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Volume 15, Supplement 1, August 2008

GUEST EDITORIAL

Primary Care Physicians and Urologists - Partners in "Shared Care"

The "Urology Update for Primary Care Physicians 2008" supplement to the current issue of The Canadian Journal of Urology (CJU) provides a timely and succinct overview of common urologic conditions encountered in primary care. The content grew out of a unique meeting hosted by the journal in Montreal, Canada, in April 2008, during which urology and primary care experts discussed areas of mutual concern, approaches to diagnosis and treatment from the primary care perspective, and "shared care" of patients with urologic disease.

The authors have admirably presented a wealth of specialized information in a user-friendly and practical manner. The topics covered address urologic conditions with a high prevalence, especially in the aging population. Primary care physicians (PCPs) are likely to see these patients before the urologic specialist and, as such, need to be comfortable with symptom recognition, initial assessment, first-line treatment, and timely and appropriate referral.

Erectile dysfunction (ED) and testosterone deficiency are easily recognizable and treatable by the primary care physician. Treatment of ED with penile implants is rarely indicated following the successful and widespread use of oral phosphodiesterase inhibitors (sildenafil, vardenafil, and tadalafil). The overlap of testosterone deficiency and metabolic syndrome is an area of emerging interest to both urologists and PCPs.

Overactive bladder (OAB) (frequency, urgency with or without urge incontinence), interstitial cystitis/painful bladder syndrome (IC/PBS), and stress urinary incontinence (SUI) are common diseases of the lower urinary tract. Although there is no pharmacologic treatment for SUI, an understanding of its basic pathophysiology will help the PCP to recognize symptoms and initiate patient weight loss and pelvic floor exercises before urologic referral. OAB and IC/PBS respond to pharmacologic, behavorial, and holistic treatment approaches and rarely require surgical intervention.

Benign prostate hyperplasia (BPH) and prostate cancer (PCa) are highly prevalent in aging baby boomers. The use of alpha blockers and 5 alpha-reductase inhibitors has made BPH more of a "medical" disease with less need for surgical intervention (transurethral resection, prostatectomy, or minimally invasive surgery) than before. The widespread use of the serum prostate specific antigen (PSA) test as a prostate cancer screening tool — albeit a somewhat imperfect tool — has resulted in the PCP and urologist being involved in earlier diagnosis and treatment counseling. Earlier diagnosis and treatment notwithstanding, some men will develop hormone-refractory prostate cancer (HRPC) following androgen deprivation therapy (ADT) and will require palliation for bone pain and chemotherapy to help prolong survival.

Hematuria can be a harbinger of significant urinary tract pathology (stones, kidney/ureter/bladder cancers) and a simple assessment by urinalysis, cytology, and genitourinary tract radiologic imaging is within the capability of the PCP prior to referral to a urologist for cystoscopic evaluation. Pharmacological treatments are the mainstay of treatment for the majority of conditions discussed in this supplement, and the article on uropharmacology provides an excellent review of commonly used drugs including their mechanisms of action, side-effects, and dosing.

This supplement highlights symptom recognition, "focused" primary care assessment, initial treatment, and indications for urologic referral, and provides brief descriptions of surgical, oncological, and minimally-invasive treatments. The references are up to date, and the tables, algorithms, and take-home message sections summarize the key take-away points for the PCP. The questions from the PCP at the end of each article add to the practical utility of the contributions.

The publishers and Editorial Board of the CJU are to be congratulated on their foresight in publishing this supplement. Primary care physicians should find it to be practical, informative, and relevant. The "shared care" approach espoused by the authors should improve the care and quality of life of patients with urologic conditions.

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GUEST EDITORIAL

Keep it Simple, Effective, and Safe

It is unfortunate that the study of urological disease is not a mandatory requirement in the training of primary care physicians (PCPs) in either the United States or Canada. The prevalence of urological problems facing PCPs such as ourselves that are identified in this supplement is high, yet adequate clinical awareness by PCPs of ways to evaluate and manage patients with urological disease is often low. In addition, in a busy primary care practice, patients' urological complaints can often be underrated and treated as mere "quality of life" issues, possibly due to a false perception that such medical problems are not potentially associated with high morbidity/mortality. That being said, there is a tremendous opportunity for the PCP to make a difference in both the quality of life and, in some cases, the survival of our patients.

Such urological training is often unavailable in primary care resident-training programs. The solution to this shortcoming lies in continuing education. We were undeniably pleased when approached by The Canadian Journal of Urology (CJU) to take on the role of special editors for what is believed to be the first such journal supplement devoted to this crucial topic. The forward-thinking CJU publishers and members of the editorial board are to be commended for initiating and following through on this project.

In planning this supplement, our goal became one of bridging the gap between the PCP and the urologist. This supplement is based on presentations and in-depth discussions at a consensus development conference, "Urology Update for Primary Care Physicians 2008," which was held this past April 12th in Montreal, Quebec, and which brought together leading urologists and PCPs with a special interest in urology. The exchanges between the PCPs and urologists led to a better understanding of the issues facing PCPs. The group shared information about the general needs of PCPs who practices in an office setting and about their knowledge gaps relating to medical urology topics such as prostate cancer, benign prostatic hyperplasia, overactive bladder, interstitial cystitis, hematuria, erectile dysfunction, testosterone deficiency, and uropharmacology.

We hope that we have crafted a supplement with articles that reflect what the PCP needs to know, is capable of, or has time for, in managing patients with urological diseases. Equally important, another goal of the supplement is to give the PCP a clearer sense of when to refer a patient to a urologist. Central to this, of course, is the patient's well-being. As we reviewed the articles, we challenged the authors as urology specialists to maintain the focus on what the PCP should know and do prior to possibly referring a patient to a urologist.

We believe that this boils down to three key points:

- Keep the evaluation SIMPLE.
- Keep the treatment EFFECTIVE.
- Keep the patient SAFE.

We congratulate the authors on their hard work in distilling some very complex issues and diseases down to these critical aspects. The following papers can serve as key additions to the literature about how PCPs can deal with patients who have urological diseases. The reader of this supplement will find that better knowledge of these disease states and possible treatments can make a significant difference in the lives of their patients. We hope that these well-written and comprehensive review articles will readily serve as references for years to come for the PCP's initial foray into the very exciting field of what we will now call "Medical Urology".

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Update on the diagnosis and management of prostate cancer

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LASPINA M, HAAS GP. Update on the diagnosis and management of prostate cancer. The Canadian Journal of Urology. 2008;15(Supplement 1):3-13.

Early detection of prostate adenocarcinoma (prostate cancer) through screening tests such as a serum prostate-specific antigen (PSA) test and a digital rectal examination (DRE) enables primary care physicians and urologists to offer patients a broader choice of treatments that are also more likely to provide a cure. Whether men are being over treated or over diagnosed through the widespread use of screening tests remains controversial. This review aims to provide general practitioners with a better understanding of different prostate cancer tests that can be performed and to help them decide which patients should be referred to a urologist for an ultrasound-guided biopsy.

Key Words: prostate adenocarcinoma, early cancer detection, prostate-specific antigen, digital rectal exam

Introduction

The leading type of cancer in men in the United States and Canada is prostate adenocarcinoma. It is estimated that in 2008, there will be more than 230,000 cases of prostate cancer diagnosed in the United States and more than 24,700 cases diagnosed in Canada.[1] In Canada alone, it is estimated that over 4,000 men will die of prostate cancer this year and one in eight men will develop prostate cancer during his lifetime. Recent advances in screening in the last two decades have enabled physicians to detect prostate cancer earlier and to offer different treatment options tailored to patient health status and preference. Compared to 10 years ago, prostate cancer death rates have declined by 2.9% likely due to earlier detection and better treatment. Detecting prostate cancer as an occult condition enables physicians to find a cure while the disease is still confined to the gland. Once the malignancy is locally advanced (extends beyond the prostate capsule) or metastasizes to the pelvic lymph nodes, distant organs, or bones, a cure is not considered to be attainable. Physicians have thus been strongly motivated to detect prostate cancer early. Some physicians believe that prostate cancer mortality decreases with earlier detection, but this belief has been challenged by others.

Our objective in this review is to examine the importance of early detection of prostate cancer, particularly in the setting of the office of a primary care physician. While it remains controversial about whether early detection of prostate cancer decreases

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mortality, this review aims to inform the primary care physician about the usefulness of early prostate cancer detection, and also aims to provide information that can be used to guide treatment decisions for patients who may have this fatal disease. By acquiring knowledge of the basic diagnostic protocols, treatments, and side effects, the primary care physician will be better prepared to answer questions that an anxious patient might ask.

Background

In 1986 the US Food and Drug Administration (FDA) approved the use of a prostate-specific antigen (PSA) test to monitor disease progression in patients with prostate cancer. Shortly after, many asymptomatic men with no known disease underwent PSA testing, which led to early diagnosis of early-stage tumors.[2] In 1991, Dr. William Catalona, an expert in urological cancer, presented data that demonstrated the clinical usefulness of PSA screening for early detection of prostate cancer.[3] Despite the limitations of these findings, since they came from a non-randomized study, increasingly, PSA testing came to be widely used. Questions began to arise about the long term benefit of PSA screening, however, particularly when it identified clinically insignificant disease. The debate began about the merits of screening all men to detect early prostate cancer without the proven benefit of longer survival versus the merits of evaluating only symptomatic men in whom the suspicion of prostate cancer is higher. The American Cancer Society (ACS) has maintained its stand on early detection of prostate cancer: the ACS recommends that annual serum PSA tests and digital rectal exams (DREs) be performed in all men aged 50 and older. The ACS emphasizes the need for the physician to discuss the benefits, limitations, and goals of early prostate-cancer detection.[4] In contrast, the US Preventive Services Task Force (USPSTF) has concluded that "The evidence is insufficient to recommend for or against routine screening for prostate cancer using prostate-specific antigen testing or digital rectal examination."[5] Like the USPSTF, the American Academy of Family Physicians agrees that the choice should be left up to patients and their primary care providers.

In Canada, PSA testing has not yet been established as a formal recommendation for routine screening. Despite national guidelines that do not include routine PSA screening, a recent report found that nearly half of Canadian men over age 50 have had PSA tests done.[6] Our goal is not to convince the primary care physician to choose one side or the other of this controversial issue, but rather to review the literature on early cancer detection, prevention, and the benefit of early detection.

Epidemiology

Prostate cancer is one of the leading causes of death from cancer in men.[7,8] In 2007, the National Cancer Institute (NCI) reported that an estimated 218,890 new cases of prostate cancer were identified in the United States, and it was the most diagnosed malignancy in men. The report also noted that in the same year, approximately 27,000 deaths in the United States would result from prostate cancer. Worldwide, prostate cancer is the fourth most common malignancy in men.[9] The mortality rate for prostate cancer has steadily risen over the last few decades — sharply rising in the late 1980s and peaking in the early 1990s as a result of better detection. Since then, there has been a slow decline in prostate-cancer-related deaths, which are currently estimated to be 30 in 100,000 men worldwide.

According to the 2004 NCI survey, 17.6% of white men will develop prostate cancer during their lifetimes and 4.7% will die from prostate cancer. In African American men, the incidence of prostate cancer is 1.6 times higher than in white men. Similar results were found in the 2005 ACS survey: compared to white men, African American men had a 2.4-fold higher rate of mortality from prostate cancer, and they were diagnosed with prostate cancer at an earlier age. There are no clear reasons why this discrepancy exists. Some physicians suggest that this racial difference is a reflection of differences in socioeconomic factors, while others suggest that there may be a genetic basis to this difference and aggressive campaigns to increase both awareness of prostate cancer and screening for this disease should be implemented.[10] Autopsy studies examining early prostate cancer in young patients did not reveal any statistically significant difference in factors such as cancer stage or size between white and African American men.[11]

Risk factors

Age, of course, is a well-known, significant risk factor for prostate cancer. While Sakr et al noted that precancerous lesions can be found in men younger than 40 years old,[11] the incidence of prostate cancer rises rapidly after the fifth decade of life. In fact, the rate of prostate cancer diagnosis is 100 per 100,000 men in their 50s, and rises to 600 per 100,000 men in their 60s and 1000 per 100,000 men in their 70s.[12] Genetic and environmental components have been observed in prostate cancer. One study showed that a family history of prostate cancer increases a man's

risk of prostate cancer.[13] A meta-analysis of 22 reports found that men had a 2.5-fold increased relative risk of prostate cancer if they had a first-degree relative with this disease.[14] Men who have at least three immediate family members who were younger than 55 years old when they were diagnosed with prostate cancer are said to have a "hereditary" risk of prostate cancer. About 85% of cases of prostate cancer, however, are classed as sporadic (not hereditary).[15] Prostate cancer susceptibility genes have been isolated.

African Americans have the highest risk for developing prostate cancer. White men have the next highest risk of having prostate cancer, especially if they live in a cooler climate, possibly due to decreased vitamin D levels as a result of decreased sunshine. Low vitamin D levels have been associated with higher risk of developing prostate cancer.[16] Asian men and men who live in the Pacific Island have the lowest incidence of prostate cancer.

Environmental factors such as diet (especially a high intake of polyunsaturated fat), obesity, alcohol consumption, and tobacco use have also been implicated in prostate cancer. High animal fat intake and low vegetable consumption appear to increase the risk of prostate malignancy.[17,18] Furthermore, high fat intake has been found to induce chronic inflammation due to oxidation at the cellular level. Chronic prostatic inflammation exposes the prostate to carcinogens and subsequently renders prostate cells vulnerable to genome damage.[19,20]

Exposure to sexually transmitted diseases (STDs) has also been implicated in the development of prostate cancer. Human papillomavirus (HPV) is one such STD that is believed to cause prostate cancer. Some studies cast doubt on the existence of a link between HPV infection and prostate cancer.[21,22]

The benefits of a healthy diet and physical activity have been investigated to evaluate their potential in reducing the risk of prostate cancer. Vitamins and minerals are linked to the reduction of prostate cancer; Clark et al noted a decrease in prostate cancer in men taking selenium supplements.[23] Phytoestrogens, lycopene, and vitamin E have also been shown to play a role in preventing prostate cancer; large clinical trials to examine these factors are ongoing. Sexual activity has been found to offer a protective effect.[24] Vasectomy has been shown to be weakly correlated with increased incidence of prostate cancer,[25] but this may be due to patients having more frequent interactions with urologists, which increases detection.

In recent years, more consideration has been given to evaluating the potential effects of medications for preventing prostate cancer.

Hypercholesterolemia and a high-fat diet have been linked to an increased risk of prostate cancer.[26,27] Statin medications (such as simvastatin), which are used for lowering cholesterol, have been evaluated for a potential role in preventing prostate cancer. Recently published studies from the United States and Finland (where the rates of cancer are tightly monitored in a national registry), reported that statins reduced the rates of advanced prostate cancer, but they did not reduce the overall risk of prostate cancer.[28,29] In another recent study, non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin were linked to a reduction in rates of prostate cancer.[30]

Circulating testosterone is converted to more potent androgens by 5-alpha reductase in the prostate and can have a profound effect on prostate growth. The Prostate Cancer Prevention Trial (PCPT) deserves recognition for its elaborate work on 5-alpha reductase inhibitors. In a 10-year study, finasteride (Proscar, Merck, Inc.), a type 2, 5-alpha reductase inhibitor commonly given to men with benign prostatic hypertrophy (BPH), was used to reduce the risk of prostate cancer. This study reported a 24% reduction in the incidence of prostate cancer, but this was primarily in low-grade tumors.[31] A major concern was that this trial also found an increase in high-grade tumors in trial participants, and, as a result, the use of finasteride as a cancer prevention medication was diminished. Recent studies dispute that finasteride induces higher-grade cancer. These studies suggest that this observation occurred because finasteride facilitates the detection of high-grade cancers by improving the ability of PSA tests, DREs, and prostate biopsies to detect high-grade cancers.[32-34] Dutasteride (Avodart, GlaxoSmithKline), a newer generation 5-alpha reductase inhibitor, was shown to reduce prostate cancer in short-term studies.[35,36] The ongoing Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial will provide further insights into results with this medication.

Diagnostic tests

Prior to the 1980s and the introduction of PSA testing, early detection of prostate cancer was uncommon. Because prostate malignancy generally occurs in the periphery, away from the urethra, symptoms were seldom felt by the patient. When present, symptoms could consist of lower urinary tract symptoms, bone pain, and even renal failure. Prior to the introduction of the PSA testing, diagnosis was made upon finding an abnormal DRE result. Unfortunately, by then, the malignancy was likely to be locally advanced or metastatic.

Since the widespread use of PSA testing, there has been a tremendous reduction in the incidence of advanced prostate cancer.[37] Today, most cases of prostate cancer are detected from elevated PSA levels and/or from abnormal DREs. Early detection of prostate cancer has rapidly increased. New staging parameters have been developed to predict the true extent of disease, assess prognosis, and aid in determining the best treatment options. Stage T1 prostate cancer refers to a non-palpable tumor, and T1c cancer is a subset where malignancy is detected from an elevated PSA level. T2 disease indicates a palpable tumor, and T3 disease indicates that the cancer extends beyond the prostate capsule or to the seminal vesicles.

Digital rectal examination

A DRE allows the primary care physician to examine the contour, firmness, symmetry, and presence of nodules of the prostate. A DRE is a useful screening tool to detect prostate cancer, but it can miss cancer that is confined to the prostate, so this means it misses nearly half of the cases of prostate cancer.[38] When combined with a PSA test, an accurate DRE improves the detection of prostate cancer.[39] An abnormal DRE may detect prostate cancer that is higher grade and different from that detected by PSA tests. Anatomically, the prostate is divided into different zones; the peripheral zone is the most common site of malignancy and this may be palpable, unlike malignancies in the transitional zone, which may not be palpable but can manifest as obstructive urinary symptoms.

Prostate-specific antigen tests

PSA is produced by prostatic glands and secreted into the seminal fluid, which liquefies the ejaculate. The concentration of PSA in serum (which is expressed as ng/ml) is lower than the concentration in seminal fluid. Different prostate diseases, such as cancer, BPH, and prostatitis can affect serum PSA levels. Prostate disease can alter the normal microanatomy of the prostate gland, which then allows PSA to leak freely into the serum. An elevated PSA level is not specific for prostate cancer. There is no specific threshold or "normal" PSA level that would prevent over or under diagnosis of prostate cancer, or that would detect only life-threatening cancer. Prostate cancer is rarely found in a man with a serum PSA level of less than 2.0 ng/ml. In our office, needle biopsy of the prostate is recommended for men who are younger than 60 years old and who have a serum PSA of 3.5 ng/ml or higher or certain increases in PSA velocity (discussed later).

A large study addressed the clinical implications of using PSA determinations to detect prostate cancer.[40] The investigators evaluated and biopsied men who had a serum PSA level of at least 2.5 ng/ml or an abnormal DRE. They found that using this PSA cutoff, the diagnosis of prostate cancer was higher, but the specificity was lower than by using an abnormal DRE to make the diagnosis. This study did not, however, take into account age-related or race-related PSA, or PSA velocity.

In the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial that screened over 34,000 men for prostate cancer, a diagnosis rate of 18% was found in men who had a PSA > 4.0 ng/ml.[41] Thirty-four percent of the men who had a positive DRE were diagnosed with prostate cancer. Most men with prostate cancer had stage T1 to T2 disease. There did not appear to be any difference in cancer stage among men who had an abnormal DRE and those who had PSA levels less than 10 ng/ml. Men who had serum PSA levels greater than 10 ng/ml and had a positive DRE were found to have a higher stage of cancer.

In addition to having a higher rate of prostate cancer, men older than 50 have a higher rate of BPH. BPH may result in an elevated serum PSA level. Men with BPH may have a normal DRE (but enlarged prostate) and chronically fluctuating PSA levels. When clinical exam and serum PSA findings are inconclusive, other serum tests may be used to help determine whether a biopsy is warranted.

The PSA density test was developed to help detect prostate cancer when the prostate size is increased as a result of BPH. PSA density is calculated by dividing the serum PSA level by the volume of the prostate measured by transrectal ultrasound.[42] A PSA density value above 0.15 indicates an increased likelihood that the prostate harbors malignancy.[43] It is important to note that men with BPH who are treated with a 5-alpha reductase inhibitor, such as finasteride (Proscar) or dutasteride (Avodart), have a 50% reduction in their PSA levels after 6 months of treatment. To interpret the PSA value, it needs to be adjusted for use of a 5-alpha reductase inhibitor. For example, if a patient has a serum PSA of 4 ng/ml prior to starting treatment with a 5-alpha reductase inhibitor and 1 year later he has a serum PSA of 3.2 ng/ml, this should be interpreted as being equivalent to a PSA of 6.4 ng/ml had the patient not been taking a 5-alpha reductase inhibitor.

PSA velocity, the rate at which PSA rises, is another useful indicator to determine whether a patient should undergo a prostate biopsy. To determine PSA velocity, three consecutive PSA values are obtained. For PSA values between 4 ng/ml and 10 ng/ml, an increase in

PSA velocity that is greater than 0.75 ng/ml per year suggests the presence of prostate cancer. For PSA values below 4.0 ng/ml, an increase in PSA velocity of 0.35 ng/ml per year should trigger doing a prostate biopsy.[44]

Reduction in free PSA is another test that reflects the presence of prostate cancer. Most PSA is bound to protein, but 5% to 30% remains free. When prostate cancer is present, the total amount of PSA is not increased; rather, more PSA leaks into the serum as a result of architectural changes in the prostate. PSA produced in malignant prostate cells, however, tends to bind to serum proteins, thereby lowering the amount of free PSA. A ratio of free-to-total PSA can help determine whether the prostate harbors a malignancy. The lower the free-to-total PSA ratio is, the higher the likelihood that prostate cancer is present. There is no cut-off value, although several studies have used a free PSA of 0.18 ng/ml to 0.20 ng/ml as a cut-off value, and found a 90% sensitivity for detecting prostate cancer.[45]

Besides monitoring PSA levels and performing a DRE, it has been suggested that additional tests be done to help determine whether a patient should undergo a prostate biopsy. In one study, determining the value for free PSA, in addition to performing a DRE and determining the value for total PSA, helped reduce the number of false-positive prostate cancer screening tests.[46]

Often, a primary care physician will look for a cut-off value from a single serum PSA test. As previously stated, we use certain PSA levels to prompt us to recommend that a patient has a prostate biopsy. Many studies have attempted to provide serum PSA cut-off values. Morgan et al determined the age- and race-specific reference ranges for the PSA test that provide a high specificity and sensitivity for detecting prostate cancer.[47] According to their findings, the upper limit for a normal serum PSA value for white men is 2.5 ng/ml for age 40 to 49 years and 3.5 ng/ml for age 50 to 79 years; for African American men, the upper limit for a normal serum PSA value is 2.0 ng/ml for men aged 40 to 49 years, 4.0 ng/ml for men aged 50 to 59 years, 4.5 ng/ml for men aged 60 to 69 years, and 5.5 ng/ml for men aged 70 to 79 years.

Transrectal ultrasound-guided needle prostate biopsy

Needle biopsy of the prostate is recommended when the PSA level is abnormal or a DRE demonstrates significant asymmetry, induration, or nodularity of the prostate. A histologic diagnosis is required to make the diagnosis of prostate cancer. Once it is determined that the patient needs a prostate biopsy and the patient agrees, the patient should be instructed to stop taking anticoagulants (e.g., aspirin, Plavix, non-steroidal anti-inflammatory drugs [NSAIDs], and coumadin) for at least a week prior to the biopsy. The morning of the biopsy, the patient should expect to have a cleansing enema (usually a Fleet enema). He will receive one dose of oral fluoroquinolone 30 minutes prior to the biopsy. The procedure is usually and safely done in an office setting. The patient will be taken to the padded biopsy table and placed in a lateral decubitus fetal position (lying on his side in a fetal position). An ultrasound probe about the size of an adult's thumb is placed into the rectum. The seminal vesicles are identified and lidocaine is infiltrated to where the seminal vesicles meet the prostate, to perform a local block. No general anesthesia or light sedation is required unless the patient encounters significant pain or cannot tolerate an anal probe (for example, if he has a rectal stricture or fissure). The prostate is scanned under sonography and measured. Although hypoechoic lesions may appear in the prostate, these are not specific for prostate cancer. Under ultrasound guidance, an 18-gauge needle core biopsy device is used to perform a double-sextant 12-core, extended biopsy. Additional samples may be taken if there are suspicious lesions or nodules. After all 12 core samples are obtained and sent to the pathology laboratory, the patient can return home with instructions to continue taking antibiotics for 3 more days and to avoid anticoagulants for another week. The patient may expect to see hematuria, hematochezia, and hematospermia, which generally resolve on their own. Excessive bleeding warrants further evaluation. The risk of infection is 2%, and patients generally require hospitalization for intravenous antibiotics if they develop fever or infection. Vasovagal responses occur infrequently, and the procedure may be terminated and completed at a later date. The patient returns to see his urologist in 7 to 10 days to discuss the pathology results and is evaluated for any symptoms resulting from the prostate biopsy.

Previously, needle biopsy of the prostate involved taking only sextant cores. Recently, multiple studies have consistently demonstrated that many prostate cancers can be easily missed using this method. Review of radical prostatectomy specimens by a pathologist demonstrated that most sextant needle biopsies missed a harboring malignancy elsewhere within the prostate.[48]

A more extensive biopsy method (double sextant) improved the detection of early cancer. Generally, we take 12 needle-core biopsies in a double sextant

fashion. Biopsies are taken at the mid and lateral peripheral zones of the prostate. It is logical to assume that performing more biopsies would lead to increased cancer detection. In fact, several studies have examined the utility of taking additional biopsies. However, in one study, increasing the number prostate biopsies beyond double sextant did not lead to higher detection rates.[49] A recently published study of approximately 3500 patients found that extending the number of biopsies (that is, performing triple sextant biopsies) did not statistically improve the cancer detection rate, but did increase the number of clinically insignificant prostate cancers.[50]

Often, biopsy specimens that are reviewed by a pathologist are deemed to be benign lesions. These lesions include normal prostate tissue, hypertrophy of the prostate, and inflamed lesions of the prostate. Inflammation in the specimen may require further investigation to determine the etiology (which might be prostatitis or an STD, for example). The patient is informed that he should continue to have regular serum PSA tests and an annual DRE. A repeat serum PSA test should be performed 6 months after the prostate biopsy. If serum PSA levels continue to rise, or if other parameters such PSA density change, the patient should be referred for a repeat biopsy in case prostate malignancy was missed or was not present at the initial biopsy. Observations such as an enlarging nodule or new nodules related to an abnormal prostate should be recorded and monitored. In our office, if a patient continues to have a rising PSA level after a negative prostate biopsy, or if he has new findings on a DRE, we generally suggest a repeat biopsy to ensure that an occult malignancy was not missed.

Abnormal pathology specimens in prostate cancer can range from a precursor lesion to an aggressive malignancy. High-grade prostatic intraepithelial neoplasia (HGPIN) are precancerous lesions. If HGPIN are present, and if an adequate double sextant prostate biopsy was performed, then a repeat serum PSA test and careful monitoring with a DRE are warranted in 6 months. If less than a double sextant biopsy had been obtained, then the prostate biopsy should be repeated.[51] Occasionally, a diagnosis of "atypical small acinar proliferation" (ASAP) is made, which is not a definite diagnosis of prostate cancer, but instead suggests that the prostate cancer was marginally sampled. Recent evidence recommends that when ASAP is found, aggressive patient follow-up and serious consideration for a repeat biopsy are needed.[51]

The pathologist determines the location, volume, and grade of malignant lesions. A prostate tissue sample is assigned a Gleason grade from 1 to 5 depending on the differentiation and architecture of the glands. Grade 1 indicates the most differentiated glands and therefore is benign, and Grade 5 indicates the most undifferentiated glands. Two grades (from the most common and the second most common patterns) are added to obtain a Gleason score, which ranges from 1 to 10. Virtually no prostate specimens are assigned a Gleason score of 2 to 4. Gleason scores from 5 to 6 are considered to indicate low-grade lesions. A Gleason score of 7 (4+3 or 3+4) indicates an intermediate-grade lesion. A Gleason score of 8 or more indicates a high-grade tumor.

