prostatitis based on acuity, symptoms and laboratory values.
- Antibiotic treatment of appropriate duration is indicated for acute bacterial prostatitis (NIH category I) and chronic bacterial prostatitis (NIH category II). A single course of empirical antibiotics may be beneficial in category III or category IV prostatitis, but repeated use of antibiotics should be avoided.
- Prostatitis workup requires a careful history, thorough physical examination including digital rectal examination and urinary studies including 2-glass test when indicated.
- Fluoroquinolones should be used with caution given the black box warning for tendonitis and concerns for aneurysm rupture.

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Study Questions Volume 40 Lesson 28

1. The NIH classification scheme for prostatitis categorizes men based on their:
   a. acuity of presentation and presence or absence of infection and inflammation
   b. prostate size and induration on digital rectal examination
   c. prior response to antibiotic treatment
   d. age and comorbidities

2. A 34-year-old man is seen with frequency, urgency, dysuria and perineal pain. He has been diagnosed with "prostatitis" twice in the emergency room and each time was treated with ciprofloxacin for 2 months, despite negative voided urine cultures. He has had some improvement while on antibiotics. He has now been off of antibiotics for 3 weeks and is again symptomatic. A 2-glass test reveals no white or red blood cells on the first urinalysis, 10–20 WBC/hpf on the post-prostatic massage urine, and negative pre- and post-prostatic massage cultures. The patient's diagnosis is:
   a. category I (acute bacterial prostatitis)
   b. category II (chronic bacterial prostatitis)
   c. category IIIa (chronic prostatitis/chronic pelvic pain syndrome—inflammation present)
   d. ategory IIIb (chronic prostatitis/chronic pelvic pain syndrome—no inflammation present)

3. A 52-year-old man with obstructive and irritative voiding symptoms is diagnosed with category II prostatitis on a 2-glass test. His post-void residual is 35 cc with a bladder scanner. The recommended treatment is culture-specific antibiotic treatment and:
   a. sitz baths
   b. prostatic massage
   c. an alpha blocker
   d. a 5α-reductase inhibitor

4. The commonly accepted duration of antibiotic therapy for acute bacterial prostatitis is:
   a. 7–10 days
   b. 2–4 weeks
   c. 6–8 weeks
   d. 10–12 weeks

5. Most cases of viral prostatitis are associated with:
   a. immunosuppressed state
   b. recent antibiotics
   c. prostate cancer
   d. pandemics