Most prostate tumors are located at the periphery of the prostate, and the rest are located in the transitional zone. Most tumors are multifocal and bilateral.

Many studies have examined the clinical significance of prostate cancer based on Gleason score, PSA level, and prostate volume. Some clinicians define prostate cancer to be clinically significant when the cancer has a Gleason score of 7,[53] while other authors consider tumors to be clinically significant when prostate volumes are greater than 0.5 ml, or when cancer extends to the seminal vesicle or beyond the prostate capsule and there is metastasis to the lymph nodes.[54] A recent investigation noted that increasing the number of biopsies in the prostate region increased the number of clinically significant prostate cancers.[55]

If the prostate cancer is of intermediate or high grade (Gleason score > 6, or PSA > 10 ng/ml), further imaging is warranted. A bone scan and computed tomography of the abdomen and pelvis are performed to look for the presence of bone lesions and lymphadenopathy, respectively. Metastasis to the bone is the most common extrapelvic site of advanced prostate cancer. If a bone scan is positive for uptake of a radioactive tracer, then the scan should be repeated without the tracer. This is important if there is uptake of a radioactive tracer in weight-bearing joints or if the patient has bone pain.

Standard double sextant biopsies have false negative rates ranging from 15% to 35% for detecting clinically significant prostate cancer.[56] The dilemma for both the healthcare provider and the patient is whether a repeat biopsy should be undertaken if clinical suspicion of cancer remains elevated. Patient monitoring should include PSA levels and DREs. A new finding in the DRE should prompt further investigation. Similarly, a PSA velocity greater than 0.75, a serum PSA level higher than 10 ng/ml, or a total-to-free PSA ratio of less than 0.2 raise clinical suspicions that the initial biopsy may have missed a malignancy. We recommend checking serum PSA levels every 6 months for the first year after a biopsy. The clinician should consider a patient's family

TABLE 1. **Indications to re-biopsy after initial needle biopsy of the prostate is negative for malignancy**

Inadequate specimen
High-grade prostatic intraepithelial neoplasia (HGPIN)*
Presence of atypical small acinar proliferation (ASAP)
Prostate-specific antigen (PSA) velocity (change in PSA level over time) > 0.75 ng/ml per year
Abnormal digital rectal examination (DRE) when compared to previous exam

*If double sextant biopsies not performed (at least 12 cores not obtained) or clinical suspicion remains elevated

history and concerns when recommending a needle-biopsy of the prostate. Whether or not a saturation biopsy (extending the number and areas of biopsy) provides better sensitivity than a double sextant biopsy is controversial.[57] Generally, we wait approximately 1 year before we re-biopsy. See Table 1 for indications to perform a repeat biopsy.

Treatment options

After the urologist has obtained the patient's test results — serum PSA value, Gleason score, and clinical cancer stage results from the biopsy — he or she will discuss with the patient not only the diagnosis but also the prognosis and treatment options. For organ-confined disease (stage T1 to T2c), radical prostatectomy is the standard treatment. It is imperative that the patient is informed about and understands his other options as well as the inherent risks and benefits of these options. Risks of surgical intervention include erectile dysfunction, urinary incontinence, or urinary retention due to urethral stricture disease.

Conservative therapy can be either watchful waiting or active surveillance. Watchful waiting has been used to manage patients who have a predicted life expectancy of less than 10 years. This decision is made on the premise that the patient will not gain any benefit from radical treatment. Rather, surgical intervention, hormone ablation, or radiation is reserved for palliative care for such things as bladder outlet obstruction or painful bony metastases.

Active surveillance, another form of conservative treatment, may be chosen by men who have prostate cancer but do not wish to undergo more drastic treatment. According to the 2007 American Urological Association (AUA) guidelines, the goals of active surveillance are "to provide definitive treatment for young men with localized cancers that are likely to progress and to reduce the risk of treatment-related complications for men with cancers that are not likely to progress." In our practice, we have seen younger patients who have elected to follow this treatment option for low-grade prostate cancer (typically Gleason score of 6 [3+3], serum PSA < 10 ng/ml). Ideal patients for active surveillance are those with good treatment compliance and low-grade, low-stage tumors. We monitor the patients' serum PSA values twice a year. If there is a significant rise (or consecutive rises) in serum PSA values, then a repeat biopsy is considered, to restage the prostate cancer. One criticism for this approach is that men with aggressive prostate cancer are undertreated. A commonly adopted way to monitor men on active surveillance is based PSA doubling time; serum PSA is checked every 6 months, and if the PSA has doubled in less than 3 years, radical treatment is recommended.[58]

Radiation therapy (external beam radiation, brachytherapy, and a combination of both) is an option for patients who do not wish to undergo surgery. Patients with significant comorbidities may benefit from this treatment modality. Risks include cystitis, proctitis, and gradual loss of erectile function.

Cryoablation (freezing) of the prostate is being used more frequently to treat prostate cancer. As with radiation, the prostate is not removed and no prolonged hospitalization or surgical procedure is required. However, long term data for cancer-specific survival is lacking. Erectile dysfunction is the most common side effect, as the neurovascular bundles for erections are ablated along with the prostate.

A newer modality has emerged to treat localized prostate cancer: high-intensity focused ultrasound (HIFU). This technique uses high, intense energy (non-ionizing radiation) that is emitted into prostate tissue in an accurate and precise manner. Thermal ablation of prostate tissue occurs as temperatures rise up to 100°C without injuring adjacent structures. This minimally invasive and precise technology offers advantages over external beam radiation and surgery by reducing side effects. As with cryoablation, long term data is unavailable. HIFU is approved for use in Europe, Japan, and Canada, and clinical trials of HIFU are currently underway in the United States.

Hormonal treatment with androgen deprivation therapy may be more appropriate for older men who are in poor health and_cannot tolerate a stressful procedure. Hormonal therapy is not curative but enables long term remission. Hormone deprivation may be achieved with intramuscular injections of luteinizing hormone-releasing hormone (LHRH) agonists (e.g., leuprolide or goserelin) combined with anti-androgens (bicalutamide, nilutamide) or via scrotal bilateral orchiectomy. Risks include decreased libido, gynecomastia, osteoporosis, and symptoms associated with low levels of testosterone. Men on hormonal ablation should have a dual-energy x-ray absorptiometry (DEXA) scan to be evaluated for osteoporosis and they should be given vitamin D and calcium supplements.

It is important to note that neo-adjuvant hormone treatment prior to radiation treatment has been found to decrease the incidence of prostate-related death.[59] After radiation treatment is completed, hormonal treatment is given for an additional 2 years.

If the patient ultimately decides to undergo radical prostatectomy, different approaches may be used. The open radical retropubic approach is still used, but is becoming less common. Minimally invasive laparoscopic radical prostatectomy with or without the daVinci robot is becoming increasingly more popular, due to the shorter hospital stay and decreased perioperative pain with this procedure, which cuts down on healthcare costs.

If a patient has locally advanced disease (such as cancer that involves the seminal vesicals or has extended to the prostatic capsule), surgical treatment may not be the best option and the patient may need to discuss other treatment options with his physician.

Table 2 summarizes the advantages and disadvantages of different treatments for adenocarcinoma of the prostate.

Post-treatment PSA monitoring

After a radical prostatectomy, a patient's serum PSA level should be undetectable (< 0.1 ng/ml). We usually monitor PSA levels every 6 months for the first 5 years after surgery and annually thereafter. Detectable PSA in prostate cancer patients after

TABLE 2. **Advantages and disadvantages of different treatment options for prostate cancer**

Treatment	Advantages	Disadvantages
Conservative treatment Watchful waiting Active surveillance	Lowers risk of treatment-related complications	Can delay aggressive treatment for potentially curable disease
Radiation External beam radiation Brachytherapy	Minimally invasive Reduces risk of surgical complications Option for poor surgical candidates	Cystitis Proctitis Gradual erectile dysfunction
Radical prostatectomy Retropubic Robotic/laparoscopic	Removes source of disease Standard of care	Invasive Highest risk of morbidity and mortality Urinary incontinence or retention Delayed recovery of erectile function
Hormonal treatment Androgen ablation Orchiectomy	Noninvasive Option for poor surgical candidates	Recurrence is common Osteoporosis Symptoms similar to that of low testosterone Gynecomastia
High-intensity focused ultrasound (HIFU)	Precise Minimally invasive option	Unknown long term data
Cryoablation	Minimally invasive Reduces risk of surgical complications Option for poor surgical candidates	More long term data needed Erectile dysfunction

treatment with surgery is defined as "PSA failure." Patients treated initially with radiation (external beam radiation or brachytherapy) reach a nadir (the lowest point) in PSA values. The American Society for Therapeutic Radiology and Oncology (ASTRO) defines "PSA failure" as three consecutive rises in PSA values following surgery or radiation for prostate cancer. No guidelines for defining PSA failure currently exist for cryotherapy, although many physicians have adopted the same ASTRO criteria used for surgery and radiation. If patients have PSA failure and their malignancy is considered to be localized to the prostate, salvage therapy may be an option. Similarly, patients with PSA failure months after undergoing radical prostatectomy may undergo radiation treatment of the surgical bed or they may undergo hormonal treatment. Regardless of the treatment used, PSA failure warrants a prompt visit to the urologist.

Summary

Early detection of prostate cancer through screening tests enables primary care physicians and urologists to offer patients a broader choice of treatments that are also more likely to provide a cure. Whether men are being over treated or over diagnosed through the widespread use of screening tests remains controversial. This review aimed to provide primary care physicians with a better understanding of different prostate cancer tests that can be performed and to help them decide which patients should be referred to a urologist for an ultrasound-guided biopsy.

Disclosure

None declared. □

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DISCUSSION

Question (Dr. Laroche):
What are factors that could falsely increase the PSA value with no underlying pathology?

Answer (Dr. Haas):
Manipulation of the prostate, such as catherization, biopsy, or even vigorous rectal examination can elevate the PSA. Urinary tract infection or prostatitis can raise PSA to very high levels. Vigorous sexual activity, bicycle or stationary bike riding, horse back riding within 4 to 5 days of testing may also result in false elevation. On the other hand, several classes of medications, such as 5-alpha reductase inhibitors, anti-inflammatory agents, and statins may decrease PSA levels.

Question (Dr. Greenberg):
What are the PSA levels to be expected after prostate cancer treatment, and what would be the role of the Primary Care physician in following these?

Answer (Dr. Haas):
Primary Care physicians should work closely with the urologist who treated the patient and communicate well regarding the appropriate follow-up. Patients after treatment for prostate cancer should be followed closely, examined regularly, and have their PSA evaluated according to regular schedule. I recommend follow-up every three to four months during the first year after treatment, four to six months after the first year, and every six months after the second year up to five years. Annual examinations should be carried out thereafter, presuming that the patient remains disease free.
The PSA should be zero or undetectable after radical prostatectomy, and any elevation or gradual rise in the PSA level heralds recurrent or residual disease. After therapies which do not remove the entire prostate, such as external radiation therapy, brachytherapy, cryosurgery or HIFU, PSA levels should nadir bellow 1 ng/ml, preferably bellow 0.5 ng/ml, and remain low. Occasional fluctuation of PSA levels may occur, but consistent rise on consecutive measurements may be evidence that the patient is failing. The Primary Care physician should then consult with the urologist regarding the timing of diagnostic studies and intervention.

Hormone-refractory prostate cancer: a primer for the primary care physician

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Potvin K, Winquist E. Hormone-refractory prostate cancer: a primer for the primary care physician. The Canadian Journal of Urology. 2008; 15 (Suppl 1):14-20.

Objective: *To provide a current and evidence-based clinical review of practical value to primary care physicians encountering men with hormone-refractory prostate cancer (HRPC) in their practice.*
Methods: *Evidence-based narrative review by two expert clinicians incorporating results of systematic reviews and randomized trials whenever available.*
Results: *HRPC represents the final common pathway to death from prostate adenocarcinoma, the single most prevalent cancer in Canadian men. However, primary care physicians will not encounter these patients with a frequency adequate to develop confidence in their care. HRPC is defined by progressive disease despite castration, and biologically is a characterized by androgen hypersensitivity. It is important to understand that HRPC is a disease spectrum ranging from asymptomatic patients with only a rising prostatic-specific antigen (PSA) level and a prognosis measured in years to extremely symptomatic patients with widespread metastases requiring end-of-life care. Numerous effective management options are now available for HRPC and are selected based on the phase of the disease natural history, and patient comorbidities and preferences.*
Conclusions: *Men with HRPC have therapeutic options that can improve and maintain both the quality and quantity of their lives. A co-management approach including a medical oncologist and the patient's urologist and primary care physician is preferred.*

Key Words: prostatic neoplasms, drug therapy, review, radiotherapy, metastases

Prostate adenocarcinoma (prostate cancer) is the single most common serious cancer diagnosed in Canadian men. A high survival rate means that prostate cancer survivors comprise 0.8% of the male population.[1] With marked heterogeneity in the natural history of prostate cancer, and the availability of multiple treatment options, the task of providing care and counsel to men with the disease presents a growing challenge. Primary care physicians have the opportunity to play a central role in prostate cancer management. This can range from advice on screening, counseling about treatment options, through to administration of androgen deprivation therapy (ADT), managing adverse effects of treatment, and palliative care.

Although most men diagnosed with prostate cancer will be cured, or die of competing causes, approximately 20%-25% of men will die from their cancer. Hormone-refractory prostate cancer (HRPC) is the final common pathway to death from prostate cancer, and will be the focus of this review. Although a primary care physician may see many men with prostate cancer, the number of patients with HRPC an individual physician may see in their practice will likely be small. This review aims to provide primary care physicians with a summary of the approaches taken by oncologists in the management of these patients. Every effort is made to shape management guidelines from the best available evidence, including

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randomized trials and systematic reviews where available. However, where high-quality studies are lacking, the opinions expressed may reflect the biases of the author based on experience and interpretation of the available evidence—so *caveat lector*!

Pathophysiology

Although some cancer patients die from complications of local recurrence, in the vast majority death is due to the effects of distant metastases. This is also true for prostate cancer, though it remains a puzzle why some prostate cancers are cured with local treatment, while others metastasize. High tumor grade (the Gleason grading system is used most commonly), high pretreatment blood prostatic-specific antigen (PSA) level, and a more advanced tumor (T) stage may provide clues to an increased risk of eventual distant recurrence. However, these predictors are limited in their ability to provide an estimate of the risk of prostate cancer death for any individual patient.

The availability of PSA testing has transformed our understanding of the natural history of prostate cancer over the past 20 years. Most of this effect is due to the clinical "lead time" that an elevated PSA test provides. Historically, men were diagnosed with the disease on tissue examination following transurethral resection (TUR) of the prostate based on the presence of symptoms. In the modern era, men are most commonly diagnosed with prostate cancer by elevated PSA, in the absence of symptoms or palpable disease. Similarly, recurrent disease is most often identified based on an elevated or rising PSA, rather than by symptoms or clinical detection of metastases.

The identification of such PSA or "biochemical" recurrence is often the trigger to initiate androgen deprivation therapy (ADT). Reduction in circulating androgens is achieved by chemical castration with depot luteinizing hormone releasing hormone [LHRH] agonists, or less commonly, with bilateral orchidectomy. ADT is highly effective at reducing PSA levels, as well as relieving the signs and symptoms of metastatic disease. The duration of cancer control is associated with the degree of PSA drop while on ADT.[2] However, ADT is not curative, and progression of cancer is inevitable in all patients that survive comorbid conditions. Typically, progression is first identified as a persistently rising PSA despite ADT.

Such progression represents the first indication of the emergence of "hormone resistant" or "androgen independent" prostate cancer that will ultimately lead to hormone-refractory prostate cancer (HRPC). Although widespread in use, these terms are misnomers. Recent studies point to the progression of prostate cancer in the castrate state as being caused by the emergence of cancer cells that have become hypersensitive to extremely low levels of circulating and intracellular androgens.[3] It remains controversial whether the cells giving rise to these subclones arise spontaneously via mutations, or are present in the earlier stages of the prostate cancer. ADT does not completely eliminate androgen production; the adrenal glands continue to produce androstenedione and dehydroepiandrostenedione, which can activate the androgen receptor. A strong parallel exists in postmenopausal breast cancer, where despite very low levels of sex hormones, hormone-receptor expressing cancer cells remain able to proliferate and potentially thrive, and may respond to further hormonal and non-hormonal interventions.

Clinical assessment

Hormone-refractory prostate cancer is most commonly diagnosed at an asymptomatic stage, with the identification of consistently rising PSA levels in a man with a history of recurrent disease who has been receiving ADT. However, men with HRPC can present anywhere along the spectrum of their natural history, from those with no symptoms or clinical findings, to men with symptomatic disseminated metastases, Figure 1.

When evaluating a patient with suspected HRPC, a history of the prostate cancer and its treatment including current and past use of hormonal therapies should be reviewed. As the natural history of prostate cancer can be lengthy, this can often be complex.

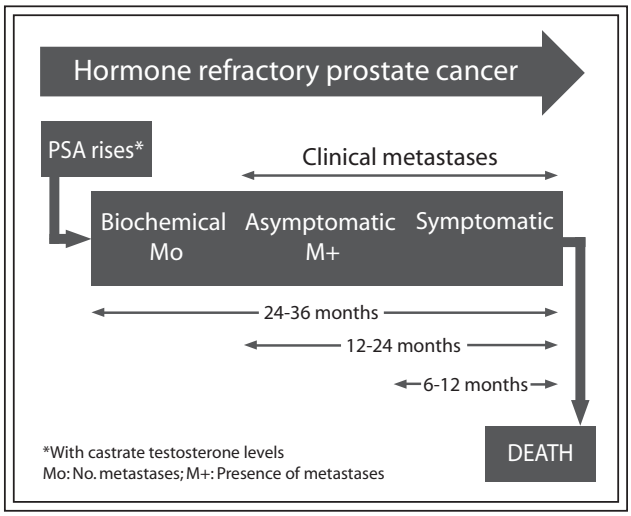

Figure 1. Progression of advanced prostate cancer.

A history of concurrent medical problems should be obtained, as prostate cancer typically affects older men whose comorbidities may influence the treatment options available to them.

Review of systems should include the identification of local and systemic symptoms. Prostate cancer has a proclivity to metastasize to bone and lymph nodes. Focal symptoms include pain, lower urinary tract symptoms, and leg edema. Systemic symptoms such as weight loss, fatigue, and anorexia should be identified, and often reflect a greater disease burden. Often, changes in a patient's activities or behavior patterns can provide clues to the impact of their cancer. Men with HRPC typically die from the systemic effects of their increasing cancer burden, typified by wasting, bone marrow failure, and immunosuppression rather than critical organ failure. The onset of these may be insidious. Rarely, men with HRPC may develop lung or liver metastases. Finally, some patients develop uncontrolled pelvic recurrence, which becomes the major challenge in treating and controlling their cancer.

Physical examination should include inspection for anemia and jaundice, and examination of the lymph nodes areas in the neck, axillae, and groins. Patients receiving chemotherapy may be alopecic. Palpation or percussion of the spine and costovertebral areas may provide clues to bone metastases or hydronephrosis. If the history is unclear regarding bilateral orchidectomy, scrotal examination should be performed. Digital rectal examination to assess for local recurrence at baseline and in the presence of new or worsening lower urinary tract or rectal symptoms is mandatory. The lower extremities should be examined for edema which may be a clue to intra-abdominal or pelvic lymphadenopathy, pelvic mass or deep venous thrombosis. If symptoms suggestive of spinal cord compression, radiculopathy, or focal neurological deficit are present, a focused neurological examination should be performed.

As biochemical (PSA) or clinical progression in the presence of a castrate testosterone level is the *sine qua non* of HRPC, the serum testosterone level should be checked to confirm that the patient's androgen levels are adequately suppressed. This is unnecessary in men treated with bilateral orchidectomy. Anemia is common in men with HRPC, and renal obstruction not uncommon, hence laboratory investigations should include a complete blood count and routine biochemistry including creatinine, bilirubin, and liver enzymes in addition to the PSA. Patients receiving chemotherapy may be neutropenic, and if this suspected a differential white blood cell count should be included. Rarely, disseminated intravascular coagulation can occur; if bleeding stigmata are present, INR, PTT, and fibrinogen level should be checked. Despite the high frequency of bone metastases, hypercalcemia is extremely rare in HRPC.

Usually a routine chest radiograph and whole bone scintigraphy are adequate for restaging. However, the suspicion of intra-abdominal disease generated by symptoms such as unexplained leg edema or abdominal pain may justify investigation with an abdominopelvic computed tomographic (CT) scan. Intractable back pain, leg weakness, or sensory loss in a patient with known bone metastases should prompt urgent magnetic resonance imaging of the spinal cord to rule out spinal cord compression. The high incidence of neurological impingement in HRPC and need for early intervention justify this practice.[4]

Symptom palliation

Symptom control is the first and essential step in managing the patient with metastatic HRPC, Figure 2. Pain is the most important symptom, and the timely use of appropriate non-narcotic and narcotic analgesics titrated to adequately control pain is essential for optimal palliation. Men with prostate cancer are often older and may have other medical conditions which complicate the choices of analgesics.[5] Aggressive prophylaxis of constipation is essential if narcotics are used, as fear of this complication often affects analgesic adherence. When stronger analgesics are required, use of hydromorphone may be preferable to morphine in older patients, or those with impaired renal function, to minimize adverse effects.

Short course external beam radiotherapy may be highly effective for focal areas of bone pain, and is also used for treatment of neurological impingement

Maintain androgen suppression (< 0.7 nmol/l)

If no metastases or symptoms consider:

- Antiandrogen withdrawl and observation
- Secondary hormonal manipulation
- Experimental therapy

Optimize symptoms (analgesics, focal RT)

Prophylactic zoledronic acid

Docetaxel-based chemotherapy

Palliative RT, radio-isotopes, bisphosphonates

Figure 2. Approach to HRPC.

syndromes. Multifocal pain, or pain in previously radiated areas may require consideration of systemic therapies. Lymphedema typically does not improve and may even worsen if treated with radiotherapy and drug therapy. Conservative measures such as elevation and compression may be required. Renal obstruction may require TUR, ureteric stents, or even percutaneous nephrostomy tubes. Chronic fatigue and anorexia are harder to treat. Anemia due to cancer may require packed red cell transfusion or a trial of erythropoietic stimulating agents. Through communication with a patient's oncologist and urologist, the primary care physician can not only identify the need for these palliative interventions, but can also contribute to the delivery and management of treatment in all of these scenarios.

The development of rising PSA levels despite ADT can be alarming to a man used to the regular reassurance of an unchanged PSA. The primary care physician can play an important role in education, counseling, and support to decrease the anxiety and fear that often accompany entry into this ultimately incurable phase of prostate cancer.

Secondary hormonal manipulations

It is a tenet of palliative medicine to use the most effective and least toxic interventions first, and this remains the most compelling argument for trials of secondary hormonal manipulations in men with HRPC. Although there is no data from randomized trials, current practice is to maintain ADT despite the presence of disease progression. Discontinution of LHRH agonist therapy may lead to the recovery of gonadal function and a rise in serum testosterone levels, which may stimulate prostate cancer growth. Androgens have antiapoptotic effects on prostate cancer cells in animal models, and this may contribute to reduced effectiveness of radiotherapy and chemotherapy in the clinic.[6] Case reports of this phenomenon have been reported.[7]

For patients with asymptomatic PSA progression on testicular ADT alone, the addition of an oral antiandrogen is a simple and often effective intervention. Nonsteroidal antiandrogens are preferred since they are more effective in combination with gonadal ADT, as identified in a meta-analysis of complete androgen blockade in men with metastatic prostate cancer when compared to steroidal antiandrogens (e.g. cyproterone acetate).[8] These data are considered generalizable to the hormone-refractory setting. Several nonsteroidal antiandrogens are available (flutamide, nilutamide, and bicalutamide), with bicalutamide considered the optimal choice by most clinicians, based on the convenience of once daily dosing and the most favorable toxicity profile. There is little evidence that switching between these agents, if PSA progression has occurred on one, is beneficial.

For patients receiving treatment with complete androgen blockade (LHRH agonist or bilateral orchidectomy plus oral antiandrogen) who are experiencing cancer progression, discontinuation of the oral antiandrogen may result in a drop in PSA levels and even symptomatic response.[9] This "antiandrogen withdrawal" phenomenon is incompletely understood, but may result from the acquisition of androgen receptor mutations over time and exposure to antiandrogens that may paradoxically stimulate the androgen receptor.[10] As a result, discontinuation of the antiandrogen in effect results in a secondary androgen deprivation effect. However, this phenomenon is typically seen only in patients with prolonged continuous antiandrogen exposure, and is rare in patients only briefly exposed (i.e. less than 2 years). Nevertheless, obvious disease progression on antiandrogen therapy justifies discontinuation of these agents whether antiandrogen withdrawal is anticipated and observed or not.

For patients progressing on oral antiandrogens, therapeutic options include observation, low dose corticosteroids with or without ketoconazole, and investigational agents. The value of corticosteroids in this setting lies in their ability to suppress adrenal androgen production through suppression of ACTH. A PSA response of 21% and subjective response of 56% were reported with prednisone 5 mg qid in one randomized trial.[11] Hydrocortisone and dexamethasone have each been used for this purpose, but typically prednisone 10 mg daily is prescribed in Canada. Few side effects are seen with this low dose; bruising of the forearms due to capillary fragility is common, while worsened glucose tolerance is far less common. Ketoconazole acts directly on gonadal and adrenal steroidogenesis to rapidly and completely inhibit androgen synthesis. Doses of 200 mg orally twice daily have been shown to achieve this, but doses up to 400 mg tid have been used based on hypotheses of direct anticancer effects. Typically ketoconazole is given along with corticosteroids to avoid hypoadrenalism, so the incremental benefits of ketoconazole over prednisone alone are difficult to discern. It is unclear if this if worthwhile in view of the serious potential toxicities of ketoconazole including hepatotoxicity. Men with early HRPC are often excellent candidates for clinical trials of investigational therapies, and this should not be forgotten as a treatment option.

Bisphosphonates

Primary care physicians are familiar with oral bisphosphonate drugs for the treatment of postmenopausal osteoporosis. Bisphosphonates are now commonly used in oncology, although typically more intensive intravenous dosing is used. Over 90% of men with HRPC eventually develop skeletal metastases, and their presence predisposes to skeletal-related events such as pain, pathological fracture, and neurological impingement. As skeletal metastases in prostate cancer tend to occur first in the axial skeleton, advancing disease can also result in cytopenias and ultimately bone marrow failure. The skeleton may also serve as a reservoir for a large burden of metastatic cells that contribute to systemic symptoms and wasting.

Zoledronic acid is the current standard treatment to prevent skeletal-related events in metastatic HRPC. The dose is 4 mg IV every 3 weeks and may require adjustment for renal dysfunction. Adverse effects are modest, but 5%-10% of patients experienced anemia, myalgia, lower limb edema, or dizziness with zoledronic acid in the randomized trial that established its benefits in HRPC.[12] Osteonecrosis of the jaws is a rare complication associated with bisphosphonate potency, duration, IV route of administration, and dental health.[13] Zoledronic acid is probably optimally used in men with demonstrated bone metastases and minimal pain (less than 30 mg morphine equivalent per day). The optimal duration of treatment is uncertain. Bisphosphonates may also have modest effects on bone pain in HRPC. Data from randomized trials suggests modest benefits of intravenous and oral clodronate, intravenous pamidronate, and intravenous zoledronic acid on pain in men with HRPC.[14] It is unclear if one agent is superior to others or to radiation for this indication. Radiotherapy, radioisotopes, and chemotherapy appear to have much greater effectiveness for the relief of pain in this setting, and should be considered first for pain relief along with optimized analgesic therapy.

Chemotherapy

Chemotherapy represents a safe, effective, and probably underutilized treatment option for appropriately selected men with HRPC. Typically mild single agents are used, and most treated men derive some degree of benefit with only mild or modest adverse effects. The use of chemotherapy for palliation of symptoms by disease control in HRPC is a relatively recent development in the oncology world. The delay in adopting use of chemotherapy related to the challenge of determining efficacy in the pre-PSA era. As most patients have bone predominant disease, objective assessment of "response" to treatment was difficult if not impossible. Ground breaking work by Ian Tannock at the Princess Margaret Hospital using palliative response (based on self reported pain and analgesic use) established mitoxantrone as a standard palliative agent for HRPC causing pain in the early 1990's.[15] The subsequent use of PSA to identify active drugs in HRPC has accelerated clinical research.

Docetaxel was first isolated from the needles of the European yew tree, and is currently used to treat many cancer types including those of the breast, lung, and head and neck. Docetaxel was identified as active in HRPC in the late 1990's, and has now become the standard first-line chemotherapy agent for HRPC. Docetaxel demonstrated higher palliative and quality of life response rates, as well as a modest improvement in overall survival, when compared to mitoxantrone in two large randomized trials.[16,17] The optimal timing of the initiation of chemotherapy remains a topic of debate. Currently, men without evidence of metastases should not be offered cytotoxic chemotherapy outside the setting of a clinical trial. Men with unequivocal symptoms should be considered candidates for a trial of docetaxel. In these authors' view, men with metastases, relatively indolent disease, and absent or minimal symptoms should progress through the steps outlined above (symptom palliation, secondary hormonal manipulations, bisphosphonates) prior to proceeding with a trial of chemotherapy. Immediate chemotherapy may be justified for men with metastases and very worrisome PSA kinetics, visceral organ involvement, or who are in failing health at the time they present for assessment. Even though disease progression has occurred on low dose prednisone and ADT, this author usually continues both throughout chemotherapy treatment, as the presence of even low levels of adrenal androgens may antagonize its apoptotic effects.

Barriers to the use of chemotherapy in men with HRPC include misinformation or fixed beliefs of patients and referring physicians, age bias of medical oncologists, and timely referral of patients. A standard approach after the failure of docetaxel remains to be defined, and is an active area of clinical research. Agents currently under study, and of potential future interest in HRPC, include cell-based immunotherapy (APC8015), drugs targeting tumor angiogenesis (bevacizumab and aflibercept), patupilone, the endothelin inhibitors atrasentan and ZD4054, and abiraterone (a selective cytochrome P450 inhibitor).

Radioisotopes

The bone predominance of metastatic HRPC in most patients makes the idea of a "therapeutic" bone scan appealing. Prior to the advent of palliative chemotherapy, hemibody irradiation was often used for palliation of pain in widely symptomatic bone metastases from HRPC. Beta-emitting bone-avid radioisotopes currently available in Canada include strontium-89 and samarium-153. Strontium-89 was observed to confer palliative benefits in a Canadian randomized trial, which has lead to recommendations for its use in men with HRPC.[18] Samarium-153 also has supportive data from randomized trials.[19,20] It has the advantages of less myelosuppression, making repeated treatments more feasible. Both therapies are limited by access, as they are only available at specific centers in Canada. As well, they currently are not preferred for use early in HRPC as they compromise bone marrow reserve, and increase the risk of serious and prolonged cytopenias if chemotherapy is subsequently administered. Radioisotopes are probably best for patients who are not suitable for or refuse chemotherapy, or have exhausted chemotherapeutic options and have diffuse bone pain or pain in previously radiated sites.

Conclusions

Primary care physicians are an important part of the health care team for men with HRPC. They provide familiarity, continuity of care, and an additional point of access to the health system that patients often need and value during their cancer journey. Unfortunately, primary care physicians may lose touch with their patients once they enter the cancer care system. Primary care physicians may also feel excluded due to their lack of familiarity with the disease process, and the increasingly complex and changing array of cancer treatments available for specific cancer types. It is hoped that this expert review can increase the level of comfort of primary physicians as participants in the care of patients with HRPC, by providing a succinct yet comprehensive guide to the natural history of the disease and the general approach to its treatment.

Disclosure

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DISCUSSION

Question (Dr. Greenberg):
What is prostate-specific antigen doubling time (PSADT) and does it have a role in treatment decision-making in HRPC?

Answer (Dr. Winquist):
A number of prognostic factors of potential value in HRPC have been identified including: hemoglobin, lactate dehydrogenase, and alkaline phosphatase levels; age, Gleason sum; performance status; the presence of visceral metastases; and the presence of pain. The total PSA level has not been demonstrated a reliable marker of survival in HRPC; however, the rate of PSA change may be. For example, a drop in PSA level by at least 30% from baseline by 3 months with docetaxel-based chemotherapy appears to be associated with a better prognosis. Shorter PSADTs have been associated with a shorter time to the development of bone metastases and survival in men with HRPC. The value of PSADT in HRPC depends very much on the disease context, and it should not be used in isolation to make treatment decisions. A rapidly shortening PSADT may be of particular value in assisting decisions in asymptomatic patients with and without metastases.

Question (Dr. Miner):
What is a prostate-specific antigen "flare" during chemotherapy for HRPC?

Answer (Dr. Winquist):
Theoretically, a "flare" refers to the apparent worsening of disease due to the initiation of therapy. For example, true "flare" of disease can occur with the initiation of LHRH agonist therapy for hormone-naïve metastatic prostate cancer. Rising PSA levels following chemotherapy may indicate true progressive disease, delayed response, or "marker flare" due to a surge of release of PSA from HRPC cells undergoing rapid apoptosis (an uncommon phenomenon). The pattern of PSA over time following chemotherapy may be highly variable, and the presence of a stable or rising PSA level does not exclude palliative benefits of treatment. Decisions about discontinuing or changing chemotherapy should not be based on serial PSA patterns alone, and never be based on isolated PSA values.

Management of benign prostatic hyperplasia by the primary care physician in the 21st century: the new paradigm

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BARKIN J. Management of benign prostatic hyperplasia by the primary care physician in the 21st century: the new paradigm. The Canadian Journal of Urology. 2008;15(Supplement 1):21-30.

Benign prostatic hyperplasia (BPH) is one of the commonest causes of lower urinary tract symptoms (LUTS) in men over age 50. Fifty percent of men over age 50 will require some type of management for BPH/LUTS symptoms. Until about 15 years ago, the most common management for BPH was a transurethral resection of the prostate (TURP) operation. Initially, once a diagnosis of BPH has been made, most men are treated medically. One must first rule out other serious causes of these symptoms, such as prostate cancer, bladder cancer, and other obstructions. For men with an enlarged prostate, there is a good chance that therapy with a 5-alpha-reductase inhibitor (5-ARI) can prevent disease progression and the need for surgery. There has been a lot of recent work on different combination therapies for the treatment of BPH/LUTS. If a patient's serum prostate-specific antigen (PSA) level is greater than 1.5 ng/ml and his prostate volume is greater than 30 cc and he has significant LUTS, then combination medical therapy of an alpha blocker with a 5-ARI is the most effective therapy. After a careful workup, it is quite reasonable and appropriate for the primary care physician to initiate this therapy for a patient with BPH/LUTS.

Key Words: BPH, LUTS, PSA, combination medical therapy, 5-ARI, alpha blocker, prostate cancer

Introduction

It is estimated that by 2020, approximately 4 million Canadian men will have benign prostatic hyperplasia (BPH) with lower urinary tract symptoms (LUTS) that require treatment. Most of these men will receive either prophylactic therapy (to prevent BPH progression or to prevent possible development of prostate cancer),[1] or therapy for BPH, which is initiated by their primary care physicians.

This raises many questions, such as "Who should receive treatment? What treatment should they get? When should they receive treatment? How long should they be treated for?" and "What are the risks and benefits of medical versus interventional therapy for BPH?"

This article is written to provide guidance for the primary care physician who is faced with a patient who has symptoms associated with BPH. It also aims to serve as a reference for providing therapy for patients who are at high risk of developing prostate cancer.

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Diagnosis

Not all men who present with LUTS have BPH. The primary care physician must try to differentiate LUTS from true BPH. The symptoms of many conditions such as urethral strictures, bladder stones, recurrent urinary tract infections, bladder cancer, and even prostate cancer can mimic those of LUTS. BPH is, however, by far the most common cause of LUTS in middle-aged to older men.[2]

Why should we try to treat BPH? We know that the natural course of BPH is one of progression,[3-5] which can lead to any number of potential side effects and complications. The patient can start to have recurrent urinary tract infections, hematuria, early signs of renal failure, and finally, can progress to acute urinary retention and even the need for surgery. He may also have concomitant and significant interference with his lifestyle. Men with prostates that have the largest volumes and who have significant symptoms at the time of presentation to a physician have the highest risk for progression of BPH.[6] Patients who are asked to identify their most worrisome and significant concerns about their symptoms of BPH would most likely identify their fear of needing a catheter for acute urinary retention or of ultimately requiring surgery.

How then should we diagnose BPH? We need to first obtain a complete patient history and then do a physical examination that is targeted for BPH/LUTS, Table 1.

Patient history

In taking a patient's history, we are always interested in how the patient's symptoms started. Although fluid balance is often overlooked in primary care, it is critical to document this in the patient who presents with BPH/LUTS. It is often amazing to find out how much fluid a patient is imbibing. Patients are very often surprised when they discover that a reason for their frequent nocturnal bathroom visits could be because they are ingesting 3 to 4 liters of fluid on a daily basis.

In taking the history of a patient with BPH, it is also important to note the medications that the patient is receiving, whether or not he smokes, and the types of possible bladder or prostate irritants (most commonly tea, coffee, alcohol, or spicy foods) that he is ingesting. Activities such as frequent and lengthy bike, car, or airplane rides can also sometimes aggravate the bladder or prostate.

We try to separate the patient's symptoms into two categories: obstructive versus irritative symptoms. Obstructive (voiding) symptoms include weak stream, hesitancy, sensation of incomplete emptying, intermittent stream, and prolonged urination. Irritative (filling) symptoms include frequency, urgency, nocturia, and urge incontinence.

These symptoms can be quantified by using the American Urological Association-Symptom Index (AUA-SI) for BPH.[7] This questionnaire has become the gold standard for assessing BPH symptoms, as part of a medical check-up or as part of a clinical trial. The responses to the questionnaire give the physician (or investigator) an objective means of assessing how the patient might respond to therapy. The patient is asked to fill in the questionnaire on repeated occasions. The maximum possible total score is 35, where a score of 0 to 8 indicates mild BPH symptoms; a score of 8 to 20 indicates moderate BPH symptoms; and a score of 20 to 35 indicates severe BPH symptoms. Changes in scores over time reflect improvement or deterioration in the patient's BPH symptoms.

TABLE 1. **Clinical assessment of a patient with benign prostatic hyperplasia**

History and physical examination
Digital rectal examination (DRE)
Urinalysis
Prostate-specific antigen (PSA) determination
To rule out prostate cancer
To assess prostate size (PSA 1.5 ng/ml = 30 cc prostate)
Symptom assessment
Patient interview
Symptom score on patient questionnaire (AUA-SI for BPH; IPSS)
Quality-of-life assessment

AUA-SI = American Urological Association-Symptom Index; BPH = benign prostatic hyperplasia; IPSS = International Prostate Symptom Score

The final question on the AUA-SI for BPH questionnaire is what I call the "motivation" or "quality-of-life" question. This asks: "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?" The possible responses range from "0" (delighted) to "6" (terrible). This question can also be described as a "bothersome index." It provides an idea as to how much the symptoms are bothering the patient as well as his motivation to obtain and accept treatment to lessen his symptoms.

Studies have shown that patients will make significant lifestyle changes in response to their BPH/LUTS.[8] They might avoid going to sporting activities, the theater, or church, or avoid long car rides, which can have a dramatic negative impact on their quality of life. Usually they will decrease fluid intake, which could lead to the development of kidney stones!

Prevalence of BPH increases with age. Approximately 50% of men who are 50 years old have clinical evidence of BPH, but by age 80, more than 80% of men have clinical evidence of this condition.[2,9] BPH symptoms progress over time. As they progress, a man's chance of developing acute urinary retention or the need for surgery increases. Age is the greatest risk factor for the sequelae of BPH.

Physical examination and other tests

After taking a patient's history, the physician should do a focused urological examination of the patient. This involves palpating the flanks to determine if there is kidney enlargement. Next, he or she should palpate and percuss the supra-pubic area to determine if there is an enlarged bladder that contains a significant amount of residual urine. The physician should examine the external genitalia to look for any congenital abnormalities, a tight phimosis, or possibly a meatal stenosis. In addition, he or she needs to assess the testicles to ensure that they are a good size and quality and that there is no obvious evidence of a large hydrocele that could also cause some degree of obstruction by deviation or sheer compression of the urethra.

The final and most important aspect of the physical examination is the digital rectal examination (DRE). It is this critical assessment of the prostate that will provide an estimate of the size, shape, quality, nodularity, and consistency of the prostate. This interpretation will help the investigator to conclude whether the patient has benign enlargement of the prostate or possibly prostate cancer. Ultimately, it is the size of the prostate, when the prostate is benign, that will help us to predict the likelihood that the patient's symptoms or disease will progress.

Many studies have determined that an "enlarged prostate" is a prostate volume that is 30 cc or larger.[6,10] In cases where it is difficult for the physician to determine the prostate volume of a patient, a transrectal ultrasound can be performed. Many studies have shown, however, that a serum prostate-specific antigen (PSA) value of at least 1.5 ng/ml indicates that the prostate volume is at least 30 cc.[4] This makes it easy to identify patients with BPH and enlarged prostates who are at high risk of BPH progression. It is critical to request a serum PSA test for any patient who presents with symptoms of BPH or for whom one is considering medical or interventional therapy for BPH.

Physicians should also request a urinalysis and a creatinine test for patients who present with BPH/LUTS. Other tests that could be included in a patient's baseline assessment include determination of his uroflow rate, post-void residual volume, and sexual functioning.

Treatment

Based on the results of a baseline assessment, the physician can determine if a man needs treatment for BPH. The Canadian Urological Association (CUA) has established algorithms for patient management, which is based on a combination of the degree of symptoms, the amount of bother, and the size of the prostate. Figure 1 and 2.[11] Several studies have shown that that patients who seek treatment for BPH are those with moderate to severe symptoms and enlarged prostates.

If a patient has recurrent urinary tract infections, hematuria, significant residual volume, or any sign of renal failure, aggressive therapy is warranted. These patients should be referred early to a urologist. Any patient with an age-related elevated serum PSA level or a rapidly changing PSA level (a change of > 20% per year or > 0.75 ng/ml per year), or an abnormal DRE should also be referred to a urologist.

Oesterling and colleagues randomly selected men from Olmstead County, Minnesota, who were asymptomatic for prostate cancer. Of the original 537 subjects, 471 completed a DRE, a transrectal ultrasound (TRUS), and PSA testing and had no evidence of prostate cancer. These individuals were the basis for the study population from which the following PSA cut-offs for upper normal limits were derived: < 2.5 ng/ml at age 40 to 49 years; < 3.5 ng/ml at age 50 to 59 years; < 4.5 ng/ml at age 60 to 69 years; or < 6.5 ng/ml at age 70 to 79 years).[12]

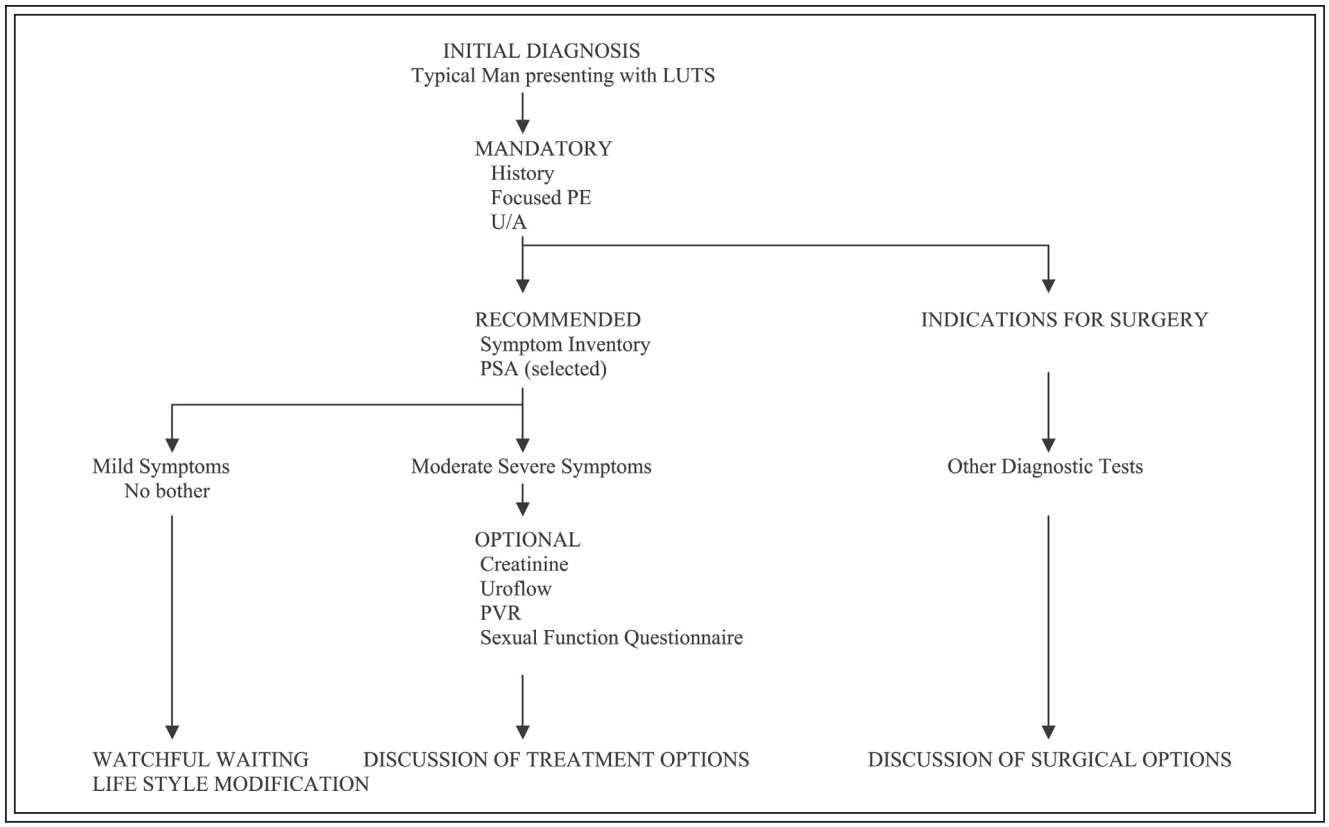

Figure 1. Diagnostic algorithm.[11]

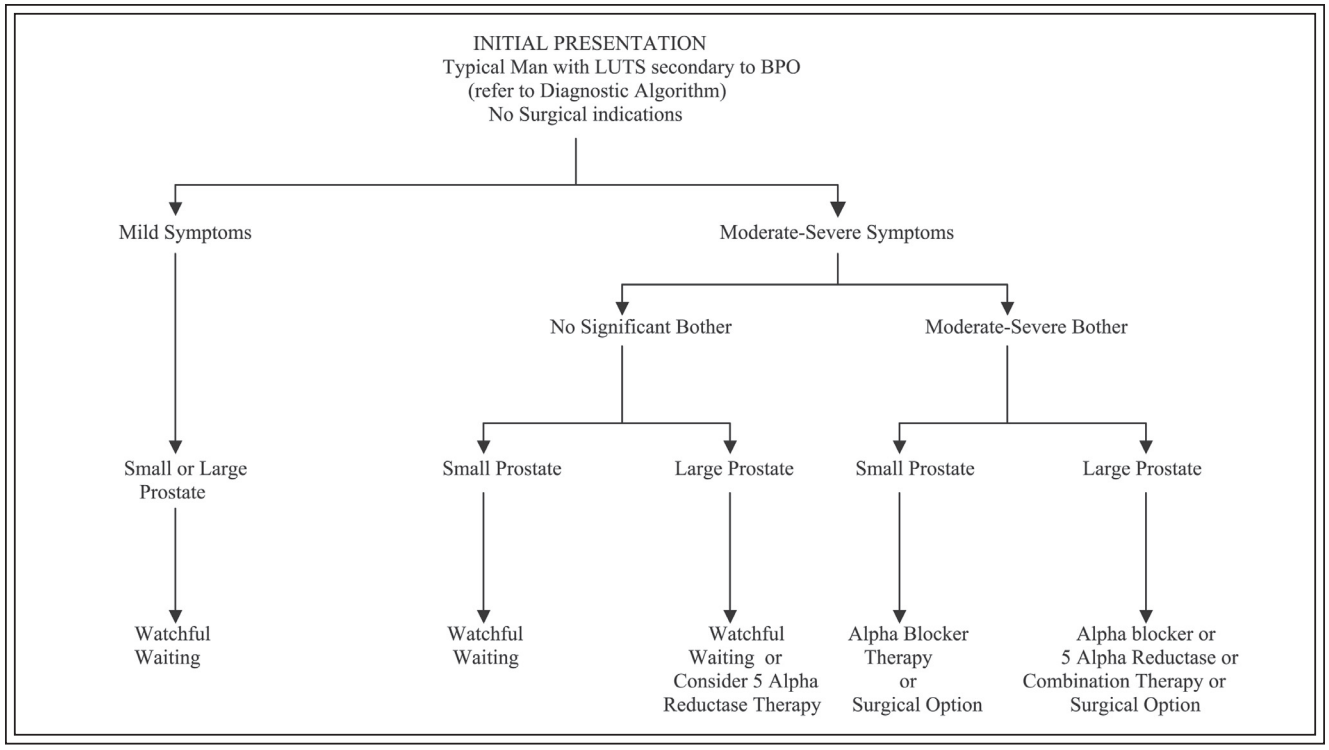

Figure 2. Treatment algorithm.[11]

Interventions other than pharmacotherapy

There are a number of aggressive interventional therapy approaches. The ultimate goal is to diminish the bulk of the prostate. This can be done by either resecting the prostate using electrocautery, or vaporizing or enucleating the prostate using a laser approach. One could also "incise" the prostate in certain individuals with small prostates and tighter bladder necks. This will prevent the most common side effect of prostate surgery, which is "retrograde ejaculation." Some centers still try to heat the prostate using microwave therapy. These invasive approaches are often used for patients who have symptoms or signs of significant BPH (i.e., urinary retention, recurrent infections, or renal failure) and have disease that has advanced to the point where medical therapy (which can be much slower) would be ineffective and allow disease progression and patient harm.

Interventional therapy, regardless of the energy source, can lead to ongoing side effects. The patient has a moderate risk of erectile dysfunction, an almost 5% chance of needing a second surgery within 10 years of the primary treatment, and a 1% to 3% chance of some incontinence.[13]

Because of these risks from interventional therapy and the discovery of novel pharmaceutical agents, pharmacotherapy has become very popular to for the management of patients with BPH.

Pharmacotherapy

The types of obstructions that patients can experience with BPH can be classified as either "dynamic" (changing) or "bulky" (fixed).[14] The dynamic component of obstruction is related to the preponderance of alpha receptors that are found in the bladder neck and prostate area. The increased tone of these smooth muscle fibers causes a tightening or "spasming" at the bladder neck and within the prostate. This leads to a functional obstruction. This stimulation of alpha receptors can be blocked with alpha-blocker medications. Over the years, we have moved from what were considered non-selective alpha blockers (which could cause orthostatic hypotension and other vascular side effects) to more uro-selective alpha blockers (which should not affect blood pressure).[15-17] There are two concerns about alpha blockers: they might not prevent progression of prostate disease, and they might cause significant sexual side effects. The major side effect is that it affects ability to ejaculate. Usually, there is no ejaculation, which is due to the decreased propulsion from the seminal vesicles that have lost their alpha stimulus.[18] This can be very disconcerting for men of all ages.

Studies show that from an efficacy standpoint, there is not a huge difference in the performance of different alpha blockers.[19] The most significant characteristic of alpha blockers compared to 5-alpha-reductase inhibitors (5-ARIs) is the speed of symptom response with alpha blockers. Patients can expect symptom relief from as early as 24 hours to a maximum of about 7 to 10 days after taking an alpha blocker.[19] This can be very gratifying for the patient and physician. The caveat to this is that if we prescribe an alpha blocker for a younger man, we can expect that he will become less responsive to treatment after a few years.[4] The prostate will continue to grow, the patient's response to the treatment will diminish, and the disease will continue to progress, since with time, alpha receptors develop resistance to alpha-blocker effects.[20] As well the prostate continues to grow.

Dihydrotestosterone (DHT) is the active metabolite of testosterone, which leads to the growth of the prostate cells and glands. DHT is created by the conversion of testosterone to dihydrotestosterone and estrogen, which is stimulated by the enzyme 5-alpha-reductase.[21] Many years ago, investigators discovered that a number of related men in the Dominican Republic had ambiguous external genitalia as well as very small prostates. Researchers discovered that these men lacked the 5-alpha-reductase enzyme. The scientists hypothesized that if one could reduce the level of DHT after a man had reached puberty, his prostate would not grow, or could potentially shrink. That led to the discovery and development of the 5-ARI family of drugs. Finasteride (Proscar, Merck, Inc.) was the first ARI to be launched in the marketplace. Dutasteride (Avodart, GlaxoSmithKline) was the second 5-ARI to be marketed. Differences between the two drugs are likely related to their different actions on the two 5-alpha-reductase iso-enzymes (type 1 and type 2). Finasteride inhibits type 2, 5-alpha-reductase, whereas dutasteride inhibits both type 1 and type 2, 5-alpha-reductase.[22]

Treatment with finasteride results in an approximately 70% reduction of DHT levels within the prostate, whereas treatment with dutasteride results in a more than 90% reduction of DHT levels within the prostate. The only head-to-head study that compared the two 5-ARIs was the Enlarged Prostate International Comparator Study (EPICS), which concluded that clinically, there were no significant differences between the two 5-ARIs in efficacy, safety, or side-effect profiles for the treatment of BPH.[23] This was a 1-year study.

Preliminary findings from other studies suggest that type 1, 5-alpha-reductase is more prominent in cancer tissue within the prostate, which suggests

that there may be a more profound effect in using dutasteride to help prevent prostate cancer. Studies that may confirm this are not yet completed.

A few years ago, a significant study was published on the ability of a 5-ARI to prevent the development of prostate cancer. This study, the Prostate Cancer Prevention Trial (PCPT), enrolled only American subjects and compared finasteride versus placebo, in men thought not to have prostate cancer. At randomization, the men had a normal PSA and a normal DRE. The study was terminated early, because there was a profound, 25% lower incidence of prostate cancer in men in the treatment arm versus the placebo arm.

Initially, there was some concern about the findings from this trial, because it appeared that men in the treatment arm who did develop cancer, had a higher-grade cancer (Gleason score 8-10) that was more virulent (aggressive). The presently accepted explanation for this finding is that this was a result of a "volume artifact." The higher-grade cancer was there from the outset, but was missed because the prostate was bigger in the placebo group. After the prostate shrank under the influence of the 5-ARI, the investigator had an increased chance of hitting the focal area of high-grade cancer with the biopsy needle.

A similar study is currently underway in patients at higher risk of prostate cancer. This study, the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial compares dutasteride versus placebo in patients who have already had a biopsy that was negative for prostate cancer, where the biopsy was performed because the men were deemed to be at high risk of prostate cancer since they had an elevated serum PSA level, an abnormal DRE, or a significant family history of prostate cancer. All patients in the REDUCE trial will receive a routine biopsy at 2 and 4 years.

Several monotherapy studies (such as the Prospective European Doxazosin and Combination Therapy [PREDICT] and the Proscar Long-term Efficacy and Safety Study [PLESS] studies) using either finasteride or dutasteride for the treatment of enlarged prostates (greater than 30 cc) have shown that monotherapy can provide a durable and prolonged prevention of disease progression in BPH. The studies have also demonstrated that one can achieve a significant volume reduction of the prostate with 5-ARI therapy.

BPH combination therapy

The question then arose as to whether the combination of an alpha blocker and a 5-ARI would be more effective than either agent alone in preventing disease progression, acute urinary retention, or the need for surgery in the long run. This question was addressed in a large study with published results, the "Medical Therapy Of Prostate Symptoms" (MTOPS) trial, and is being investigated in a second large study, "Combination of Avodart and Tamsulosin" (CombAT), which has completed 2 of the 4 years of its planned duration.

In MTOPS, patients were randomized to receive 1 of 4 types of treatment: monotherapy with the alpha blocker doxazosin (Cardura), monotherapy with the 5-ARI finasteride (Proscar), combination therapy with both agents, or placebo. The patients were followed for 5 years. At the end of 5 years, compared to patients treated with placebo, those who received combination therapy had a 67% lower risk for clinical progression of BPH. There was no significant difference in disease progression among patients treated with either monotherapy, although there was a trend to better outcomes with finasteride. Treatment efficacy was similar with either monotherapy and was superior to placebo but was not as good as combination therapy.[4]

Other studies such as the Veterans Administration Cooperative (VA-Coop) Study and PREDICT that looked at monotherapy and combination therapy that included finasteride also did not show a huge difference between monotherapy treatment arms, but showed a benefit from combination therapy. In the VA-Coop study, there appeared to be no difference in the short-term response to 5-ARI versus placebo.

These studies led to the belief that it was the "small volume" prostates (less than 30 cc) that prevented the differentiation of the efficacy of the alpha blocker (doxazosin) compared to the 5-ARI (finasteride). The patients with small volume prostates did not seem to get any significant symptom response over that achieved by the placebo in these one-year trials. That belief stimulated the development of the MTOPS and the later CombAT study.

To be included in MTOPS, patients had to have symptoms of benign enlargement of the prostate, no evidence of prostate cancer, a serum PSA value of less than 4 ng/ml, and only at least mild symptoms on the International Prostate Symptom Score (IPSS) scale.

In the CombAT trial, the investigators recruited patients who were at "higher risk" for disease progression.[4,24] They had to have a prostate volume greater than 30 cc (as determined by transrectal ultrasound), a serum PSA value of 1.5 ng/ml to 10 ng/ml, and an IPSS score of at least 12, which meant that these patients all had at least moderate IPSS symptoms of BPH. As previously stated, this would suggest that these patients were at a higher risk for disease progression. The actual baseline average prostate

volume was 54 cc. Compared to MTOPS, CombAT used different drugs: the alpha blocker tamsulosin (Flomax) and the 5-ARI dutasteride. The 2-year data of this 4-year trial demonstrated a significant reduction in IPSS scores in the combination arm compared to either monotherapy arm. For the first time, even with symptom management, as early as 15 months, the 5-ARI showed greater efficacy than the alpha blocker. This was unexpected and significant.[25]

MTOPS did not use questionnaires to assess quality of life in the same way that CombAT did. At the recent European Urological Association Congress (EUA) meeting in Milan, Italy, I reported the responses to the quality of life question in the CombAT trial (question number 8 on the AUA-SI BPH questionnaire) after 2 years of treatment. The responses to this question showed that patients in the combination arm had a greater improvement in their response to the "Quality of Life" question than patients in either monotherapy arm. By about 18 months, patients who received the 5-ARI dutasteride monotherapy had a better response than patients who received the alpha blocker tamsulosin alone.[26]

In MTOPS also, the incidence of acute urinary retention (AUR) decreased and there was a significant decrease in the need for surgery in patients in the combination arm compared to those in either monotherapy arm. We are awaiting the 4-year results of the CombAT trial to see if the same pattern will be reported.

The next question that needs to be asked is: "If a man is prescribed combination therapy, does he have to continue taking this therapy for the rest of his life?" This question has been addressed previously, using finasteride and either a non-selective alpha blocker (Hytrin or Cardura) or a uro-selective alpha blocker (tamsulosin). More recently, results were reported from a trial that looked at dutasteride and the uro-selective alpha blocker, tamsulosin, the "Symptom Management After Reducing Therapy-1 (SMART-1), trial. Patients received combination therapy for 6 months, in a blinded manner. At the end of 6 months, some patients in the combination arm continued treatment and some patients in the alpha-blocker arm discontinued treatment. Three months later, when some patients were receiving monotherapy with dutasteride and some were still receiving combination therapy, they were asked "Do you feel the same, better, or worse compared to the way you felt 3 months ago?". This same question was asked again 3 months later. The results demonstrated that at 6 months, approximately 77% of men receiving monotherapy felt as well as men who were receiving combination therapy.

A similar study that was even closer to real life was completed recently: the PRoscar and alpha-blOcker combinAtion followed by disContinuation Trial (PROACT). In this study, if a patient was already taking an alpha blocker, he continued taking the same alpha blocker in combination with Proscar for 9 months. If he was not already taking an alpha blocker, he was prescribed tamsulosin. At the end of 9 months, the alpha blocker was dropped in some patients. Patients were asked a similar question about their satisfaction with their present therapy, and the patient "satisfaction level" of responses were similar to those in the SMART-1 trial.

Both studies (SMART-1 and PROACT) support the belief that one could consider prescribing combination therapy for 6 to 9 months followed by discontinuation of the alpha blocker. The physician could expect that a significant number of patients would continue to be very comfortable remaining on 5-ARI monotherapy.

The main side effects that one might see with the 5-ARIs include gynecomastia, decreased libido, and some degree of erectile dysfunction, which occur in less than 5% of patients.

Over the last 25 years that we have been actively treating BPH with medical therapy, there has been a significant evolution in the specificity and efficacy of both alpha blocker and 5-ARIs. Today, most men — if they do not have absolute indications for intervention (as discussed earlier) — should at least be offered a trial of medical therapy to try to treat BPH symptoms and prevent disease progression, acute urinary retention, and the need for surgery. Table 2.

It seems that the "golden number" for the prostate volume that will respond to 5-ARI treatment is 30 cc. If a man has a prostate volume of at least 30 cc, or has a serum PSA level of at least 1.5 ng/ml (which is used as a surrogate marker for a prostate volume of 30 cc), then he can expect a significant response from treatment with a 5-ARI, which will shrink the prostate and alleviate his symptoms. The monotherapy of the 5ARI will cause symptom relief much more slowly than the combination therapy of an alpha blocker and a 5ARI. If a patient's symptoms are more significant, then the combination of an alpha blocker plus a 5-ARI is the most effective initial form of medical management. The patient and physician can decide together the duration of combination therapy and whether the patient can switch to monotherapy with a 5-ARI. If the patient's prostate volume is small, and if his symptoms are significant enough to require treatment, then an alpha blocker alone will help to provide a very rapid and significant symptom response.

TABLE 2. **Drugs commonly used to treat benign prostatic hyperplasia**

Monotherapy	**Combination therapy**
Phytotherapeutic agents	-
Saw palmetto	
Alpha blockers	Alpha blocker + 5-ARI combination rationale:
Quick onset of action (weeks)	Prostate greater than 30 cc or serum PSA level
Do not shrink prostate size	greater than 1.5 ng/ml
No effect on serum PSA	Based on MTOPS and CombAT trials
Non-selective agents (doxazosin, terazosin)	Better than alpha blocker or 5-ARI monotherapy
May need dose titration	Reduced risk of symptom progression
Cardiovascular side effects	Reduced risk of acute urinary retention
Selective agents (tamsulosin, alfuzosin)	
No titration	
Minimal cardiovascular side effects	
Sexual dysfuction (tamsulosin, silodosin, alfuzosin)	
5-alpha-reductase inhibitors (5-ARIs)	Potential future combinations
Slow onset of action (3-6 months)	Alpha blocker + anti-cholinergic
Reduce prostate size by approximately 25%	(anti-muscarinic) drug
Reduce serum PSA by 50% after 6 months	5-ARI + anti-cholinergic drug
No dose titration	Alpha blocker + PDE5 inhibitor
Sexual side effects	5-ARI + PDE5 inhibitor
Prostate cancer chemoprevention	
In development	
PDE 5 inhibitors (tadalafil, sildenafil, etc.)	-

5-ARI = 5-alpha-reductase inhibitor; CombAT = Combination of Avodart and Tamsulosin;
MTOPS = Medical Therapy Of Prostate Symptoms;
PDE5 = phosphodiesterase-type 5; PSA = prostate-specific antigen

The other benefit from medical therapy is that any side effect is usually easily reversed by stopping the medication.

Even when a patient with BPH is treated with combination therapy (a 5-ARI and an alpha blocker), he might sometimes still have the same voiding symptoms seen in patients with primary overactive bladder (OAB).[27]

The patient may report that he is voiding with a greater stream and less hesitancy, but still has voiding frequency and urgency, and possibly urgency incontinence. In this case, treating him with an added anticholinergic agent,[28] an antimuscarinic agent,[29] or a bladder relaxant might be very helpful[a] in providing relief and control of symptoms. Concern that this treatment will precipitate acute urinary retention is usually unfounded.

Recently, it has been shown that phosphodiesterase-5 (PDE5) inhibitors such as sildenafil (Viagra, Pfizer) can affect the treatment of LUTS associated with BPH. The addition of a PDE5 inhibitor appears to increase oxygenation (because of the decrease in the nitric oxide metabolism) and stabilize the prostate and bladder. Voiding frequency and urgency may improve. It is interesting to note that there is no increase in the uroflow rates in these patients.

Conclusions

Compared to 25 years ago, the management of BPH today has undergone a paradigm shift. Years ago, TURP was the most common operation performed by a urologist to treat symptoms associated with BPH, and many men with BPH presented with acute, or chronic urinary retention. In the 21st century, most men are initially treated medically for their BPH/LUTS, and if they receive proper care, only a very small percentage of patients will develop urinary retention or will require surgical intervention to manage their BPH.

Take-home messages

To diagnose and treat patients with BPH/LUTS:

- The primary care physician can determine if BPH is the cause of LUTS.
- If the patient has hematuria, recurrent urinary tract infections, signs of renal function deterioration, signs of urinary retention, an abnormal serum PSA value, or an abnormal DRE, or if the patient is refractory to or rejects medical therapy, he should be referred to a urologist.
- A serum PSA cutoff of 1.5 ng/ml can be used as a surrogate for a prostate volume of at least 30 cc (which is the smallest prostate volume that has the best chance of responding to therapy with a 5-ARI).
- If a man has an enlarged prostate and is significantly bothered by LUTS, combination therapy with a 5-ARI and an alpha blocker is likely the most effective therapy.
- After many months of combination treatment with a 5-ARI and an alpha blocker, discontinuing the alpha blocker might need to be considered.
- 5-ARI medications may help prevent prostate cancer developement without increasing the risk of causing a high-grade cancer.
- When a patient who is receiving combination therapy with a 5-ARI and an alpha blocker still experiences LUTS, adding an antimuscarinic agent can be considered.

Disclosure:

Dr. Jack Barkin is an active urologist and Chief of Staff at the Humber River Regional Hospital in Toronto. He sits on the medical advisory board for Abbott, GlaxoSmithKline, Merck Frosst, sanofi-aventis and Boeringer-Ingelheim. He has done the clinical research on Avodart, Flomax, Hytrin, Xatral and Proscar, both in monotherapy and combination. He has spoken all over the world for all of the companies outlined. □

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DISCUSSION

Question: (Dr. Miner)
From the PCP's point of view what is the primary reason for treatment of BPH? How do we share with patients that it is not just a matter of the lifestyle or aging? What is the morbidity and mortality of BPH? Can the severity of the impact on lifestyle be compared to that of COPD?

Answer: (Dr. Barkin)
We know that symptomatic BPH will progress over time if it is not treated in 85% of men. The progression can lead to increased urinary tract infections, hematuria, potentially hydronephrosis, urinary retention and the need for surgery. Most men will compensate early on from the symptoms and signs of BPH by adjusting their lifestyles. For example, no long car trips, no movies, no golf etc. Studies had shown that moderate symptoms of BPH can impact on quality of life as much as severe COPD.

Question: (Dr. Miner)
In a busy PCP's practice, how does one assess urination (i.e. what is a quick and easy screening questions to evaluate urinating)? How reliable is the presence of nocturia, frequency and urgency in differentiating LUTS of BPH from OAB?

Answer: (Dr. Barkin)
In a busy PCP practice the best way to quantify and assess the severity of BPH/LUTS is to ask the patient to answer the 7 question IPSS Questionnaire. The score of less than 8 signifies mild, 8-20 moderate and more than 20 severe disease. A patient with a score of moderate to severe will definitely progress. Question 8-on the quality of life question is the one that will indicate if the patient is motivated to or will accept some type of treatment. That is the question that addresses the patient's desire to tolerate the symptoms for now or the rest of his life. BPH is one of the commonest causes of LUTS symptoms in a man over the age of 50. By doing a urinalysis, focused clinical physical examination including a DRE (digital rectal examination) and creatinine one can rule out most of the other serious causes and offer a "TRIAL of Therapy". If the patient does not respond to the latter, referral to the urologist would be appropriate.

Question: (Dr. Rosenberg)
If a 30-year-old male with no family history of prostate disease comes in to PCP's office with symptoms of LUTS, what are the guidelines on PSA screening?

Answer: (Dr. Barkin)
A 30-year-old male with LUTS, but no family history of prostate cancer should not have a PSA unless the digital rectal examination (DRE) is abnormal. The recommendation is to start PSA testing at the age of 50, unless the family history is significant for prostate cancer (first degree relative) or the patient has an abnormal DRE or belongs to a high risk group, such as African-American/Canadian males.

Question (Dr. Greenberg)
What is the existing evidence on using 5-ARI for prophylaxis in males over 50 years of age with no symptoms or family history of prostate disease?

Answer: (Dr. Barkin)
In the recent 7 year PCPT (Prostate Cancer Prevention Trial) for men over 50 that had no clinical evidence of prostate cancer by PSA or DRE, there was a 25% lower incidence of detecting prostate cancer in those treated with daily finasteride versus placebo. Another study that enrolled only "high risk" patients meaning those that had had a "negative biopsy" that had been done because there was a suspicion of prostate cancer based on an abnormal DRE, elevated PSA or a strong concern because of a positive family history, is now more than half -way finished. This trial compares dutasteride to placebo for 4 years to determine if there is a difference in the incidence of prostate cancer detection. This study is called "REDUCE" The patient that is considering a 5-ARI for "chemo-prevention" of prostate cancer has to weigh the benefit of decreased prostate cancer incidence with the risk of potential drug side effects.

Overactive bladder

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Overactive bladder (OAB) is a common condition (prevalence 14%-18% of Canadians) and has a significant negative impact on quality of life. OAB may be idiopathic or may occur with other common conditions such as bladder outlet obstruction, neurological disease, or stress incontinence. Primary care physicians may safely diagnose this condition by history and physical exam with a minimum of widely available lab tests. Management with behavioral therapies and pharmacotherapy is generally quite successful and warranted. Multiple anticholinergic medications are available and have been shown to be effective. Subtle differences in structure and mechanism of these agents may yield improved therapeutic benefit or tolerability and thus it is reasonable to try more than one drug to achieve the optimal results. For patients that fail behavioral and initial pharmacotherapy or when other complicating conditions are identified, referral to a specialist is indicated; however, the majority of patients with OAB do not require cystoscopy or urodynamics. Successful treatments for OAB do exist and it is worth screening for these disabling complaints at the primary care level.

Key Words: urinary incontinence, overactive bladder

Definition

Overactive bladder (OAB) is a condition characterized by urgency with or without urge incontinence, generally in the presence of frequency and nocturia.[1] The hallmark symptom of urgency is defined as the sudden compelling desire to pass urine which is difficult to defer. Normal frequency in a 24-hour period is eight micturitions and nocturia up to once per night is considered normal. OAB is often subcategorized as OAB wet or OAB dry depending upon whether there is accompanying urge incontinence.

Demographics

The prevalence of OAB in Canada was estimated at 14%-18%[2,3] based on two large scale phone surveys of thousands of men and women. A similar prevalence of OAB of 16% for men and 16.9% for women was found in The National Overactive Bladder Evaluation (NOBLE) study of more than 5000 adult men and women in the United States.[4] OAB occurred with a similar frequency in women and men[4] but OAB wet was more common in women[4] and rates increased with aging.[2-4]

Impact on quality of life and costs

OAB with urge incontinence has been associated with a significant impairment quality of life. Using the generic quality of life measure (SF-36), people with urge incontinence suffered impairment compared to age and gender matched controls in the domains of physical function, social functioning, physical and emotional role functioning, and vitality.[5]

In a survey of the total impact of urinary incontinence, Jackson[6] found psychological concerns amongst individuals suffering from the incontinence along with family and caregivers. Individuals with urinary incontinence expressed embarrassment, anger, social restriction and isolation, and loss of self esteem. The

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desire to be sexually intimate was often impaired. Family and caregivers reported guilt, frustration, and concerns over social burden and job absenteeism. Physically, urinary incontinence was associated with skin rashes and breakdown, urinary tract infections, sleep disturbances, depression, and falls.[7] In women over 65 with OAB, Brown et al found higher rates of falls and resultant fractures leading to a high rate of morbidity and mortality.[8]

The economic costs of OAB and urinary incontinence are immense for both individuals and the health care system. Individual costs are associated with pads, laundry, and medications. Health care systems bare costs for diagnosis, supplies, and often long term care. One of the most common reasons for institutionalizing of an elderly patient to a long term care facility is the added burden of managing urge incontinence in the home. One study estimated the 1995 societal cost of incontinence for individuals over 65 years of age at $26.3 billion dollars.[9]

Despite the large potential impact OAB has on patients, they are often reluctant to discuss their concerns with primary care physicians or seek help. Reasons for underreporting of OAB were found to be: embarrassment, false impression that it is a natural part of aging, lack of information regarding management options, low expectations of benefit from reporting, and the fear that it is an indication of failing health.[10]

Etiology and differential diagnosis of OAB

OAB may occur as an isolated condition (idiopathic) or may be found in association with a known neurological condition (multiple sclerosis, stroke, Parkinson's Disease, spinal cord injury, etc), bladder outlet obstruction (prostatic enlargement, pelvic floor dysfunction), or other bladder irritants (urinary tract infection, carcinoma in situ or bladder cancer, etc).

OAB results from neuromuscular control problems of the bladder. Spontaneous, involuntary contractions of the detrusor muscle during bladder filling may be observed on urodynamic testing. These abnormal, overactive contractions of the bladder are associated with urgency and urge incontinence. Coordinated, control of micturition involves a complex number of nerve pathways from higher cortical centers, the pontine micturition center, spinal cord nerves, peripheral nerves, and local receptors at the bladder level. Abnormalities at any of these levels may lead to OAB.

Investigations for OAB

For most patients complaining of OAB, basic office based evaluation by primary care physicians is sufficient to safely rule out other complicating conditions and initiate first line therapy.[11] History should focus on other coexistent lower urinary tract symptoms, medical conditions such as diabetes mellitus or neurological disease, medications (diuretics), and contributors such as chronic constipation, peripheral edema, and excessive fluid or caffeine intake. Physical exam should rule out a distended bladder, check for an enlarged prostate in men or vaginal prolapse, masses, or atrophy in women, and screen for neurological deficits. A urinalysis to rule out hematuria or signs of infection, serum creatinine, PSA in age appropriate men, and fasting blood sugar may be all that are required in a healthy patient with simple OAB. An ultrasound post void residual measurement via an outpatient diagnostic center or bladder scanner would be appropriate for patients with coexistent conditions that may lead to poor bladder emptying such as benign prostatic hypertrophy, diabetes mellitus, neurological disease, and the frail elderly. Controversy exists regarding what represents a clinically significant elevation of post void residual, but a conservative measure would be considering any volume greater than 50 cc as potentially significant.[12] A frequency volume chart (patients record the time and volume of each void for a 24 hour period) may be useful to identify polyuria or isolated nocturnal polyuria as a cause of nocturia. A fluid intake diary may also identify excessive fluid intake including caffeinated beverages. Specialist investigations including cystoscopy and urodynamics are not required for evaluation and successful management of the majority of patients with OAB. The purpose of cystoscopy is to rule out other causes of urgency and frequency or factors that may exacerbate OAB such as bladder cancer, chronic inflammation, bladder stones, etc. A multichannel urodynamic study is performed by a nurse or clinician and requires the passage of small catheters into the bladder and rectum for measurement of pressures. Water, contrast, or gas is infused into the bladder and the presence of abnormal overactive bladder contractions along with their magnitude and associated leakage can be demonstrated. Testing can also be done for other types of incontinence such as stress incontinence, problems with bladder compliance, and at the conclusion of the study the presence of bladder outlet obstruction may be identified during voiding. Urodynamics will not change the management of most patients with OAB, but they may be indicated for patients with neurological bladder dysfunction (high bladder pressures may be associated with renal function deterioration), mixed incontinence, or possible bladder outlet obstruction.

Management of OAB

Patients with OAB associated with other conditions (as discussed previously) may improve with treatments targeting these coexistent pathologies. For example, relieving bladder outlet obstruction with transurethral resection of the prostate or release of an obstructing bladder neck sling may lessen OAB symptoms. Similarly, patients who have symptoms of OAB caused by diuretics prescribed for hypertension may benefit from switching to an alternate antihypertensive.

While the mainstay of therapy for OAB is generally anticholinergic medications, one cannot overstate the importance of first line or simultaneous behavioral therapy interventions. Behavioral therapy incorporates pelvic floor strengthening (Kegel exercises with or without adjuncts such as biofeedback, electrical stimulation, or weighted vaginal cones), timed voiding, urge suppression, and fluid management. Prompted or timed voiding may avoid the bladder reaching volumes that trigger urgency and practice delaying the initiation of voiding by utilizing the guarding reflex may help. Fluid intake should be encouraged evenly throughout the day and caffeinated beverages should be limited.

The importance of behavioral therapy for treating OAB was nicely demonstrated in a recent Health Education Trial.[13] During this 16 week trial patients were randomized to tolterodine alone or tolterodine with a 5 minute health education intervention. The group receiving the counseling reported significantly increased use of non-drug OAB therapies, better medication compliance, and higher levels of improvement of OAB symptoms.

The mainstay of pharmacotherapy for OAB is the anticholinergic (antimuscarinic) group of medications.

TABLE 1. **Antimuscarinic selectivity of currently available agents**

Nonselective for M3 receptors	**Selective for M3 receptors**	**Combined**
Atropine		
Propantheline	Darifenacin (M3)	Oxybutynin
Tolterodine	Solifenacin (M3 > M2)	
Trospium		

Recent years have shown an expansion of the number of agents available to be prescribed in this grouping and a brief overview of the specific receptors responsible for activity and side effects is important to aid in selection of an appropriate medication for an individual patient. The detrusor has both M2 and M3 receptors. It is felt that the M3 receptors may the most important to block with pharmacological agents. M3 receptors are also found on the salivary glands and the smooth muscle of the gastrointestinal tract. Inadvertent blockade of the receptors on these other organs is responsible for undesired side effects including dry mouth and constipation. M5 receptors are found on the heart and effects on these receptors could lead to arrythmias. Central nervous system side effects are also possible with anticholinergic agents that cross the blood brain barrier or interfere with M1 receptors found in the brain. Table 1 characterizes currently available anticholinergic agents based on their selectivity or additional mechanisms of action and Table 2 summarizes the currently available formulations of these agents. All agents with the

TABLE 2. **Currently available formulations of antimuscarinic agents to treat OAB**

Oxybutynin IR	Generic oxy	5 mg	Daily to QID
Oxybutynin ER	Ditropan XL	5 mg or 10 mg	Once daily 30 mg maximum
Oxybutynin ER	Uromax	10 mg or 15 mg	Once daily
Oxybutynin TDS	Oxytrol	3.9 mg	Twice weekly
Tolterodine IR	Detrol	1 mg or 2 mg	BID
Tolterodine ER	Detrol LA	2 mg or 4 mg	Once daily
Darifenacin	Enablex	7.5 mg or 15 mg	Once daily
Solifenacin	Vesicare	5 mg or 10 mg	Once daily
Trospium	Trosec	20 mg	BID (empty stomach)
Trospium	*Sanctura XR	60 mg	Once daily

*Available in the USA not Canada at this time

exception of trospium, have hepatic metabolism. Thus, in a patient with hepatic insufficiency or taking multiple medications which are metabolized via the liver, there may be a theoretical advantage to the use of trospium. Contraindications to the use of anticholinergic medications are: untreated narrow angle glaucoma (the majority of patients with glaucoma may safely take anticholinergics but this should be cleared by their ophthalmologist before commencing) and urinary or intestinal obstruction.

The choice of a particular anticholinergic agent should balance patient variables (age, compliance, hepatic or renal impairment, other medications, etc) with drug variables (dosing frequency, side effects, hepatic or renal metabolism, propensity to worsen cognition, etc). For patients without private drug insurance or covered on provincial drug formularies, the practical considerations of coverage and cost are often the over riding consideration when selecting an initial agent. While studies suggest that all available agents are effective at reducing symptoms of OAB compared to placebo, it is clear from clinical practice that some patients do better (efficacy and tolerability) with one agent versus another. Thus, it is often worthwhile to encourage patients to try two or three different anticholinergic agents to find the medication with the best balance or side effects and benefit.

Special considerations

Two common clinical conditions may coexist with OAB and warrant mention: prostatic enlargement in men and postmenopausal genital atrophy in women.

Lower urinary tract symptoms in men with prostatic enlargement/bladder outlet obstruction include both voiding symptoms (slow stream, hesitancy, intermittency, double voiding, post void dribble) and storage symptoms (frequency, nocturia, urgency, and urge incontinence). In men with predominately storage symptoms, there is obvious overlap with OAB. While these lower urinary tract symptoms may be due to prostatic pathology, it is also reasonable to believe that primary detrusor activity could be contributing. Thus, in men with storage symptoms who have not responded to classic benign prostatic hypertrophy pharmacotherapies with alpha blockers or 5 alpha reductase inhibitors, there is an increasing role for the addition of anticholinergic agents. The potential concern of worsening post void residual urines volumes or triggering urinary retention, appears to be very small.[14,15]

Postmenopausal women are a common demographic to suffer from OAB and a finding of vaginal atrophic changes occurs frequently in this group. There is data to suggest that women who have symptomatic vaginal atrophy (dryness, burning, etc) and coexistent OAB symptoms may benefit from local vaginal estrogen supplementation.[16] However, there is no data to suggest that full systemic hormone replacement therapy (HRT) is indicated and large trials of HRT have found higher levels of OAB symptoms in women taking HRT for prolonged periods suggesting an adverse association.[17]

Other managements for OAB refractory to behavioral and pharmacotherapy

Despite the number of new pharmacotherapies for OAB, there remains a group of patients that do not achieve a satisfactory level of control of their frequency or urge incontinence. Other options for management of such patients include off label intravesical injection of botulinum toxin A, sacral or peripheral neuromodulation, or major reconstructive surgery such as a bladder augmentation (ileal enterocystoplasty) or urinary diversion.

While botulinum toxin A is not currently approved for the management of refractory OAB in Canada or the United States, there is increasing evidence that injection of this agent into multiple sites of the bladder under cystoscopic guidance can result in significant improvement of both subjective and objective measures in both idiopathic[18] and neurogenic[19] OAB and off-label use of this agent is increasing. Botulinum toxin A inhibits the release of acetylcholine into the synaptic cleft of the motor nerve and as such can be a potent muscle relaxant of both smooth and skeletal muscle. One of the limitations to the use of botulinum toxin A is the chance of inducing urinary retention. Some elderly patients with refractory OAB may not be able or willing to consider a treatment that could potentially require them to perform clean intermittent catheterization.

Sacral neuromodulation (Interstim) and peripheral neuromodulation (Stoller Afferent Nerve Stimulator) have both been shown to reduce the symptoms of OAB and urge incontinence.[20,21] Unfortunately, the cost of these devices and the supportive programs for operation, have led to very limited access in Canada.

OAB summary

OAB is a common medical condition that is not confined to the elderly. It is associated with significant impairment of quality of life and may contribute to other serious health concerns such as falls and fractures.

Patients may fail to bring up concerns of OAB with their primary care physician for many reasons including embarrassment, so it is paramount that physicians screen for bothersome symptoms. Most patients with OAB require only simple, office-based evaluation. Primary care physicians should feel comfortable initiating behavioral and pharmacotherapies for OAB. Patients who fail to respond to these managements or have other concerns such as hematuria or high post void residual (> 50 cc) identified, should be referred for specialist evaluation.

Take-home messages

Indications for specialist referral

- Microscopic or gross hematuria
- Elevated post void residual (> 50 cc)
- History of neurological disease (multiple sclerosis, Parkinson's disease, stroke, spinal cord injury, etc)
- History of recurrent urinary tract infections
- Pelvic pain
- Previous genitourinary trauma or surgery
- Abnormal prostate exam or elevated PSA
- Not responding to behavioral therapy and a trial of an anticholinergic medication

Disclosure

Dr. Lesley Carr has received compensation for lecturing and/or participating in advisory boards for Astellas, Pfizer, Janssen-Ortho, Purdue Pharma, Triton, Medtronic, and Allergan. □

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DISCUSSION

Question (Dr. Rosenberg):
At which point should the patient be referred for cystoscopy and/or urodynamics studies?

Answer (Dr. Carr):
A patient should be referred for further investigations, possibly including cystoscopy, when evaluations by the PCP pick up other co-existent problems such as hematuria or pyuria, recurrent urinary tract infections, elevated post void residual (> 50 cc), or pain possibly referable to the urinary tract. In addition, patients with potentially contributing conditions such as bladder outlet obstruction (BPH, pelvic floor dysfunction), stress urinary incontinence, or neurological disease (multiple sclerosis, stroke, spinal cord injury, Parkinson's disease, etc) may benefit from multichannel urodynamic evaluation

Question (Dr. Greenberg):
Please comment on the impact of alcohol and caffeine on patients with OAB.

Answer (Dr. Carr):
Behavioral therapies such as diet modification may yield significant reduction in OAB symptoms. For example, attempts should be made to minimize caffeine and alcohol intake. These agents may aggravate OAB by bladder irritant effect or diuretic challenge.

Question (Dr. Laroche):
Please discuss your pharmaceutical approach when treating a patient on an active medication for cognitive impairment (Aricept, Exelon, Reminyl, Ebixa...)

Answer (Dr. Carr):
Patients with Alziemer's disease and other neurocognitive degenerative diseases frequently suffer from OAB. Behavioral therapies such as prompted voiding may be very important in this group as perception of warning time and mobility may be significant impediments to the control of urge incontinence. Caution should be used in prescribing anticholinergic agents due to potential CNS side effects especially if the patient is already taking active treatment with agents for cognitive impairment such as Aricept. Anticholinergic agents such as trospium or darafenacin may be potentially safer choices, but my recommendation is to discuss the use of any anticholinergic drug in this population with their neurologist or geriatrician prior to commencing use.

Female stress urinary incontinence

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WANG A, CARR LK. Female stress urinary incontinence. The Canadian Journal of Urology. 2008;15(Supplement 1):37-43.

Introduction: *Stress urinary incontinence is a common and costly condition amongst community dwelling women. It can have a significant negative impact on the quality of life and yet less than half of women with urinary incontinence seek medical attention. It is important for primary care physicians to have a clear understanding of stress urinary incontinence in order to screen and manage patients who may have bothersome symptoms.*

Objective: *This article aims to outline the terminology, pathophysiology, clinical evaluation and treatment of female stress urinary incontinence.*

Conclusion: *Female stress urinary incontinence can be effectively evaluated and managed in the primary setting. Specialist referral is warranted when there is complex urinary symptomatology, hematuria on work-up or failure of conservative therapy.*

Key Words: stress urinary incontinence, family physician

Terminology

Urinary incontinence (UI) can be broadly divided into three types: stress, urge or mixed. Stress urinary incontinence (SUI) is defined as the complaint of involuntary leakage on effort or exertion, or on sneezing or coughing. Urge urinary incontinence (UUI) is the complaint of involuntary leakage accompanied by or immediately preceded by urgency. Urgency refers to a sudden compelling desire to pass urine, which is difficult to defer. Mixed urinary incontinence (MUI) is a combination of both SUI and UUI.[1]

Demographics

In a Canadian nation-wide telephone survey conducted in 2002, 5.4% of men and 28.8% of women had UUI, SUI or MUI. Of the women with UI, 68% had only SUI, 11% had only UUI and 21% had MUI. The peak prevalence of SUI was in those aged 41-64 years.[2] UUI and MUI

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become more prevalent in both men and women over 75 years of age.[3]

Impact of quality of life and costs

Like other chronic health conditions, UI significantly impacts on quality of life (QoL), both physically, psychosocially and furthermore, has major economic ramifications.[4-6] SUI can results in social embarrassment,[7] adversely affect social relationships,[8] restrict physical activity,[9] impair personal hygiene and lead to avoidance of sexual relationships. There is an individual direct cost for purchasing supplies, laundry and dry cleaning specific for incontinence.[10] Despite this, less than half of the women with symptoms initiated a conversation with a physician about urinary symptoms.[11] This is possibly due to the social stigma, belief that UI is a normal part of aging or ignorance regarding available treatments [12].

Continence mechanisms in women

Continence in women is maintained by a coordinated effort between the bladder, urethra, pelvic muscles and the surrounding connective tissue. The function of the lower urinary tract is to either store (storage phase) or to expel urine (voiding phase). This depends on a bladder that is able to expand while maintaining a low constant pressure, in the absence of involuntary detrusor contractions. The body of the bladder is innervated by parasympathetic nerves via M_3 muscarinic receptors and it is responsible for bladder contraction. The bladder neck receives sympathetic innervation. Normal storage of urine is dependent on spinal reflex mechanisms that activate sympathetic and somatic pathways to the bladder outlet and tonic inhibitory systems in the brain that suppress parasympathetic outflow to the bladder.[13]

The female urethra has skeletal muscle (rhabdosphincter) and smooth muscle. The rhabdosphincter consists of small, type I fibers located predominantly in the middle third of the urethra. The urethral smooth muscle is arranged in longitudinal and circular layers. Both contribute to the resting tone and the rhabdosphincter, in addition, responds to rises in intra-abdominal pressure. Muscles of the pelvic floor (levator ani complex) also contribute to continence by pulling the vagina forward to create a backstop for the urinary tract during rises in intra-abdominal pressure. Urethral mucosal factors are important for coaptation to achieve a watertight seal. Continence is maintained when the urethral pressure exceeds intravesical pressure.

The voiding phase starts with relaxation of the urethra followed by a sustained detrusor contraction caused by an increase in the parasympathetic transmission to the bladder. The micturition reflex is normally under voluntary control and is organized in the rostral brain stem (the pontine micturition center). It requires integration and modulation by the parasympathetic and somatic components of the sacral spinal cord (the sacral micturition center) and the thoracolumbar sympathetic components.[14] Intravesical pressure increases sufficiently during voiding to allow the bladder to empty.

Aetiology and risk factors of female SUI

SUI occurs when vesical pressure exceeds urethral pressure, in the setting of increases of intra-abdominal pressure. This can be due to an anatomical change such as a loss of backstop support at the bladder neck, or because of neuromuscular dysfunction of the sphincter. Loss of bladder neck support is referred to as bladder neck hypermobility and treatments target the restoration of that support. Sphincteric dysfunction is referred to as intrinsic sphincter deficiency (ISD). It is believed that most patients have elements of both disorders in varying degrees.

Risk factors for SUI include weak collagen, age, childbearing, obesity, constipation, advanced pelvic organ prolapse and chronic obstructive airways disease. Lifestyle factors such as heavy smoking (more than 20 cigarettes per day) and tea drinking were found to be associated with SUI.[15,16]

Evaluation of SUI

The Canadian Urological Association (CUA) guideline for incontinence (2005) recommends a basic evaluation consisting of history, physical examination, evaluation of post void residual (PVR) volume and urinalysis. Completion of a voiding diary and a quality of life questionnaire by the patient or caregiver is helpful in determining the severity of symptoms, impact on lifestyle and treatment efficacy.

History

History should include an assessment of urinary storage symptoms (frequency, nocturia, urgency and incontinence) and voiding symptoms (hesitancy, poor or interrupted stream, straining and terminal dribbling). Frequency of incontinence episodes, number of pads used, conditions of loss, relations to drug treatments (e.g. ACE inhibitors, diuretics, alpha blocker), voiding habits and fluid intake need to be evaluated. The degree of bother and impact on QoL are two important aspects to assess as it will determine the need to intervene. History of urinary tract infection

TABLE 1. **International Continence Society pelvic organ prolapse quantification and staging system**[18]

0	No prolapse is demonstrated
1	The most distal portion of the prolapse is greater than 1 cm above the level of the hymen
2	The most distal portion of the prolapse is less than 1 cm above or below the level of the hymen
3	The most distal portion of the prolapse is greater than 1 cm below the level of the hymen but protrudes no more than 2 cm less than the total vaginal length
4	There is complete eversion of the total length of the lower genital tract. The distal portion of the prolapse protrudes by at least 2 cm less than the total vaginal length

or poorly controlled diabetes mellitus or insipidus can impact on lower urinary tract function and need to be elicited. Patients should also be asked about fecal incontinence and pelvic organ prolapse (POP), which may accompany SUI.

Physical examination

Physical examination is focused on organ systems that could be implicated in UI. The initial assessment includes general observations for mobility, cognitive status, peripheral edema and body habitus; abdominal examination for pelvic masses or a distended bladder, and a focused neurological examination if appropriate. Pelvic examination is performed to assess the estrogen status, presence of POP, urethral hypermobility, pelvic floor muscle tone and leakage during coughing or valsalva. Atrophic vaginitis clinically manifests as pale vaginal epithelium, often with associated inflammation characterized by patchy erythema, petechiae and increased friability.[17] POP can be assessed by asking patient to strain in the dorsal lithotomy position, with the aid of a Sims speculum or the posterior blade of a bivalve speculum. It can be classified into stages, based on the relationship of the point of maximal protrusion to the hymenal ring, see Table 1.[18] Clinical stress test can be performed with patient in the dorsal lithotomy or supine position with a full bladder and ask her to cough or strain. If urinary leakage is not demonstrated, the test can be repeated in the upright position. Urethral hypermobility refers to the descent of the bladder neck and urethra during coughing or valsalva. It can be confirmed by a Q-tip test by inserting a well lubricated cotton-tipped applicator into the urethra and assess the change in the angle from the resting position to maximal strain. An angle greater than 30 degrees indicates hypermobility.[19] The strength of the pelvic floor muscles is assessed during bimanual examination by asking patients to contract muscles around fingers of the examining physician. The ability to voluntarily contract the pelvic floor muscle as well the strength of the contraction should be noted.

Investigations

Investigations such as PVR measurement can be done with a genitourinary (GU) ultrasound, bladder scanner or in-and-out catheterization. PVR can be falsely elevated with bladder over-distension e.g. large fluid intake prior to GU ultrasound and may need to be repeated. Urine analysis (UA) is performed to exclude a urinary tract infection and hematuria. Confirmatory urine microscopy and culture may be necessary if an abnormality is detected on UA. Similarly, if glucose is positive on the UA, further serum glucose testing is necessary to establish the diagnosis of diabetes.

Bladder diary

A 3-day bladder diary documenting the type and volume of fluid consumption, voiding frequency and volume as well as incontinence episodes is useful for assessment and advise behavioral changes.

In patients with complex symptomatology (MUI or suspected voiding dysfunction), refractory SUI with prior anti-incontinence surgery or those seeking surgical treatment, cystometry or a more comprehensive urodynamic study can be performed.[20,21] Urology referral will be appropriate for these patients. Those with hematuria on work-up also require a referral to exclude urological malignancies.

Management

Behavioral modification and pelvic floor muscle training

Weight loss and exercise in morbidly obese patients reduces SUI, and also to a certain extent UUI.[22] A lowering of fluid intake can reduce SUI[23] while smoking cessation decreases the contribution of a smoker's cough to SUI.[15,16]

Pelvic floor muscle training (PFMT) involves strengthening the pelvic floor muscles (levator ani). A meta-analysis has shown that women undergoing PFMT were seven times more likely to be cured and 23 times more likely to show improvement.[24] The

current practice is for women to be taught to contract in two ways: maximum short (1 second) contractions to encourage activation of the type 2 (fast) fibers and sustained contractions (1 to > 20 seconds) to activate the type 1 (slow) fibers.[25] There is no universally agreed number of voluntary levator contractions that should be performed as part of ongoing PFMT. Twenty-four to 36 daily contractions have been recommended based on the training principles of sports physiology.[26] In addition, women are taught to perform strong, precisely timed levator contractions just before physical stressors such as coughing, sneezing and lifting. It is useful to supplement oral instructions with coaching on how to perform exercises during a pelvic examination. Referral to a physical therapist may be beneficial for women who are unable to identify their pelvic floor musculature. PFMT can be combined with biofeedback equipments such as intravaginal resistance devices or weighted vaginal cones but these have not been shown to improve the efficacy of PFMT.[24]

Pharmacotherapy

Currently there is no approved pharmacotherapy for the treatment of female SUI in Canada. Serotonin and noradrenaline reuptake inhibitors (SNRIs) such as Duloxetine have been used in Europe for the treatment of SUI. Serotonin causes bladder relaxation and increases outlet resistance by inhibiting parasympathetic activity while increasing sympathetic and somatic activity. A recent systematic review found that Duloxetine treated group reports a higher subjective cure rate, greater reduction in incontinence episode frequency and better quality-of-life scores.[27] Adverse effects such as nausea is common.[27] Duloxetine is not approved in Canada for the treatment of SUI and therefore cannot be recommended for off-label clinical use in the primary care setting. Adrenergic agonists have been investigated for the treatment of SUI but there is not enough evidence to assess their efficacy either compared to or combined with other treatments.[28] Estrogen replacement therapy has been used in the past but the Heart and Estrogen/Progestin Replacement Study showed a significantly higher risk of SUI and UUI for women on estrogen replacement with or without progestin. Initiation of hormonal therapy for SUI is therefore not indicated.[29]

Devices

Intravaginal devices work by creating a 'backstop' at the level of the bladder neck. They include a short super tampon inserted just inside the introitus and a variety of modified pessaries with a knob placed at the bladder neck. These devices are not well studied and are not universally offered as a form of treatment for female SUI. Patients who desire non-surgical treatment for SUI and demonstrate continence after a device is fitted are appropriate candidates. Pessaries require upkeep, including the need to be removed and cleaned regularly. The disadvantages include a small amount of bother with insertion, need for continued use, rare vaginal excoriation/erosion and excessive or malodorous vaginal discharge. Postmenopausal women may benefit from vaginal estrogen in combination with pessary use.[30]

Surgical treatments

Injection of bulking agents is the least invasive surgical procedure and can be done under local anesthesia in an outpatient setting, with minimal recovery time. Autologous fat, bovine cross-linked collagen (Contigen), carbon beads (Durasphere), silicone (Macroplastique), crossed-linked hyaluronic acid and dextranomer microspheres (Zuidex), Ethylene vinyl alcohol copolymers (Tegress) and calcium hydroxylapatite (Coaptite) have been used.[31] Short-term cure rates (complete dryness) for collagen ranges from 30%-78%. Long-term results (up to 2 years) suggest a continuous decline in success rates and repeated injections are often required.[32] It may be a useful option for short-term symptomatic relief amongst selected women with co-morbidity that precludes anesthesia.[33] Bulking agents are not covered by most insurance companies in Canada and thus further limit their use in clinical practice.

Colposuspensions are surgical procedures aimed at correcting urethral hypermobility. The Burch colposuspension is the most commonly performed suspension procedure whereby periurethral fascia on both side are approximated to Cooper's ligaments on the superior aspect of the pubic bone. It restores the urethrovesical junction to a retropubic location. It can be performed through an open abdominal or laparoscopic approach. For open Burch colposuspension, the overall continence rate is approximately 85% to 90% within 5 years of treatment. Seventy percent of patients can be expected to be dry after 5 years.[34] In a recent meta-analysis, cure rates are similar for the open and laparoscopic procedures at 2 years.[35]

Pubovaginal sling was originally described as an autologous rectus fascial sling positioned at the bladder neck. Albo and Richter[36] conducted a randomized controlled trial of 655 women comparing open colposuspension and autologous rectus fascial pubovaginal sling. The success rates for SUI at 24 months were 66% for the sling group and 49% for the colposuspension group. However, more women in the sling group has urinary tract infection, difficulty voiding and postoperative urge incontinence.[36]

Midurethral slings have become the mainstay of treating SUI due to its minimally invasive nature and therapeutic efficacy. The newer slings are made of type 1 macroporous polypropyline and can be inserted through a retropubic or transobturator route. It sits underneath the middle third of the urethra to act as a backstop at times of sudden rises of intra-abdominal pressure. In a randomized controlled trial comparing tension-free vaginal tape (TVT) and Burch colposuspension, the success rates at 2 years were similar.[37] A recent meta-analysis showed that TVT outperformed colposuspension in terms of postoperative continence and is equivalent to pubovaginal slings. The retropubic and transobturator tapes have similar cure rates.[38]

All surgical procedures for SUI carry risks of voiding dysfunction, de novo detrusor overactivity (DO), increased risk of urinary tract infection and failure to adequately treat stress-incontinence symptoms. A meta-analysis showed similar complication rates after TVT and Burch colposuspension, with the exclusion of bladder perforation which was more common after TVT and reoperation rate which was significantly higher after Burch colposuspension. TVT and pubovaginal slings also have similar complication rates. Comparing retropubic and transobturator tapes, the occurrence of bladder perforation, pelvic hematoma and de novo DO was significantly less common in patients treated by transobturator tapes.[39]

Artificial urinary sphincter can be placed around the bladder neck for female SUI. It is uncommonly used in patients with refractory SUI and congenital genitourinary malformation.

Research

Injection of autologous myoblasts has been studied as a novel treatment for female SUI. In preclinical studies, autologous myoblasts obtained from skeletal muscle biopsy can aid in the regeneration of rhabdosphincter and fibroblasts in the reconstruction of urethral submucosa. Strasser et al reported their 12-month results comparing ultrasound guided autologous cells (myoblasts and fibroblasts) injection and collagen injection. The success rates (completely continent) were 90.5% (38 out of 42) and 9.5% (2 out of 21) respectively.[40] In a Canadian clinical trial pioneering muscle-derived stem cell injection in an outpatient setting, five out of eight patients reported improvement with a mean follow-up of 16.5 months.[41]

SUI summary

SUI is common in women but it is under-reported and under-treated. It negatively impacts on the QoL of those affected and patients may fail to initiate conversation regarding their urinary symptoms due to embarrassment. Most SUI can be evaluated in the primary care setting after careful history and simple clinical assessment. Treatment with behavioral modification and PFMT can be then initiated. Refractory SUI to these measures warrants specialist referral. Midurethral slings have become the mainstay of surgical treatment due to its minimally invasive nature and equivalence in outcome compared to other surgical treatment options.

Take-home messages

- Stress urinary incontinence (SUI) amongst community dwelling women is a common and often distressing condition. Over half of those affected will not seek medical attention so it is important for primary care physicians broach this subject to identify those who need help.
- Simple evaluations such as history, physical examination, assessment of postvoid residual, urine analysis and completion of a bladder diary are all that is required prior to initiating treatment.
- Behavioral modification such as limiting oral fluid intake, weight loss and smoking cessation as well as pelvic floor muscle training have been shown to be effective in the treatment of SUI.
- Specialist referral is appropriate in patients with complex symptomatology (significant urge component or suspected voiding dysfunction), failed conservative therapy and hematuria on work-up.
- Midurethral slings have become the mainstay of surgical therapy but other surgical options such as injection of bulking agents, various suspension procedures, pubovaginal sling and insertion of an artificial sphincter may be appropriate in selected patients.

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DISCUSSION

Question (Dr. Miner):
Most PCPs treat SUI as they would treat OAB, it is quite reasonable since most of these disorders are mixed. Please comment on treatment options (drugs/surgical/behavioral) of the urge component versus stress component of these mixed disorders.

Answer (Dr. Carr):
Mixed urge and stress incontinence in women commonly coexist. A specific history should attempt to elicit the predominate complaint between these two conditions and initial therapy should focus on this most problematic component. Fortunately, behavioral therapies (dietary, pelvic floor rehabilitation), as outlined above, may benefit both types of incontinence. When urge incontinence is the major contributor, anticholinergic medications are the treatment of choice. Even if the stress component is not remedied, the overall level of incontinence may lessen to a level that is manageable for the patient. When stress incontinence is the major component or anticholinergic medications have not brought the overall incontinence to an acceptable level, then it is reasonable to refer the patient to a specialist for consideration of surgical intervention for stress urinary incontinence.

Question (Dr. Rosenberg):
Please comment on how a PCP could assess urethral mobility, if at all, in his office.

Answer (Dr. Carr):
The assessment of urethral mobility is important in the context of choosing an appropriate surgical repair for stress incontinence. For example, a retropubic suspension or mid urethral tape are more appropriate choices when a degree of urethral hypermobility is present and a bladder neck sling may be more appropriate for women with a very rigid, scarred urethra. To this end, the assessment of urethral hypermobility by a PCP is really not as important as checking for contributing conditions such as postmenopausal atrophy, prolapse, and muscle tone. I would recommend that a PCP take the time to teach a properly executed pelvic floor muscle contraction (Kegel) rather than focus on assessing urethral hypermobility.

Question (Dr. Laroche):
What is your clinical experience when treating stress incontinence with Cymbalta: do you feel others SSRIs could be effective?

Answer (Dr. Carr):
I have no personal experience using SSRIs or SNRIs to manage stress incontinence. Clinical trials suggested that Duloxetine (Cymbalta), a SNRI, may significantly reduce the number of stress incontinence events likely due to potentiating the effect of the pudendal nerve on the striated sphincter. While Duloxetine has been approved for the use in depression, it has not been approved in North America for stress incontinence and at the moment the potential adverse effects associated with this drug mitigate against its use for stress incontinence.

Interstitial cystitis/painful bladder syndrome for the primary care physician

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Interstitial cystitis also known as painful bladder disorder refers to individuals with chronic bladder inflammation of unknown cause. The presentation of disabling symptoms of urgency, frequency, nocturia, and varying degrees of suprapubic discomfort, is one that the primary care physician will encounter frequently as the prevalence of interstitial cystitis ranges from 10.6 cases per 100,000 to as high as one in 4.5 women, depending upon the criteria used for its diagnosis. Many etiologies are possible. The disorder can be divided clinically into two groups—ulcerative and non-ulcerative—based on cystoscopic findings and response to treatment. In general the diagnosis is made by excluding known treatable causes of bladder irritation. Criteria for the disease are lacking. Management follows an approach of applying the least invasive therapy that affords sufficient relief of symptoms. This monograph attempts to guide the practicing primary care physician from the clinical presentation to a sensible diagnostic work-up and reviews the present management strategies in patients with interstitial cystitis.

Key Words: interstitial cystitis, bladder

Introduction

More than a century has passed since Max Nitze, the German inventor of the modern cystoscope, first described a discreet circumscribed inflammatory lesion of the bladder, identifiable endoscopically, that caused patients to have "heftige Beschwerden".[1] As the microscopic appearance was of inflammatory cells extending into the submucosa Nitze termed the disorder "cystitis parenchymatosa," and described it as a chronic bladder inflammation of unknown cause and no effective treatment. This presentation of disabling symptoms of urgency, frequency, nocturia, and varying degrees of suprapubic discomfort, is one that the primary care physician will encounter frequently.[2] Since the days of Nitze, the presentation has inspired the invention of many evocative identifiers including, painful bladder disease, sensory bladder disease, chronic abacterial cystitis and perhaps the most commonly used current term, interstitial cystitis/bladder pain syndrome (IC/BPS).[3] The many names coined for this disease do not reflect an understanding of its cause which remains as speculative as it was a century ago. The disorder continues to plague sufferers and puzzle researchers. This article reviews this disorder in detail with an emphasis on its recognition by the primary care physician. Correlating the clinical presentation to a sensible diagnostic work-up and pathologic evaluation in patients with interstitial cystitis will hopefully lead to a better future for interstitial cystitis sufferers today than in the time of Nitze.

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Demographics

The prevalence of interstitial cystitis ranges from 10.6 cases per 100,000 to as high as one in 4.5 women, depending upon the criteria used for its diagnosis.[4-7] The disease is more common in women than men, with a female to male ratio of approximately 10:1.[8] Subtyping is suggested by differences in endoscopic and clinical presentation and is important because it reflects fundamental differences in etiology which influences response to treatment.[9] Histologically there are fundamental differences between the two subtypes, ulcer interstitial cystitis presenting a severe abnormality of the urothelium and characteristic inflammatory cell infiltrates while inflammation is scant in nonulcer IC. Regulation of urinary nitric oxide synthase activity has been proposed to be of importance for immunological responses in IC and recent evidence suggests profound differences between the two subtypes concerning nitric oxide production, mirroring the differences in inflammatory response.[10]

Ulcerative

GA Hunner, professor of obstetrics and gynecology at the Johns Hopkins Hospital, deserves the credit for establishing the clinical entity of the ulcerative subtype of interstitial cystitis. "Hunner's ulcer" which was described as a localized submucosal fibrosis was seen through the cystoscope as a discreet area of reddened mucosa with central scar that ruptures and bleeds with increasing bladder distension.[11] We see this uncommon lesion in 5% of out referral population of IC patients. The ulcer is visible at low volumes of bladder fill. Histologically, the ulcer is associated with marked infiltration with chronic inflammatory cells including mast cells.[12] Because it seems to come and go, it has also been called an "elusive ulcer." The patients with ulcers tend to be older and have significantly smaller bladder volumes than patients without ulcers. Most importantly for the clinician, their response to various treatments may be different (for example oral pentosanpolysulfate has less of an effect on ulcerative variety whereas surgical intervention which removes diseased bladder is more successful in this subtype).[9,13] Patients with ulcerative subtype IC have been found to have high levels of NO in the bladder. The highest levels of NO were found in patients in the initial phase of ulcerative IC. The significance of NO levels has been debated and remains an area of investigation.

Non-ulcerative

Patients with non-ulcerative disease do not reveal lesions in the bladder at low volumes on cystoscopy. Patients are typically younger at diagnosis and symptom onset.[14] Under general anesthesia, this group typically has larger bladder capacity. Subjects with non-ulcerative variety have not been found to have significantly increased NO levels in the bladder.

Overview

It is important to emphasize that primary care physicians will most likely be seeing IC early in the natural history of the disease. The disease is diagnosed by symptoms, and the primary care physician will probably be the first medical professional to encounter them. Characteristic symptoms of pain and urinary frequency and urgency should not be forgotten by the primary care physician in the context of IC. Perhaps the most common error made relating to IC is one of omission during the process of methodically excluding other urinary tract diseases. See Table 1. Many patients with IC will prove to have simple UTIs after careful evaluation. A graver pitfall is assigning a diagnosis of IC when, in fact, a urinary tract malignancy is causing symptoms that mask the real problem and suggest IC. Table 2 is included for guidelines for seeking the referral by a urologist. It is reasonable that the primary care physician establishes the diagnosis of IC using the initial tests described in this report. Most of the time, the initial treatment will be initiated by the primary care physician as well.

TABLE 1. **IC/PBS - general observations**

Ulcer variant (Hunner's ulcer) uncommon
Non-ulcer variant much more common
Not confined to women
Can occur in men and children
Prevalence increasing
Greater awareness
Knowledge of overlap with other conditions
Overlapping conditions
Chronic cystitis (UTIs)
Overactive bladder syndrome (OAB)
Gynecologic chronic pelvic pain
Chronic pelvic pain syndrome in men (prostatitis, prostatodynia)
Gastrointestinal disease (irritable bowel syndrome etc)

TABLE 2. **Clinical suspicion of IC/PBS in primary care practice**

Women with symptoms of:
Cystitis with negative urine cultures/non-response to oral antibiotics
Overactive bladder syndrome (frequency, urgency, nocturia etc.) unresponsive to oral anti-cholinergic (anti-muscarinic)
Chronic pelvic pain after gynecologic causes have been identified/treated
Men with symptoms of:
Chronic pelvic pain (scrotal, bladder) and irritative voiding symptoms
Prostitutes/prostatodynia unresponsive to antibiotics, alpha-blockers etc.

Symptom complex

The hallmark of interstitial cystitis is the presentation of irritative voiding symptoms in the presence of cytologically negative urine. Irritative voiding symptoms consist of urinary frequency, urgency, and nocturia and bladder pain. When considering norms in bladder function, it is important to remember that there is great variation in what represents an individual's normal state. The clinician should delineate the patient's normal state of bladder function, and the degree to which symptoms deviate from this state. This is often more important than comparing the patient's symptoms to definitions that apply strictly to a general population. In general terms, urinary frequency occurs when patients need to void more than seven times in 24 hours. Nocturia is present when patients need to get out of bed during the night more that one time. Urgency refers to a strong desire to void, accompanied by the fear that incontinence will occur. Pain associated with interstitial cystitis is often localized to the suprapubic area. In patients with ulcerative interstitial cystitis, pain is often the most bothersome symptom and can be localized to the site of the ulceration. Irritative voiding symptoms can be associated with impairment of normal sexual function and a sexual history should be elicited. Gastrointestinal symptoms are quite common with the disorder and interstitial cystitis often coexists with irritable bowel syndrome.[15]

Etiologic theories

Although numerous theories of pathogenesis have been proposed, an etiology of this disorder that goes beyond our appreciation of its symptoms remains conjectural. Diverse causes of interstitial cystitis have been proposed that include autoimmune, infectious, neurologic, psychologic and epithelial factors.[16-19] The disparity in these areas of study suggests that we haven't really begun to understand the pathophysiology at play in interstitial cystitis. Much has been discussed about a purported causative defect in the glycosaminoglycan component of the bladder epithelium. Glycosaminoglycan (GAG) is a general structural term describing molecules in the form of long unbranched polysaccharide chains composed of repeated disaccharide units. Actually, there is an almost limitless variation in the structure of these molecules, and they are a ubiquitous component of the extracellular matrix. These features imply that the function of glycosaminoglycans is complex, important and diverse, and the function of these complex molecules in the extracellular matrix has been an area of intense study by matrix biologists.

What is known about glycosaminoglycans has been translated into a popular theory to explain interstitial cystitis. This theory poses that the problem of interstitial cystitis results from a defective bladder epithelium, namely in the bladder's lining of glycosaminoglycans (GAGs). GAGs contain a high density of negative charges, allowing them to attract and retain water. In the extracellular space (such as on the luminal surface of uroepithelial cells) low concentrations of GAGs can form hydrated gels rich in water. It is tempting to visualize GAGs as forming a hydrated protective gel that prevents noxious invading substances from attacking the bladder interstitium. A "leak" in the GAG layer, presumably due to bladder injury, could somehow expose sensory nerves in the interstitium to irritants and triggers a noxious sensation.[18] This theory set the stage for popularizing medications that are said to restore the defective bladder lining. Whether the attempt to pin interstitial cystitis to a defective or absent biomolecule or whether the end result of chronic inflammation seen in interstitial cystitis represents more complex cause or causes remains to be seen.

Current work-up

Clinical suspicion for interstitial cystitis should be high when patients manifest chronic (i.e., for more than 6 weeks) disturbing lower urinary tract symptoms such as urinary frequency, urgency, discomfort, pain (suprapubic, pelvic, and perineal), and dyspareunia in the presence of sterile urine. History physical exam and cystoscopy are important in the evaluation; however the diagnosis of this disorder remains one of exclusion.[20,21] Fasting blood sugar and urinalysis will be useful in this differential. As many disorders can be associated with irritative bladder complaints, the clinician should rule out a checklist of pathologies before making a diagnosis of interstitial cystitis, Table 3. The greatest overlap of symptoms occurs with urinary tract infection and many patients may routinely be treated with empiric antibiotics without a urine culture thereby postponing a definitive diagnosis. A high index of suspicion for interstitial cystitis should therefore be held for patients without rapid response to empiric antibiotics. In such cases urine culture should be obtained. Antibiotics should be discontinued at the time of specimen collection. Unusual infections are also possible. TB, manifesting as tuberculous cystitis, is an example of an uncommon, but well-characterized infection that causes symptoms of bladder irritation and should be considered in some patients.

Questionnaires for the evaluation of voiding symptoms are myriad and widely used. Intended as an aid for distinguishing interstitial cystitis from other diagnoses and quantifying response to therapy, these questionnaires cannot be used to define the disorder. Although the specificity of these instruments in the primary care physicians' office has not been tested, in the urology patient population, two instruments, the O'leary-Sant Symptom Index and Problem Index and the Pain, Urgency, Frequency Symptom Scale are validated for discrimination of interstitial cystitis. As such these instruments appear to be useful as a first screen to evaluate potential patients with interstitial cystitis for further diagnostic procedures.[22-24]

TABLE 3. **Diagnosis of IC/PBS**

Clinical diagnosis by exclusion
History and physical
Urinalysis to exclude UTI, hematuria
Urine culture and cytology (if hematuria present)
Exclusion specific bladder disease
Use of symptom questionnaires
Potassium sensitivity bladder testing
Cystoscopy with hydodistension and possible bladder biopsy
To distinguish ulcer vs. non-ulcer disease
Rule out carcinoma in situ etc
Hydro-distension under anesthesia therapeutic (small % patients, short-lived response)

Cystoscopy and biopsy of the bladder should be performed even if no lesion is seen.[25] Bear in mind that the primary purpose of doing this is to rule out the possibility of malignancy, not to identify interstitial cystitis. The cystoscopic identification of the Hunner's ulcer will guide ultimate treatment and should include biopsy of the abnormal tissue. There is no pathognomonic histologic finding that is diagnostic for interstitial cystitis. The pathologic features seen with interstitial cystitis consist of a nonspecific chronic inflammatory cell infiltrate, edema, and vasodilation of the submucosa and detrusor layers of the bladder wall.[26] A number of studies have suggested that mast cell infiltration of the bladder wall is associated with interstitial cystitis.[3,27,28] Observation of a strong relationship among detrusor mast cell density, especially degranulated mast cells and degree of epithelial loss, submucosal inflammation, epithelial ulceration, urinary pyuria and response to treatment has been noted.[29] Mastocytosis in interstitial cystitis is best documented by tryptase immunocytochemical staining. Standard surgical stains such as Giemsa and toluidine blue routinely underestimate the degree of mastocytosis. Detrusor mastocytosis occurs in both classic and nonulcer IC. Mucosal mast cell increase is present in nonulcerative IC. Mast cells have been reported to be 6- to 8- fold higher in the detrusor compared with controls in ulcer type interstitial cystitis and 2- to 3-fold higher in the nonulcerative variety. Mast cell activation without typical exocytosis occurs in the mucosa and submucosa. Activation of mast cells, irrespective of bladder location or degree of mastocytosis, is significant. Mast cell-derived vasoactive and proinflammatory molecules may contribute to the pathogenesis of at least some forms of the disease.[30]

Hydrodistention of the bladder under general or spinal anesthesia has been one of the most commonly performed diagnostic tests for interstitial cystitis. First reported by Bumpus in 1930, the procedure has been used for both diagnostic and therapeutic purposes.[31] Anesthesia allows distention of the bladder to a volume greater than the patient's awake capacity because of the severe discomfort which naturally would be expected by this nonphysiologic and traumatic

procedure. With distension, diffuse hemorrhagic spots called "glomerulations" are typically seen.[32] It is important to remember that "glomerulations" are not pathognomonic for interstitial cystitis. It is possible that such traumatic lesions are seen when a normal bladder is distended beyond its normal capacity. Aside from anesthetic risks, the test is not without morbidity as bladder perforation and vesical necrosis have been reported.[33] Although commonly performed, the hydrodistention procedure appears to offer little therapeutic benefit and finding glomerulations offers little specificity.[32,33]

In an effort to discriminate normal individuals from those with symptoms originating in the bladder due to abnormal epithelial permeability, Parsons devised a test called the potassium sensitivity assay.[34] The test is based on the simple hypothesis that a normal individual would be unable to identify a solution of potassium versus water or at least would experience no symptoms with a solution of intravesically placed potassium. Various authors have reported that roughly 70% of patients with interstitial cystitis will be potassium sensitive.[35,36] The test involves bladder instillation of sterile water followed by a 400 mEq/l potassium solution, with subjective grading by the patient as to which solution provoked pain and/or urgency. Although simple to perform in the office, the test remains controversial as to its usefulness.[37-39] Unlike most other diseases, IC lacks a "gold standard" diagnostic test. Without such a reference, there can be no meaningful estimation of the sensitivity and specificity. Continuing this line of thought leads to the dilemma with PST in determining its value in determining treatment decisions. For example, a patient with symptoms of IC in whom other possible diagnoses have been ruled out is probably best treated for IC regardless of the result of the PST. Furthermore, it would make little sense to treat a patient without symptoms of IC solely because of the result of the PST .

Diagnostic criteria

With increased recognition of patients with chronic irritative voiding symptoms in the 1980's, the overall lack of precise diagnostic criteria for interstitial cystitis made research difficult. In 1988, members of a panel organized by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) met and developed a set of criteria for accrual of patients in NIH-sponsored studies on interstitial cystitis.[25] The original intention was only to specify and standardize criteria for entrance into research protocols, and as such the NIDDK criteria have been shown to be restrictive for clinicians as the diagnostic definition of interstitial cystitis.[40,41] It is helpful to always keep in mind that at present, interstitial cystitis represents a symptom complex and there are no pathognomonic findings associated with the disease.[42]

Management

As is typical of a disorder with no known cause, treatments are myriad and come and go with great frequency. The following is not meant to be an all-inconclusive list of treatments for interstitial cystitis but rather a brief review of those most commonly utilized today, Table 4 Certainly, as with any disease that tends to be of chronic nature and requires continuous or at least intermittent treatment, one main tenet is to apply the least invasive therapy that affords sufficient relief of symptoms.

TABLE 4. **Treatment of IC/PBS**

Oral pharmacological agents
Sodium pentosanpolysulfate
Amytriptyline
Hydrolyzine
Anti-cholinergic
Non-steroidal anti-inflammatory
Intravesical drug therapies
Dimethyl sulfoxide
Heparin
Steroids
Lidocaine
Bicarbonate
Combinations of above
Surgery - rarely indicated
Focal ulcer therapy (Hunner's ulcer)
Denervation
Urinary diversion
Cystectomy
Peripheral nerve stimulation (pudenda, sacral)
Pain management - may need pain specialist
Non-narcotic medications
Narcotic medications
Psychotherapy
Pelvic floor rehabilitation
Physiotherapy
Internal pelvic floor massage
Supportive care
Support groups
Meditation and relaxation

Supportive therapy

Avoidance of urinary tract infection

Although there appears to be a low incidence of recurrent UTI's in patients with interstitial cystitis followed longitudinally, bacterial infections do occur and can be the source of a symptom flare.[43] Urine culture and sensitivity with treatment appropriate to the organism is therefore an important management guideline in the care of interstitial cystitis patients.

Support groups

Patients with interstitial cystitis use support group meetings for social support and to learn coping skills.[44] This form of therapy is extremely helpful in a chronic disease with no known cure. Physician encouragement is an important factor in attendance of these groups. Groups such as the Interstitial Cystitis Association (ICA) are dedicated to disseminating knowledge of the disorder to the lay public as well as supporting the self-help of the sufferers. Other associations and web based groups are also available.

Oral agents

Amitriptyline (titrated up to bedtime doses of 50 mg-100 mg)

The use of amitriptyline for interstitial cystitis was first proposed by Hanno and Wein for treatment of refractory interstitial cystitis due to its known efficacy in many chronic pain disorders.[45] The agent facilitates urine storage by decreasing excitability of smooth muscle in the area. This class of drugs (tricyclic antidepressants) has anticholinergic and antihistaminic activity, the ability to block re-uptake of released amine neurotransmitters serotonin and noradrenaline as well as the theoretical stimulation of beta adrenergic receptors in the bladder body. The drug is analgesic even in the absence of depression.[46] A central mechanism of analgesia is implied in the drug's ability to blunt the pain of pelvic organ distension.[47]

Hydroxyzine (50 mg-75 mg per day)

Hydroxyzine is an H-1 histamine receptor antagonist and as such has garnered much interest as a treatment for interstitial cystitis with its known association to mast cells. Hydroxyzine has been shown to reduce carbachol-induced serotonin release from rat bladder in vitro through a mechanism which was unrelated to its H-1 receptor antagonistic properties.[48] The ability of hydroxyzine to inhibit bladder mast cell activation by neurogenic stimuli along with its anticholinergic, anxiolytic and analgesic properties, may explain the clinical efficacy of this drug in reducing IC symptoms. A recent multi-center clinical trial of hydroxyzine resulted in a 31% response rate for interstitial cystitis participants.[49]

Pentosan polysulfate sodium (100 mg PO three times per day)

Based on studies done in animals showing that replacement of the natural surface layer of the bladder with intravesically or orally administered synthetic polyanions could significantly reduce the incidence of infection, Parsons promoted the use of synthetic polyanions in relieving ongoing irritation of the bladder.[50] Oral administration of pentosan polysulfate sodium (PPS) (Elmiron) which is thought to "resurface" the bladder lining during its urinary elimination has become a commonly used Food and Drug Administration (FDA) approved treatment for interstitial cystitis.[51] PPS is related to heparin and has anticoagulant activity. Response rates vary by study ranging from 34% to 80% benefit with the treatment.[13,49,51] Initiation of PPS treatment within 6 months of establishing the diagnosis of IC may be associated with greater improvement in patient symptoms and symptom bother.[52] The medication has the advantage of being well tolerated with low incidence of headache and diarrhea.[53] PPS can prolong prothrombin time and partial thromboplastin time--some have advocated patients on this drug have coagulation monitoring.[54]

Bladder instillations

Dimethyl sulfoxide

Dimethyl sulfoxide (DMSO) was approved by the FDA for the treatment of interstitial cystitis in 1977 and has been a commonly used therapeutic intervention.[55] Having anti inflammatory, analgesic and anti-collagen deposition effects, the medication diffuses through the tissues it is applied to and relieves symptoms in roughly 40% of patients.[56] DMSO is given as a 50% solution bladder instillation and is usually given on a weekly or biweekly basis for a 6 week trial. If effective, further doses are usually needed and some patients can be taught to instill the agent themselves at home.

Combination solutions

Although many combination agents have been proposed, a solution of lidocaine, sodium bicarbonate and heparin is currently one of the most popular. Described by Parsons in 2005, the solution consists of 40,000 U heparin, 8 ml of 1%-2% lidocaine and 3 ml 8.4% sodium bicarbonate administered intravesically.[57]

In 2008 Welk et al evaluated 23 consecutive patients with interstitial cystitis using this combination as an intravesical agent.[58] Although the study was not placebo controlled, they found this solution given three times weekly for 3 weeks provided relief of voiding symptoms, pain, and dyspareunia in a large percentage of patients based on validated symptom questionnaires.

Surgical intervention

Focal therapy of the ulcer

This approach applies only to patients in whom a localized discreet ulcer is evident. The goal is to decrease pain by either removing or modulating the diseased tissue. Transurethral resection of the Hunner's ulcer first described by Kerr in 1971 has been reported to relieve pain in 73% of patients. The majority of successfully resected patients will require repeat resection at a later date.[59] Use of an Nd: YAG laser to resect the Hunner's ulcer has been reported to be 85% effective in eliminating pain. Recurrences with this modality are frequent and a 5% rate of bowel perforation is noted.[60] Steroid injections for treatment of Hunner's ulcerations have been reported to be effective.[61]

Although a list of surgical procedures that have been proposed over the years would be substantial, it is generally believed that surgery is a treatment of last resort for interstitial cystitis and therefore should be definitive. The goals of bladder sparing surgery have been either to denervate the bladder and therefore decrease its sensation or to excise the inflamed bladder tissue with or without substitution using bowel. Patients with ulcerative variety interstitial cystitis typically gain little response from a non-operative approach and seem to get better responses when operative treatment is used compared to the non-ulcer patients.[9]

Denervation procedures

In an effort to relieve symptoms surgically yet minimize perioperative complications and functional morbidity, denervation procedures have been described for interstitial cystitis and chronic pelvic pain syndrome. Turner-Warwick described supra-trigonal cysto-cystoplasty in 1947 in which the distensible portion of the bladder above the trigone was separated and then reattached as a means of separating the neurologic connections between the segments.[62] This operation was later replaced by the cystolysis procedure which achieved denervation by blunt dissection and transsection of various neurovascular bundles to the bladder. Significant complications have been reported with both of these procedures including postoperative urinary retention and bladder necrosis; however, lack of long term improvement seems to be the main reason for limited interest in this form of therapy.[63,64]

Partial cystectomy

Excision of Hunner's ulcerations was reported by Guy Hunner in his original manuscript as the treatment of choice when a discreet ulcerative lesion could be found. Performed through a suprapubic extraperitoneal incision the procedure was deemed to be effective in this group of five patients, although little follow-up was reported.[11] In the modern era, partial cystectomy is usually performed in conjunction with augmentation of the bladder capacity using a detubularized segment of intestine. Bowel augmentation can incur significant morbidity including both perioperative problems and postoperative difficulties with urinary retention and recurrent inflammation in the bowel segments used.[65,66] A recent review of patients undergoing reconstructive surgery for interstitial cystitis revealed complete long-term relief of symptoms was only likely in patients with the ulcer type of the disease.[9]

Urinary diversion

When all bladder sparing treatment has either failed or is not indicated, urinary diversion through creation of a bowel conduit that provides continuous urinary drainage through an ostomy can be expected to provide immediate and permanent cure.[15] Whether to simultaneously remove the bladder remains controversial.

Conclusion

The development of urinary urgency, frequency and bladder pain—the hallmarks of interstitial cystitis—impacts the sufferer with what Nitze described as "violent bodily complaints" which are at once emotional, sexual, psychosomatic and behavioral.[1] The problem is usually first encountered by the primary care physician with the urologist or urogynecologist becoming involved when simple measures are unsuccessful. Unfortunately, little has changed in our understanding of the disorder and its optimal management.

There is reason to hope. The disease is now understood to be a clinical syndrome with potentially multiple underlying etiologies masquerading as the same symptoms. Subtyping of the disease is showing some correlation with specific treatment outcomes perhaps allowing a more tailored approach. Newer

medications are being looked at including neurotoxins, (botulinum toxin, resiniferatoxin) and anti-rejection medication (cyclosporin A) with some success.[46,47,67,68] Ever increasing research efforts are being focused on interstitial cystitis: how it occurs, how to evaluate it, and how best to correct it. Only through a clear explanation of the problem as well as appropriate recommendations for treatment will this devastating disorder be relieved.

Take-home messages

Principles of care of patient with IC/PBS

- Multi-disciplinary care
  - Primary care physician
  - Specialists
    - Urologists/urogynecologists
    - Gastroenterologist
    - Pain specialist
    - Gynecologist
- Holistic approach
  - Specific pharmacologic therapies
  - Alternative/complimentary therapy
  - Supportive care
- Multi-modality approach essential
  - Multi-disciplinary specialists/PCP
  - Multi-modality combinations of drugs

Disclosure

None declared. □

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DISCUSSION

Question (Dr. LaRoche):
How long does it take to see a treatment response to oral medication?

Answer (Dr. Klutke):
Response in interstitial cystitis to therapy is extremely variable. This holds true for any of the many therapies that are currently in use. Furthermore, in the majority of patients, none of the available treatment modalities are likely to totally and permanently cure the disorder. For these reasons, the principle of using the least invasive therapy that affords improvement continues to be sound. We tend to move slowly between successive options and generally wait months before deciding whether or not an individual treatment approach is effective.

Hematuria: etiology and evaluation for the primary care physician

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Asymptomatic microscopic and gross hematuria are common problems for the primary care physician. The exact definition of microscopic hematuria is debated, but is defined by one group as > 3 red blood cells/high power microscopic field. While the causes of hematuria are extensive, the most common differential diagnosis for both microscopic and gross hematuria in adults includes infection, malignancy, and urolithiasis. Clinical evaluation of these patients often involves urological consultation with urine cytology, urine culture, imaging studies, and cystoscopy. Patients who have no identifiable cause after an extensive workup should be monitored for early detection of malignancy or occult renal disease.

Key Words: asymptomatic microscopic hematuria, gross hematuria, primary care

Introduction

Blood in the urine can originate from any site along the urinary tract and can be a sign of a serious underlying disease process. The prevalence of hematuria in adults ranges from 2.5% to 21.1%[1] and appropriate evaluation of these patients is critical as 5% of patients with microscopic hematuria and 20% to 40% of patients with gross hematuria will be found to have a malignancy.[2] This is an important point for the primary care physician who is often the first to see these patients. Patients may present with symptomatic (fever, nausea, vomiting, flank pain, dysuria, urgency, frequency, etc.) or asymptomatic hematuria. Patients who are symptomatic often have a readily identifiable cause such as urinary calculi stone or urinary tract infection. Appropriate evaluation is based on the presenting signs and symptoms. The focus of this article will be the etiology and evaluation of asymptomatic microscopic and gross hematuria in adults.

There are no formal guidelines from the American Urological Association, American Cancer Society, or the U.S. Preventive Services Task Force in screening asymptomatic patients for hematuria, although a routine urinalysis if often included as part of a routine physical examination.[3] It is imperative that the decision to screen an asymptomatic patient be left to the primary care physician after a thorough history and

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TABLE 1. **Risk factors for significant urological disease**

Smoking history
Occupational exposure to chemicals or dyes (benzenes or aromatic amines)
History of gross hematuria
Age > 40 years
Previous urological history
History of irritative voiding symptoms
History of urinary tract infection
Analgesic abuse
History of pelvic irradiation
Cyclophosphamide

physical along with careful attention to risk factors. Table 1 reviews risk factors for significant urological disease in patients with hematuria.

Definitions

Hematuria can be classified as gross (visible to the naked eye) or microscopic. Gross hematuria must be distinguished from other causes of red urine outlined in Table 2. There is controversy in the literature over the exact definition of microscopic hematuria but the latest American Urological Association (AUA) guidelines define it as > 3 red blood cells (RBC) per high powered field on two of three properly collected urine analysis specimens in both males and females. Because the degree of hematuria does not necessarily correlate with the severity of disease, patients at high risk for malignancy, as outlined in Table 1, should have an evaluation after a single microscopic exam revealing 3 RBC per high powered field.[3]

Although there is considerable overlap, hematuria in the clinical setting can be most broadly classified into medical and surgical causes to help facilitate initial management, Table 3. Young patients with medical causes, such as glomerulonephritis, may benefit from a renal biopsy to guide medical management whereas patients with surgical causes often require urological intervention to diagnose and treat the problem.

TABLE 2. **Causes of discolored urine**

With a positive dipstick for blood	**With a negative dipstick for blood**
Red urine	
Hematuria	**Drugs**
Hemoglobinuria	Aminosalicylic acid
Myoglobinuria	Phenazopyridine
Menstrual contamination	Laxatives (Phenophtalein, Senna)
	Ibuprofen
	Rifampin
	Methyldopa
	Phenytoin
	Foods
	Beets, berries, food coloring (rhodamine B)
	Metabolic
	Porphyrins
	Serratia marcescens
	Urate crystalluria
Orange urine	
	Phenazopyridine
	Sulfasalazine
	Carrots
Dark yellow urine	
	Bilirubin
	Vitamin A

TABLE 3. **Medical and surgical causes of hematuria**

Medical	**Surgical**
Urinary tract infection	Urinary calculi
Glomerulonephritis (IgA nephropathy most common)	Urinary tract malignancy
Interstitial nephritis (most often drug related; many described including penicillins and a wide variety of antibiotics)	Benign prostatic hypertrophy
Exercise induced hematuria	Iatrogenic from recent instrumentation or surgery
Anticoagulation	Trauma
Papillary necrosis (ischemic in diabetics or sickle cell disease or drug related including non-steroidal anti-inflammatory agents)	Urethral stricture
	Cystocele
Hypercalciuria	Abdominal aortic aneurysm
Radiation cystitis/nephritis	Renal artery stenosis
Lymphoma	Ureteropelvic junction obstruction
Urethrorrhagia	Vesicoureteral reflux
Arteriovenous malformation	Posterior urethral valves
Benign familial hematuria	
Alport syndrome	
Hematologic or coagulation abnormalities	
Endometriosis	

Detection of microscopic hematuria

Urine should be collected from a freshly voided, clean catch, midstream urine specimen. A urine sample for analysis should not be left at room temperature for more than 2 hours and if necessary, it should be refrigerated.[2] The urinary dipstick is the most common test used to evaluate urine. Hemoglobin catalyzes an oxidation reaction resulting in a color change proportional to the concentration of hemoglobin, thus providing a semi quantitative analysis of the number of RBCs. A positive dipstick (whether trace or 3+) should immediately be followed by a confirmatory microscopic examination as a false positive test can result from hemoglobinuria, myoglobinuria, or contaminants such as hypochlorite and povidone-iodine.[1-3] Dip sticks may also yield additional information concerning the etiology of hematuria such as the presence of proteinuria suggesting intrinsic renal disease or the presence of leukocytes suggesting infection or inflammation. In a patient with a urinary diversion such as a urostomy, microscopic hematuria is frequent benign finding and the need for further evaluation based on the clinical setting.

A formal microscopic exam of the urine involves centrifuging 10 cc of urine at 2000 rpm for 5 minutes. The supernatant is discarded and the sediment is resuspended in 1 cc and examined under high power (40X). Significant hematuria is defined as more than 3 RBCs per high power field.[1,3] Numerous squamous or epithelial cells suggest contamination and, if necessary, a catheterized specimen should be obtained.

Etiology

The most common causes of hematuria in adults include urinary tract infections (UTI), neoplasms, and urolithiasis. In children, glomerulonephritis accounts for half the cases of hematuria followed by UTI as the second most common cause. The most common causes of hematuria by age are outlined in Table 4.[2] Hematuria can be further categorized into the following areas: inflammatory, neoplastic, metabolic, traumatic, and miscellaneous causes.

TABLE 4. **Most common causes of hematuria by age**

Age	Cause
0 to 20 y/o	Acute glomerulonephritis Urinary tract infection Congenital anomalies Hypercalciuria
20 to 60	UTI Bladder cancer Urolithiasis
60 and older	UTI Bladder cancer BPH

Modified from Gillenwater JY, Grayhack JT, Howards SS, et al (ed): Adult and Pediatric Urology, 3rd ed. Chicago, Mosby-Year Book, 1996.

Inflammatory

Urinary tract infections (pyelonephritis, cystitis, prostatitis, urethritis) can lead to hematuria and are often found in association with pyuria or bacteruria.

Glomerulonephritis is a common cause of hematuria in the pediatric population and is less commonly seen in adults. Primary IgA nephropathy (Berger disease) is the most common type of glomerulonephritis throughout the world. History and physical findings suggestive glomerulonephritis can include flank pain and hematuria which usually starts within 24 hours a day of an upper respiratory tract infection. IgA nephropathy can also be seen in poststreptococcal glomerulonephritis (PSGN), Henoch Schonlein purpura (HSP), systemic lupus erythematosus (SLE), and hemolytic uremic syndrome (HUS). Rarely, HIV, liver failure, celiac disease, and auto immune diseases (rheumatoid arthritis, ankylosing spondylitis, etc) and be causative of IgA nephropathy. Other less common types of glomerulonephritis include membranoproliferative glomerulonephritis, focal glomerular sclerosis and rapidly progressing glomerulonephritis.

Glomerulonephritis is responsible for 30% of all cases of pediatric hematuria. It has the potential to cause progressive renal failure in up to 40% of patients. PSGN often follows a streptococcal pharyngitis and presents as a nephritic syndrome (hypertension, proteinuria, hematuria, and peripheral edema). HSP is a systemic vasculitis caused by deposition of antibodies in the skin and kidney. The etiology of HSP is unclear but may result from streptococcal or viral (Coxsackie, Parvovirus B19, adenovirus) infection.[4] It is characterized by palpable purpura on the buttocks and legs, abdominal pain, and vomiting. SLE has many systemic manifestations including arthralgia, joint swelling, and a malar rash on the cheeks and nose. Hemolytic uremic syndrome (microangiopathic hemolytic anemia, renal failure, and thrombocytopenia) often follows an E. coli O157:H7 diarrhea.

Laboratory urine studies will reveal dysmorphic erythrocytes, red cell casts, and proteinuria with glomerulpnephritis. Renal biopsy is necessary to confirm the diagnosis.

Radiation cystitis can be seen following radiation therapy for pelvic malignancies such as prostate, cervical or rectal cancer. Its counterpart, radiation nephritis, typically occurs when the dose to the kidney exceeds 23 Gy. Radiation induced damage to the urinary tract is much less common today due to improved delivery techniques and shielding of the kidneys.

Other pathogens can cause inflammatory hematuria. Less frequent causes include genitourinary tuberculosis, malaria, and schistosomiasis. These are uncommon in the United States and are often found in endemic regions of the world.

Neoplastic

Any genitourinary cancer can cause hematuria including renal cell carcinoma, urothelial carcinoma, urethral cancer, and locally advanced prostate cancer. Benign tumors of the genitourinary tract, other than benign prostatic hypertrophy, are uncommon. Localized early stage prostate cancer rarely causes bleeding. Patients at high risk for neoplasia, Table 1, include age > 40 years, smoking history, chemical exposure, irritative voiding symptoms (urgency, frequency, dysuria, nocturia), gross hematuria, or history of any genitourinary cancer.[3] Approximately 5% of patients with microscopic hematuria and up to 40% of patients with gross hematuria will ultimately be found to have a neoplasm, most commonly urothelial carcinoma of the bladder.[2] Painless gross hematuria should always be considered urothelial cancer until proven otherwise. The classic triad of hematuria, flank pain, and a palpable flank mass for renal cell cancer is now rarely seen as 48%-66% of renal masses are discovered incidentally on imaging studies for other reasons and thus treated before they progress to large tumors.[5]

Metabolic

Urinary calculi in the kidney, ureter, or bladder may account for one third of the cases of microscopic hematuria. The lifetime incidence of stone disease in men ranges from 4% to 9% and 1.7% to 4.1% in women. Caucasians are at highest risk and African American at lowest risk. History is particularly important as more than 50% of first time stone formers will have a second

stone in their lifetime.[6] The most common urinary calculi are calcium oxalate, calcium phosphate and uric acid.

Hypercalciuria can lead to hematuria presumably through irritation of the urothelium by microcalculi. A spot urinary calcium to creatinine ratio > 0.2 is suggestive and can be confirmed with a 24 hour urine analysis for total calcium.[6] Hypercalciuria can occur as a result of calcium supplementation, hyperparathyroidism, immobility, tubular leak of calcium, or increased GI absorption.

Traumatic

Exercise induced hematuria (also known as runner's hematuria or jogger's kidney) is thought to result from a combination of altered glomerular permeability and hypoxic damage to the nephron as a result of decreased renal blood flow during exercise and/or direct trauma to the bladder base. There is no gender predilection and hematuria is directly related to exercise intensity with hydration somewhat protective.[7]

Blunt and penetrating trauma to the genitourinary system often presents with a clearly defined history or as symptomatic hematuria. Hematuria is the best indicator of genitourinary system injury and such patients require imaging, preferably CT with intravenous contrast [8].

Miscellaneous

Urethral stricture should be considered in patients who complain of bladder outlet obstruction type symptoms (hesitancy, intermittency, weak stream, straining, or incomplete emptying of the bladder) and have a history of prior urinary tract infection, sexually transmitted infection, instrumentation or catheterization.

Anticoagulation or aspirin use should never be automatically attributed to be the cause of hematuria. A recent study examined patients hospitalized with gross hematuria on aspirin or warfarin and found malignancy in 24% and significant treatable findings in half. In the same study, 18% of patients supratherapeutic on coumadin were also found to have tumors, suggesting that any degree of gross hematuria should be evaluated in patients on anticoagulation.[9]

Medications can cause tubular necrosis and hematuria especially when given in excessive amounts. They include nephrotoxic agents (aminoglycosides, NSAIDS, antineoplastic drugs), analgesics (phenacetin), penicillins and sulfas (resulting in interstitial nephritis) and others.

Benign prostatic hypertrophy can lead to rupture of small periurethral veins and should only be a diagnosis of exclusion after more serious diseases have been ruled out.

There are numerous less common causes that are beyond the scope of this article. They include loin pain hematuria syndrome, nutcracker syndrome, endometriosis of the urinary tract, cystic renal disease, vascular malformations, ureteropelvic junction obstruction, Alports syndrome, benign familial hematuria, and uncommon bleeding diathesis.[2]

History and physical

A thorough history is critical to the evaluation of any patient and should include tobacco use, exposure to rubber or dyes, and prior urological history. Menstrual history and evidence of abnormal uterine bleeding should be sought and can be a cause for a false positive hematuria determination. Physical examination should focus on hypertension which can be seen with underlying renal pathology (nephritic syndrome or renal vascular disease), rashes with HSP, edema with nephrotic syndrome, pallor secondary to anemia with hemolytic anemia or renal failure, and a palpable mass with hydronephrosis or malignancy. A pelvic exam in females may reveal a urethral mass (caruncle or diverticulum) and a rectal exam may reveal a nodule or enlarged prostate in males.

Laboratory studies

Basic laboratory studies including serum electrolytes and creatinine, complete blood count, urine analysis with microscopic examination, and urine culture are necessary. Based on the clinical setting, evaluation for bleeding diathesis may be indicated and must be obtained prior to invasive procedures such as renal biopsy.

Many soluble tumor markers and tumor cells are released into urine, especially with storage of urine in the bladder. As a result, numerous tests have been designed for testing voided urine for the presence of cancer. Point of care assays that can be performed in the office setting include bladder tumor antigen (BTA stat), nuclear matrix protein (NMP) 22, and urinary bladder cancer (UBC).[10] Urinary cytology is the most widely used test for urothelial cancer with a sensitivity of 52% to 80% and a specificity of 92% to 97%.[11] It requires a urine sample to be sent to a central lab and the individual cells examined by a pathologist. Given its low sensitivity urine cytology is not used as a screening test. Instead, because of its high specificity, an abnormal cytology means an identifying lesion must be found. Urinary cytology has no role in the detection of renal or prostate cancer. The clinical

utility of bladder tumor markers (BTA stat, NMP-22, and UBC) will likely be in the decision to perform or delay surveillance cystoscopy in patients with already diagnosed bladder cancer and possibly to screen high risk patients for the early detection of bladder cancer. However, given the extensive experience with urine cytology and its reliably high specificity in the hands of experienced pathologists, urinary cytology should continue to remain the test of choice.

Red blood cell dysmorphology studies can help to identify glomerular from non-glomerular bleeding.[12] This is based on the principle that glomerular bleeding produces smaller and more dysmorphic erythrocytes than bleeding from other sites in the urinary tract. In the future, these studies may save patients with a glomerular source of bleeding from a full urological evaluation. However, the low sensitivity of these tests along with lack of prospective clinical data justifying their safety, reliability, and cost effectiveness currently precludes their routine clinical use.

Urology and nephrology evaluation

All patients with gross hematuria and any high risk patient with microscopic hematuria should be referred for a complete urological evaluation. The core components of urological evaluation may include upper tract (kidney and ureter) imaging, lower tract (bladder and urethra) evaluation with cystoscopy, urine analysis, urine cytology, and a urine culture. Figure 1 provides and overview of the evaluation of hematuria in adults as recommended by the American Urological Association Best Practices Guidelines.

Patients with asymptomatic microscopic hematuria and proteinuria, dysmorphic RBCs, red cell casts, or elevated serum creatinine should have an evaluation for primary renal disease by a nephrologist. Hypertension in the setting of hematuria is worrisome for chronic renal disease.

Low risk patients with microscopic hematuria attributed to benign causes such as exercise, sexual activity, or menstruation should have a repeat urinalysis in 48 hours.[13] Patients with documented urinary tract calculi and asymptomatic microscopic hematuria should have a repeat urinalysis after stone has been cleared.

Approximately 10% to 20% of patients will have no identifiable cause of microscopic hematuria after extensive urological workup.[14] These patients should be closely monitored with yearly physical examination, urine analysis, and cytology to facilitate the early detection of malignancy or primary renal disease.

It is appropriate to refer patients with microscopic or gross hematuria for evaluation by a urologist after obtaining initial laboratory studies.

Imaging

Upper tract imaging can be performed via excretory urography (EU), CT urogram (CTU), or a combination of renal ultrasound (RUS), a kidney-ureter-bladder film (KUB) and retrograde pyelography in the operating room.

The CTU has largely replaced EU as it provides superior sensitivity for stones, renal masses and when properly performed, comparable sensitivity to EU for urothelial lesions.[15,16] The CTU is a three phase CT scan with a non contrast phase evaluating for stones, a contrast enhanced nephrographic phase for renal masses, and delayed images of the renal collecting system and ureters for filling defects. It does not require oral or rectal contrast and it can be done rapidly in an outpatient setting. The AUA guidelines suggest that low risk patients with microscopic hematuria who have a finding of urolithiasis on non contrast CT scan do not need further imaging with contrast.[13] Disadvantages of CTU over EU include cost and recent concerns over radiation exposure.

RUS is a cost efficient and commonly used imaging modality in urology that does not expose the patient to radiation or potentially nephrotoxic contrast. It is good for differentiating solid from cystic masses, assessing for hydronephrosis, stones and evaluating the renal vasculature. Disadvantages of ultrasound include its low sensitivity for small renal masses and non-calcified urolithiasis along with the quality of the study being operator dependent.[17] Currently there are no prospective trials comparing CTU with RUS but CT is thought to be far more sensitive for small renal masses and urolithiasis. Thus, in patients with risk factors for urological disease, as outlined in Table 1, who can tolerate contrast, a CTU is preferred. For low risk patients a KUB and RUS are appropriate initial imaging tests.[13] A KUB can identify urinary tract stones that contain calcium, but may not identify uric acid calculi.

Magnetic resonance imaging (MRI) is not commonly used in the evaluation for hematuria because of cost, poor visualization of stones, and the time intensive nature of the study.[17] MRI provides superior visualization of soft tissue structures, particularly the kidney and adrenal glands, when compared to CT. MRI is contraindicated in patients with pacemakers, aneurysmal clips, and retained foreign bodies as the magnetic field can cause object migration.[18]

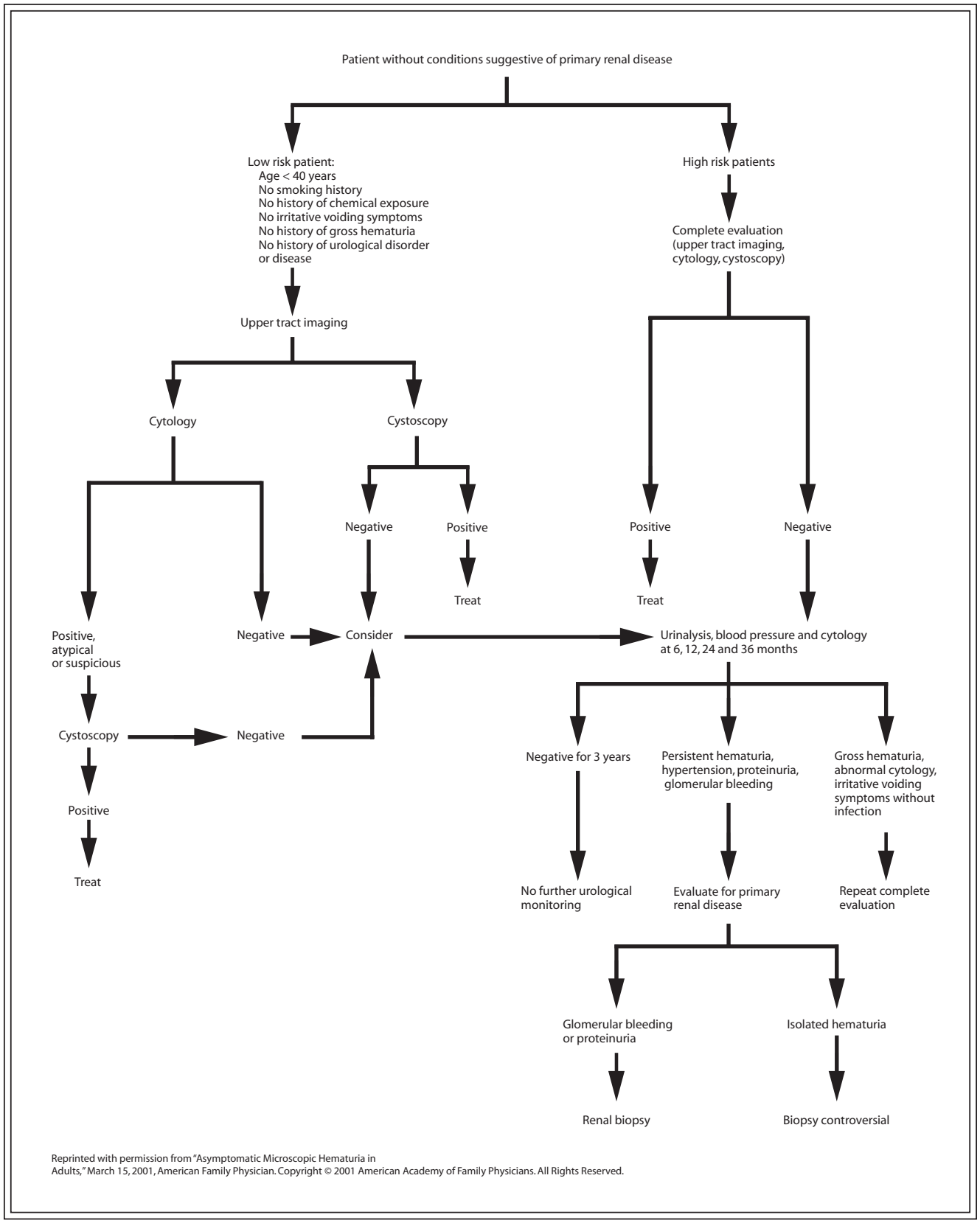

Figure 1. Workup of hematuria in adults based on AUA best practice policy recommendations

Patients with renal insufficiency and dehydration are at greatest risk for intravenous contrast nephrotoxicity and thus serum blood urea nitrogen and creatinine should checked prior to contrast administration. Many centers consider a serum creatinine of 2.0 ng/ml or greater as a contraindication to the use of IV contrast. Diabetics should not take metformin for 48 hours before and after contrast administration to minimize the risk of fatal lactic acidosis. Adequate hydration is essential to minimize any nephrotoxicity. Patients with a prior adverse reaction to contrast, multiple drug allergies, and seafood allergy are at higher risk for adverse reactions to intravenous contrast.[19] These patients should instead have retrograde pyelography performed in the operating room, to evaluate for urothelial lesions and stones, along with a renal ultrasound[13] and KUB to evaluate for renal masses and stones.

Although the bladder can be seen on imaging, the lower tracts can only be evaluated via cystoscopy. There is no substitute for direct visualization of the urothelium to determine the presence of tumors on the lining of the bladder.

Conclusions

Asymptomatic hematuria is a common problem with numerous etiologies, most commonly infection, urolithiasis, and malignancy in adults, with medical renal diseases relatively uncommon in adults as a cause. The burden to initiate an investigation for hematuria often falls on the primary care physician and should by guided by history, physical examination, and assessment of risk factors. Additional evaluation is often required by the urologist or nephrologist. After confirmation of asymptomatic microscopic hematuria, patient evaluation often involves urine culture, urine cytology, upper tract imaging, and cystoscopy. These studies, while invasive, time consuming, and potentially costly to the health care system, represent the current standard for the workup of asymptomatic and gross hematuria. Future research will hopefully identify a time and cost efficient test that spares the majority of patients without malignancy an extensive initial workup.

Disclosure

Dr. Leonard Gomella is a consultant for GlaxoSmithKline and TAP Pharmaceuticals. He is a member of the Speakers' Bureau for Astra Zeneca. □

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DISCUSSION

Question (Dr. Laroche):
Do you routinely order a urinary sediment to exclude glomerulopathy?

Answer (Dr. Gomella):
A formal urinalysis that includes a microscopic evaluation of the urinary sediment is useful especially in patients who are suspected of having glomerulonephritis or other forms of intrinsic renal disease. In patients with urolithiasis it may allow detection of the specific type of stone. Today most initial screening is by urinary dipstick, with further testing, including microscopic evaluation of the sediment based on the clinical setting.

Question (Dr. Rosenberg):
How should a PCP evaluate a patient with risk factors for renal cancer (example: smoking) with long-standing, previously described and investigated hematuria?

Answer (Dr. Gomella):
This is an area that is not well defined and clinical judgement should be employed. The data suggests that only a small percentage of small renal masses presumed to be RCC grow significantly if managed conservatively and followed with serial imaging. In fact most renal masses exhibit slow or undetectable growth. This suggests that periodic imaging where there is an increased suspicion for renal cell carcinoma is likely to detect these lesions at an early stage. This is reassuring in a patient with hematuria where initial evaluation and imaging failed to demonstrate any renal masses.

Erectile dysfunction for primary care providers

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BRIEN JC, TRUSSELL JC. Erectile dysfunction for primary care providers. The Canadian Journal of Urology. 2008;15(Supplement 1):63-70.

Introduction: *Erectile dysfunction (ED) affects more than half of men between the ages of 40 and 70 years and is associated with a significant decline in quality of life. ED in an otherwise healthy man should be considered a sentinel event for endothelial dysfunction and cardiovascular disease. Such a person should be carefully evaluated for undiagnosed risk factors including hypertension, diabetes, lipid disorders, and obesity.*
Objective: *To understand that erectile dysfunction is prevalent and may be the first sign of undiagnosed cardiovascular risk factors.*
Materials and methods: *Literature review.*
Results: *Current literature suggests that physicians should screen all men for ED, and if present, rule out concomitant cardiovascular risk factors.*
Conclusion: *ED is prevalent and may be the first sign of undiagnosed cardiovascular risk factors. With the advent of safe and effective phosphodiesterase type-5 inhibitors (PDE-5i), most patients reporting dissatisfaction with erectile function can start treatment right away. Preventative care algorithms should include screening men 40 years of age or older for ED.*

Key Words: erectile dysfunction, phosphodiesterase type-5 inhibitors, PDE-5 inhibitors, endothelial dysfunction, cardiovascular disease

Introduction

Erectile dysfunction (ED) affects more than half of men between the ages of 40 and 70 years[1] and is associated with a significant decline in quality of life.[1-3] ED in an otherwise asymptomatic man should be considered a sentinel event for endothelial dysfunction and development of cardiovascular disease. Patients should be carefully evaluated for undiagnosed risk factors, including hypertension, diabetes, lipid disorders, and obesity.[4-7] To emphasize this point, a prospective, population based study was able to use a single question about erectile quality to predict which men would eventually suffer from an acute myocardial infarction, stroke, and sudden death, independent of the risk factors used in the Framingham risk profile.[8] With greater emphasis on preventative medical care, asking men about ED is a low effort, high yield way for physicians to screen for undiagnosed cardiovascular risk factors. Since cardiovascular disease-related events typically develop 5-7 years following the onset of ED,[9] it seems reasonable to start screening men early—possibly in their forties. Screening for and initiating treatment of ED is straightforward and offers an opportunity to improve a man's quality of life, but may also uncover hypogonadism as well as cardiovascular risk factors that warrant treatment.

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Definition

The National Institute of Health (NIH) has defined ED as "*The consistent inability to obtain or maintain an erection satisfactory for sexual function*".[10] An emphasis on "satisfactory" should be made since it absolves the provider from needing to objectively determine what degree of ED exists. In other words, the patient qualifies for treatment if they, or their partner, report dissatisfaction with erectile quality. Quantifying erectile response with such instruments as rigi-scans, snap gauges, or a duplex scan can be left for those involved with research protocols.

Prevalence

ED affects more than half of men between the ages of 40 and 70 years.[1] Generally speaking, a man's age predicts his chance of having some degree of ED. For instance, a 50-year-old and a 70-year-old have a 50% and 70% chance respectively of having some degree of ED. Fortunately, most of these men report only partial loss of erectile function, with only 10% of men having complete loss of erections. The prevalence of ED in the United States is 52%, with a lower but still significant prevalence noted across other industrialized nations.[11-12]

Erectile physiology

A succinct description of erectile physiology has been succinctly described by John Carter and illustrated in Figure 1.

"In the penis, the erectile bodies are the paired dorsal corpora cavernosum and the single ventral corpus spongiosum surrounding the urethra. These contain sinusoids, which are terminal arterioles with an outer layer of smooth muscle, and venules. Normally the sinusoids are in a state of contraction while the venules are maximally dilated. Sexual stimulation triggers the release of nitric oxide (NO) from endothelial cells of arteries and sinusoids of the corpus cavernosum. NO activates guanylyl cyclase to increase cGMP production. Through several interactions, elevated concentrations of intracellular cGMP result in hyperpolarization of the muscle cell membrane and lower intracellular calcium concentration, which produces relaxation of the corpous cavernosum and penile arteriolar smooth muscle. With this relaxation come a fall in arterial resistance and an increase in arterial blood flow into the sinusoids. The dilated sinusoids passively compress the venule against the tunica albuginea, occluding venous outflow. The increase arterial inflow and decreased venous outflow produces an erection. Inhibition of [phosphodiesterase type-5 enzymes] PDE-5 [such as sildenafil, vardenafil, or tadalafil—to be discussed later] results in higher concentrations of cGMP, enhancing the effects of the NO pathway. Without sexual stimulation and the release of NO, however, no change in cGMP will occur and PDE-5 inhibition will have not effect, so spontaneous erections are not induced".[13]

Etiology

ED is considered a natural consequence of aging, where risk is found to parallel age. An exception was found with increasing levels of protective high-density lipoprotein (HDL); the Massachusetts Male Aging Study (MMAS) found that no male with an HDL over 90 experienced ED.[14] Moreover, a follow-up MMAS study found that exercise was the factor most likely to preserve erectile function irrespective of age-related changes.[15]

Age aside; there are several comorbid factors that independently worsen ED. The pathophysiology of ED is often classified as organic, psychogenic, or a combination of the two. Organic causes include neurologic (5%), hormonal (3%), vasculogenic (70%) and pharmaceutical (10%), while psychogenic accounts for 10% of ED.

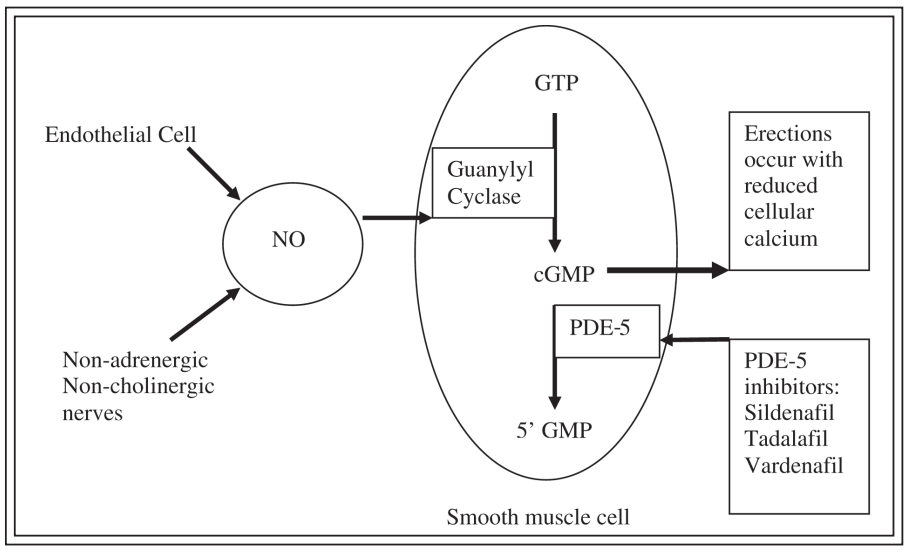


Figure 1. Erectile physiology

Neurologic

ED results from either a neuropathy (central or peripheral) or a traumatic neurological injury. Common etiologies include stroke and spinal cord injury, surgery, trauma, multiple sclerosis, Parkinson's, Alzheimer's disease, diabetes, and alcohol consumption.

Stroke/spinal cord injuries: These are classified into upper or lower cord lesions. Whereas patients with upper lesions may still have reflexogenic erections, only a few of those with lower lesions—involving the lumbar or sacral regions—are able to obtain a psychogenic erection.[16] Reflexogenic erections require

ongoing stimulation and the resultant erection, if not pharmacologically assisted, is often not rigid enough for penetration.

Surgery or trauma: Due to the close proximity of the cavernous nerves to the prostate and membranous urethra, radical pelvic surgery, pelvic trauma, and pelvic radiation will often predispose to ED. Prostate cancer treatment is the most common etiology for surgical disruption of cavernosal nerves and a common cause of ED.[17] Although randomized trials are lacking, such patients may benefit from postoperative penile rehabilitation in an effort to preserve or improve erectile function. Penile rehabilitation techniques vary and can be tailored to meet patient preference.[18]

Multiple sclerosis: ED is rare at the onset of multiple sclerosis (MS), however, after several years sexual dysfunction will eventually affect 70% of MS patients. This etiology is multi-factorial with neurogenic lesions the predominate cause while psychological and medication side effects play an important secondary role.[19] Since no reliable tests are available at present, neurogenic ED requires minimal investigation.[20]

Parkinson disease: Parkinson's is a hypokinetic basal ganglion disorder associated with loss of dopamine-containing cells from the substantia nigra. The central nervous system dopamine pathways interact with the nonadrenergic, noncholingergic (NANC) pathways, which mediate penile erections.[21-22] ED results from a paucity of dopamine interaction with NANC nerves.

Alzheimer disease: Alzheimer's is associated with ED and correlates with the onset of Alzheimer symptoms.[23] Loss of erection was reported in 53% of patients, and was not related to depression, age of onset, nor degree of cognitive impairment.[24]

Diabetes mellitus: Diabetes (both types I and II) is one of the most common causes of ED, leading to a 3-fold increase in prevalence of ED compared with non-diabetic men.[25] Diabetes affects small vessels, cavernous nerves, endothelial cells, and trabecular smooth muscle all of which will contribute to developing ED. Diabetes-associated peripheral neuropathies often compromise both cholinergic and NANC nerve function.[26] Additionally, the pre-diabetic condition, insulin resistance, may also be associated with ED by reducing NO production by down-regulating endothelial nitric oxide synthetase (eNOS) activity.[27]

Alcohol consumption: In the short-term, alcohol consumption has a sedating effect which often causes some degree of erectile dysfunction. In addition, chronic alcohol exposure (over 600 milliliters, or just less than three 8-ounce glasses, per week) predisposes to ED by causing polyneuropathies.[28] Heavy alcohol abuse may lead to liver damage and a resultant build up of estrogens—which can alter the hypothalamic-pituitary axis causing hypogonadism.

Hormonal

Hormonal etiologies for ED include hyperprolactinemia, hypogonadism, and either hypo- or hyper-thyroidism. Hyperprolactinemia leads to hyogonadotropic hypogonadism in men with a resulting decrease in libido and erectile dysfunction. However, since administration of dopamine agonist appears to improve ED state while testosterone supplementation does not, it is not clear whether the mechanism of ED is attributable to hypogonadism in these patients.[29] Elevated prolactin levels with subsequent discovery of pituitary mass by MRI make this a relatively straight forward disease process to screen for.

Hypogonadism (unrelated to hyperprolactinemia) and its related state of low libido is screened for by drawing a morning testosterone level between 8:00 am to 11:00 am. Those with a low testosterone (varies by lab) may be treated with exogenous testosterone with the goal of raising total testosterone into the 300 ng/dl-500 ng/dl range.

Screening for thyroid dysfunction should be considered in those who manifest signs for symptoms of hyper- or hypo-thyroidism.

Vasculogenic

Vasulogenic etiologies are the most frequent organic cause for ED and include both a restriction of arterial inflow, and a venous leak. Arterial insufficiency, with limited cavernosal arterial inflow, is predominate within this category with causes including: 1) trauma or surgical disruption to the cavernosal arteries, 2) atherosclerosis, or 3) other endothelial disorders brought on by hypertension, lipid disorders, diabetes, radiation, or smoking.

Veins traverse the corpora cavernosa and are normally passively compressed during a rigid erection, preventing venous outflow to maintain an erection. Veno-occlusive dysfunction may be the result of trauma to the tunica albugenia (penile fracture or development of a Peyronie's scar) as well as anatomically large veins that are difficult to occlude. Operations involving arterial revascularization or venous ligation are difficult to perform and are not durable. Therefore, unless there is a focal arterial lesion in a young male, vascular reconstruction is not routinely recommended.

TABLE 1. **Contrasting psychogenic and organic ED**

Organic	Psychogenic
Gradual onset	Acute onset
Global	Situational
Constant	Varies
Lacks nocturnal erections	Normal nocturnal erections
Poor erection	Good erection prior to affecting situation
Anxiety is secondary	Anxiety is primary
Fear is secondary	Fear is primary

Psychogenic

Psychogenic causes for ED range from situational anxiety and relational difficulties to more overt psychiatric disorders (and the medications used for their treatment). Depression often results in a loss of libido along with a loss of interest in pleasurable activities such as sexual activity.[30] On the other hand, it is well known that ED often leads to depression and performance anxiety. Having said that, only 10% of men with ED will have a pure psychogenic cause. Table 1 can be used to help in discerning between psychogenic and organic ED.

Medication

Medication-induced ED is estimated to occur in up to 25% of men. Blood pressure medications are frequent culprits with thiazide diuretics often quoted as the most prevalent pharmaceutical affecting erectile function. While not as frequent, non-specific alpha blockers clinically have the most severe effects on erectile function.[31] If a patient complains of ED after starting a particular medication, consider changing to a different class of medication whenever possible. Besides medication substitution, other strategies may include dosage reduction, drug holidays, or watchful waiting. If use of the offending medication is non-negotiable, consider supplementing the patient with a PDE-5i (see treatment section).

Opiates are currently one of the most commonly used (and abused) medications. When used chronically, opiates can result in a syndrome of low testosterone called opioid induced androgen deprivation (OPIAD).[32] Like opiates, steroid use can also suppress endogenous testosterone production. Such patients should be screened for hypogonadism and treated with a testosterone replacement regimen.[33]

Other recreational drugs should not be overlooked. Nicotine users have a 2-fold increased risk for ED. Besides increasing the risk for atherosclerosis and vascular diseases, nicotine causes vasoconstriction of the internal pudendal artery.[34] However, remission of ED symptoms has been realized in those men who have either discontinued smoking or reduced their body mass index (BMI).[35] Cocaine and marijuana can decrease libido, delay ejaculation, and cause ED. Marijuana does this by lowering testosterone, while the effect of cocaine on erectile function is less clear. Amyl nitrate "poppers," like nitroglycerine use, is a contraindication for concurrent PDE-5i use.

Clinical evaluation of ED

As previously stated, ED in an otherwise asymptomatic man should be considered a sentinel event for endothelial dysfunction and cardiovascular disease. Such a person should be evaluated for hypertension, diabetes, lipid disorders, and obesity.[4-7] A thorough history, physical exam, and brief laboratory evaluation is necessary prior to treating a man for ED.

History

A complete medical and sexual history is an important part of the initial evaluation. Validated questionnaires, such as the modified International Index for Erectile Function (IIEF-5) and the Sexual Encounter Profile (SEP) can be used to quantify a patient's degree of sexual dysfunction.[36-37] The history should focus on identifying underlying medical conditions which not only predispose to ED, but are also a risk to the patient's long-term health. Although treating these conditions will not reverse erectile loss, intervening should slow progression of ED. In addition, a focused history should touch on comorbid conditions such as depression, Peyronie's disease, premature ejaculation, and lower urinary tract symptoms (LUTS). A direct correlation between worsening LUTS and greater degrees of ED has been demonstrated in several epidemiological studies.[38-39] Successfully treating either ED or LUTS may positively impact both conditions. Lastly, a review of medication use and past surgeries may offer insight into additional ED risks.

Physical exam

Occasionally, the physical exam can provide direct evidence for the cause of ED. Examples include a Peyronie's plaque, chordee, micropenis, or genetic syndromes such as Kallmann's or Kleinfelter's. Indirect evidence for ED-risk includes evaluation of diminished peripheral pulses, elevated blood pressure, atrophic

testicles, or a lack of secondary sex characteristics such as voice qualities and hair distribution. Lastly, testing for genital and perineal sensation along with the bulbocavernosus reflex is useful in assessing for possible neurogenic ED.

Laboratory

Laboratory testing is recommended to identify conditions that contribute to ED. Typical tests include a fasting glucose, lipid profile, testosterone level, and if the patient is symptomatic, thyroid function tests. Testosterone levels should be evaluated at the outset in patients reporting low libido or, if small testes are noted on physical exam. In addition, a testosterone level could be checked in those men who report an inadequate response to PDE-5i use. If the testosterone level is low, a central process (hypothalamus or pituitary) should be ruled out by obtaining prolactin and leutenizing hormone (LH) levels.

TABLE 3. **PDE-5i adverse events**

	Sildenafil	**Tadalafil**	**Vardenafil**
Headache	Yes	Yes	Yes
Flushing	Yes	Yes	Yes
Dyspepsia	Yes	Yes	Yes
Back pain	No	Yes	No
Blue vision	Yes	Rare	Rare
Nitrate warning	Yes	Yes	Yes
Antiarrhythmic precaution	No	No	Yes

Modified from: Lue TF, Broderick GA. Evaluation and non-surgical management of erectile dysfunction and premature ejaculation. In: Campbell-Walsh Urology. Kavoussi LR, Novick AC, Partin AW, Peters CA, Wein AJ (Eds.). Philadelphia: Saunders Elsevier, 2007, 774. Reprinted with permission.

Treating ED

With the advent of effective oral medication for ED, primary care physicians currently manage the majority of cases of male sexual dysfunction.[31] To streamline ED treatment, a 3-tiered algorithm has been proposed, Table 2. First-line treatment options include the PDE-5i, which currently include sildenafil, tadalafil, and vardenafil. All three PDE-5i are safe and well tolerated, have similar efficacy and metabolic profiles, while having similar contraindications and warnings, Table 3.[31] In general, 74% of men will report improved erections when using PDE-5i.[40]

Risk for cardiac events surrounding sexual activity is a concern often raised by patients. Two separate Princeton Consensus Panels have clarified a patient's propensity for a cardiac event by developing guidelines that stratify patients into "low risk," "intermediate risk," and "high risk" Table 4.[41-42] Low risk patients are cleared for sexual activity. High-risk patients are advised against having sexual activity. Intermediate risk patients require further cardiac evaluation with subsequent reclassification into the low or high-risk categories.

Although safe and well tolerated in most patients, there are situations where PDE-5i should not be prescribed. These situations are listed in Table 5. Historically, concomitant use of alpha blockers with PDE-5i was discouraged for fear of orthostatic hypotension. This warning has been relaxed; the current recommendation is to simply separate administration of these two agents by 4 hours. Combining nitroglycerine or nitrate compounds (including amyl nitrate) with PDE-5i is well known for its risk of significant hypotension. An absolute contraindication exists regarding their combined use.

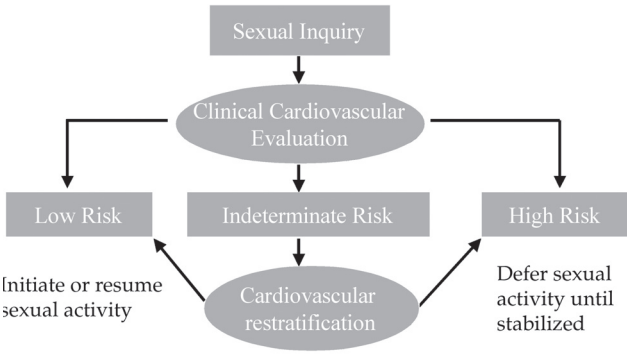
TABLE 2. **Current guidelines for treating ED**

First-line
- Treat reversible causes
- Lifestyle modification (weight loss, tobacco cessation, exercise)
- Oral agents (sildenafil, vardenafil, tadalafil)

Second-line
- Intracavernous injections (Caverject, Edex, Tri-mix)
- MUSE (Medicated Urethral System for Erection)
- Vacuum erection device

Third-line
- Surgical prosthesis
- Some men respond to hormonal therapy, penile revascularization, or sex therapy

TABLE 4. **Sexual activity and cardiac risk: Princeton guidelines**



Low risk

< 3 major cardiac risk factors
Uncomplicated past MI (> 6-8 weeks ago)
Mild valvular disease

High risk

Unstable angina
Recent MI (< 2 weeks)
Uncontrolled hypertension
Moderate-to-severe valve disease (aortic stenosis)

Intermediate risk

> 3 major cardiac risk factors
Recent MI (2-6 week ago)
LV dysfunction or congestive heart failure (NYHA II)

Modified from: DeBusk R, Drory Y, Goldstein I, Jackson G, Kaul S, Kimmel SE, Kostis JB, Kloner RA, Lakin M, Meston CM, Mittleman M, Muller JE, Padma-Nathan H, Rosen RC, Stein RA, Zusman R. Management of sexual dysfunction in patients with cardiovascular disease: recommendations of the Princeton Consensus Panel. Am J Cardiol. 2000;86(2):180. Reprinted with permission.

An additional concern among PDE-5i users is the development of nonarteritic anterior ischemic optic neuropathy (NAION). This is a condition resulting in blindness secondary to an ischemic injury to the optic nerve head. Edema of the axons within the optic disk may cause capillary ischemia resulting in nerve damage. Patients at risk for NAION have similar cardiovascular risk factors that have predisposed them to ED. There is little basis for modifying the current guidelines for PDE-5i use. Having said that, it is recommended that PDE-5i use should be avoided in men who have already experienced NAION in one eye, and medical attention sought if visual field or acuity loss occurs after PDE-5i use.[13]

Most men will experience improved erectile quality using PDE-5i. However, for complex or difficult to treat cases, consultation with a cardiologist, endocrinologist, psychologist, or urologist may be indicated. A urological consultation would be necessary for those patients requesting surgical intervention (a penile prosthesis) or, may be considered for providers who are not comfortable recommending second-line treatment options such as intracorporal injections, vacuum erections assist devices, or venous constriction devices.

Conclusion

Erectile dysfunction is prevalent and may be the first sign of other undiagnosed cardiovascular risk factors. With the advent of safe and effective PDE-5i, most patients can be treated by primary care physicians after ruling out and/or treating organic causes that may be harmful to the patients overall health. Preventative care algorithms should be optimized by screening men 40 years or older for ED.

TABLE 5. **PDE-5 inhibitor warnings**

Myocardial infarction within 90 days
Angina: unstable or during sexual activity
NYHA class II (or greater) heart failure within 6 months
Stroke within 6 months
Hypotension (< 90/50) or uncontrolled hypertension (> 170/100)
Uncontrolled arrhythmias
Tendency to develop priapism (sickle cell, leukemia)
Heredity degenerative retinal disorders (retinitis pigmentosa)

Modified from: Lue TF, Broderick GA: Evaluation and non-surgical management of erectile dysfunction and premature ejaculation. In: Campbell-Walsh Urology. Kavoussi LR, Novick AC, Partin AW, Peters CA, Wein AJ (Eds.). Philadelphia: Saunders Elsevier, 2007, 777. Reprinted with permission.

Take-home messages

When to refer to urology:

Patient desires surgery.
Patient fails non-surgical treatment.
Provider not comfortable with second-line treatment options.
Patient fails second-line treatment options.
Patient with low testosterone who desires to preserve fertility potential.
Patient with penile abnormality (Peyronie's disease).

ED = ED*

Erectile dysfunction = Endothelial Dysfunction
Erectile dysfunction = Emotional dysfunction (depression)
Erectile dysfunction = Endocrine dysfunction (low testosterone)

*Compliments of Claude Laroche, MD, Family Practitioner, Clinique Medicale Cadillac, Montreal, Quebec, Canada

Disclosure

Dr. JC Trussell is a member of the Speaker's Bureau for Pfizer. □

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DISCUSSION

Question (Dr. Miner):
How would you distinguish ED from other sexual dysfunctions (such as anejaculation and premature ejaculation?

Answer (Dr. Trussell):
I distinguish between ED and other sexual dysfunctions by history. For example, I ask patients if their "early detumescence" occurs due to an untimely (early) ejaculation (premature ejaculation) or, if they loose their erection without ejaculation (venous leak). I discern anejaculation from retrograde ejaculation by asking if the patient senses orgasm or not. For those patients without antegrade ejaculation, I order a post-ejaculate urine looking for sperm (retrograde ejaculation).

Question (Dr. Greenberg):
What is the academic rationale for using PRN versus daily continuing dosing of ED treatment medications?

Answer (Dr. Trussell):
The rationale for daily PDE-5i use is that a sustained therapeutic plasma level can be obtained in 5 days. FDA has approved dosage for Tadalafil in 2008. Theoretically, this may allow patients to take a smaller dose (possible fewer adverse events) while minimizing the need to time sexual activity. Fortunately, there has not been evidence for loss of efficacy through 12 months of daily Tadalafil use. Additional studies are needed to determine if daily dosing is more effective, more cost effective, and quite possibly, beneficial for the treatment of other symptoms such as lower urinary tract symptoms (LUTS).

Question (Dr. Laroche):
Please discuss your clinical algorithm when considering intracavernous injections or MUSE.

Answer (Dr. Trussell):
For those patients who are unable to take oral agents (for example, exposure to nitrates) or who report an incomplete response, I recommend moving to second-line therapies. These therapies include MUSE, injection therapy, and the vacuum erection device. I find that injection therapy is more reliable and start with a low dose: 10 mcg for those with organic ED, 5 mcg for those who have a psychogenic component. With MUSE I start with the 1000 mcg dose.

Testosterone replacement therapy for the primary care physician

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CASEY RW, BARKIN J. Testosterone replacement therapy for the primary care physician. The Canadian Journal of Urology. 2008;15(Supplement 1):71-77.

Testosterone replacement therapy (TRT) can have significant beneficial effects in the appropriate hypogonadal male patient. Testosterone deficiency is common in primary care practice and recognition of the signs and symptoms of this abnormality will allow physicians to choose appropriate interventions. The symptoms of clinical hypogonadism include muscle weakness, fatigue, mood changes and a reduced libido. Signs include a reduced muscle mass, osteoporosis, anemia and increased adiposity. While routine screening for testosterone deficiency, determination of testosterone levels in high risk populations, including obesity and diabetes, will help the clinician direct TRT to the patients most likely to benefit from therapy. In this article the syndrome of male hypogonadism is discussed, together with therapeutic choices available to the primary care physician.

Key Words: testosterone replacement therapy, hypogonadism, andropause, prostate cancer, erectile dysfunction

Introduction

Significant controversy still exits among the medical community regarding the appropriate use of testosterone replacement therapy (TRT). Injectable forms of testosterone have been available since the beginning of the twentieth century and the recent introduction of safe, reliable methods of testosterone supplementation (oral agents and topical gels) have renewed physicians interest in the potential therapeutic benefits of testosterone. Andropause, a term coined in the media by Gail Sheehy in the late 1980s, widened the potential scope of therapy to men with low or low normal levels of testosterone and 'softer ' symptoms. More recently, the medical community has begun to narrow this range and identify men with the clinical signs and symptoms of androgen deficiency who are likely to receive clinically significant benefits from testosterone.[1] The end organ effects of testosterone (T) are remarkable. Improved strength, better mood, stronger muscles, increased libido, the list goes on. In the truly hypogonadal patient, one cannot argue the benefits of TRT. The possible side effects of testosterone administration include hepatotoxicity, sleep and emotional disturbances, erythrocytosis and benign prostatic hyperplasia.[2] There is little long term data on prostate cancer; short term surveillance studies have shown no increased prevalence in treated patients. A recent meta analysis of 18 papers concluded that there was no relationship to the incidence of prostate cancer and serum testosterone levels.[3]

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As a Urologist, I see patients that have been 'differentiated' by their primary care physician (PCP), the tentative diagnosis of hypogonadism made and my role is confirm the diagnosis, initiate and to reassure that as long as the PCP has addressed the possible risks of TRT that he can consider a trial of testosterone, if it is indicated. The endocrinologist's role is similar. Primary care physicians, on the other hand, must wade through large numbers of male patients with hypogonadal like symptoms before actually uncovering a patient that might benefit from therapy. This is not an easy task, while considering the risk/benefit ratios. Hypogonadism shares many of the clinical manifestations of depression, erectile dysfunction and normal aging.[4] This has lead to a sense of frustration among many practitioners. The following pages are an attempt to help physicians narrow their sites and find the hypogonadal patient who requires treatment and to discuss different treatment options.

Background

Hypogonadism has a variety of biochemical definitions, but most simply can be defined as a morning serum testosterone value 2.5 standard deviations (SD) below the normal mean level in young adults. Most investigators use 300 ng/dl (Canada 7-38.0 nmol/l) as the lower limit of normal, below which many patients exhibit the biochemical and clinical signs of testosterone deficiency. Attempts to define a better marker for T deficiency (bioavailable or Free testosterone) have added little to our diagnostic abilities.[5] The other concept that is to be considered is that of "testosterone change/velocity". If one was at the upper end of the "normal" range 5 years ago, but is now at the lower "normal" (but still within) end, is that "change" significant enough for that particular individual to create the symptoms and signs of hypogonadism? Low testosterone levels are associated with a constellation of signs and symptoms including poor libido, erectile dysfunction, reduced ability to concentrate, decreased bone density, anemia, sleep disturbances, decreased lean muscle mass and fatigue. Many of these symptoms are often ignored by patients and their physicians and attributed to the natural consequences of aging. With the amount of publicity surrounding the possible 'performance enhancement' qualities of testosterone, patients have returned to their physicians to explore TRT. Andropause was coined to describe men with symptomatic androgen deficiency. While a majority of women manifest some of the symptoms of estrogen deficiency due to the rapidity of the decline, the gradual decline of testosterone in men results in a more variable and less dramatic symptom complex, hence andropause has become a less popular descriptor, replaced with symptomatic late onset hypogonadism (SLOH).[5]

As men age, there is a gradual decline in the amount of testosterone that is available at the cellular level. This is largely due to declining testosterone production from testicular Leydig cells and an increase in sex hormone binding globulin (SHBG). The result is that there is less absolute testosterone being produced and more is bound up by the SHBG, which is then isolated from the tissues. The "free" testosterone (not bound to albumin or SHBG) together with the albumin- bound testosterone, makes up what is now called "bio-available testosterone", or that component that is available to have its impact on the body. At 60, the amount of available testosterone is roughly one half that at the age of 20, suggesting that many of the symptoms attributed to aging are in part a result of reduced testosterone production.

The impact of hypogonadism on long-term morbidity is not well known. Osteoporosis and frailty have been linked to testosterone deficiency, as has erectile dysfunction and depression. A number of investigators have documented the improvement in mood, muscle strength, body composition and sexual function in hypogonadal populations appropriated treated with testosterone replacement therapy. It is largely this data, and the absence of any significant safety concerns that has convinced clinicians that TRT may have a role in improving the quality of life men with SLOH.

Effects of testosterone

Bone

Hypogonadal men are at significant risk for osteoporosis. In men over 65 years of age, the incidence of osteoporosis was twice that of eugonadal men, (12.0% versus 6.0%). In the prostate cancer population treated with androgen deprivation therapy, patients are at significant risk of osteopenia and osteoporotic fractures. Testosterone plays a role in the maintenance of bone mineral density and testosterone replacement therapy can improve bone mineral density, although its role in fracture risk reduction is unknown. Some studies have shown that minimal trauma hip fractures in men were much more common in those men with lower free testosterone than those that were eugonadal ($p < .001$).[6] Hypogonadal men, particularly those on androgen deprivation therapy for prostate cancer, should have a baseline DEXA scan with periodic evaluations depending on their clinical course.

Metabolic syndrome

There is a significant increase today in the diagnosis of metabolic syndrome.

Why be concerned about metabolic syndrome?

1) Increased risk of cardiovascular events - 2-fold

2) Increased risk of type II diabetes - 5-fold[7]

It has also been shown that there is a higher incidence of hypogonadism in men with metabolic syndrome. There is also increased risk of finding low testosterone levels in men with obesity, diabetes and hypertension, which are three of the criteria for metabolic syndrome.[8]

It seems reasonable to both look for hypogonadism in men with any of the signs of metabolic syndrome. As well, testosterone therapy in these men may help to improve upon the signs and prevent the sequelae of metabolic syndrome.

Prostate

The prostate requires the presence of testosterone for normal growth and development. The widespread use of 5 alpha reductase agents, (Proscar, Merck Inc., and Avodart, GlaxoSmithKline) which decrease intracellular levels of dihydrotestosterone, have demonstrated the dramatic reduction in prostate growth when deprived of testosterone. In addition, the effects of chemical castration on metastatic prostate cancer further demonstrates the dependence of prostate cells on androgens. There is little evidence to suggest that, the use of androgens to restore physiologic levels of testosterone could exacerbate voiding difficulties or unmask an indolent prostate cancer. Several randomized trials have failed to show an increase in prostate cancer detection in testosterone treated males.[9]

Hypogonadal patients treated with testosterone will often see an increase in prostate-specific antigen (PSA) and prostate volumes that only reach the levels of their eugonadalage-matched controls. Primary care physicians should be aware that this transient increase to age specific levels is to be expected during the first year of therapy. Subsequent PSA changes should be assessed according to the standard of care and evaluated within the context of the patients' risk factors. Always do a digital rectal examination.

Heart

Evidence suggests a modest increase in HDL levels in hypogonadal men treated with testosterone and a possible beneficial effect of testosterone on cardiovascular health. Men with lower levels of testosterone have been found to have a higher incidence of abnormal coronary angiograms. Certainly, at the present time, there is little scientific data to support a potential detrimental effect of testosterone supplementation on cardiac health. Polycythemia is most common adverse effect of TRT, patients receiving intramuscular preparations being at greatest risk. Because of this, periodic monitoring of CBC during testosterone therapy is recommended. Erythocytosis that develops in these patients responds well to cessation of therapy.[10]

Prevalence of hypogonadism in family practice populations

The range of symptoms exhibited by hypogonadal men makes them a diagnostic nightmare for the practicing physician. These patients share symptoms with large groups of other diagnoses such as depression, erectile dysfunction and obesity. What is the true prevalence of low testosterone in the typical family practice office and is it cost effective to consider screening more patients with testosterone levels?

The Hypogonadism in Males study[8] estimated the prevalence of men > 45 years of age with serum testosterone levels < 300 ng/dl visiting primary care practices in the United States. While this is a highly selected population (men seeing their physicians!), the study does give primary care physicians a rough idea of the scope of hypogonadism in their older male population. The prevalence of men with low testosterone was 38.7%. More significant though, were the comorbid conditions where low T was likely to be present. The odds ratios for men having low T levels were significantly higher in men with hypertension (1.8), hyperlipidemia (1.5), diabetes (2.0), obesity (2.4) and prostate disease (1.2). This suggests a good starting point for primary care practitioners when considering the diagnosis. When one sees a patient with any of these comorbidities it is appropriate to obtain an early morning testosterone level to use as a baseline. If significantly low and the patient seems to be refractory to treatment for their primary condition, such as diabetes, then one should consider testosterone therapy to possibly enhance the response. To date there is little evidence that low testosterone levels without the clinical manifestations of androgen deficiency poses a significant health risk. Routine screening is to be discouraged until the consequences of asymptomatic androgen deficiency are better defined.

Most men with low testosterone levels are asymptomatic and may not require treatment. The Boston Area Community Health (BACH) survey illustrated the importance of considering testosterone deficiency in the context of clinical symptoms. As

part of a general healthcare screening program, men underwent a panel of laboratory exams and answered detailed health questionnaires. Twenty-four percent of the patients studied had serum testosterone levels < 300 ng/dl, approximately 47% of men at least 50 years old with low T were asymptomatic.[8] This must be considered in context though, as a detailed history and physical exam by a trained physician might uncover significant signs and symptoms missed by patient surveys.

These data support a conservative approach to the diagnosis and treatment of androgen deficiency. An index of suspicion in the groups at high risk is likely to identify patients who might benefit from testosterone supplementation.

Diagnosis

The diagnosis of hypogonadism requires a high index of suspicion based on symptoms, exclusion of other causes and consideration of the patients' risk profile and comorbidities. In the absence of the sequelae of low T levels, patients with morning serum testosterone levels < 300 ng/dl may not require treatment.

When hypogonadism is suspected, a morning total testosterone level should be obtained. Because of the significant variablility of T levels, it is suggested that all abnormal levels be repeated before considering therapy. If the results are borderline, the test should be repeated along with LH, FSH, Prolactin and free T levels.[11]

Elevated Prolactin levels need clarification usually with an MRI of the sella turica and an endocrinology opinion. Clinical signs and symptoms are often the determining factor with respect to TRT. The threshold for initiating therapy may be lower in the anemic or osteoporotic patient, particularly if levels are in the low normal range.

A variety of questionnaires are available to assist the clinician in the diagnosis of testosterone deficiency. They are appropriate only as screening instruments due to their poor specificity. The instruments most widely used are the St. Louis University ADAM and the Aging Male Survey (AMS). Unfortunately, there are no validated instruments that can assist physicians in measuring treatment effects.[12]

Before starting testosterone, a digital rectal exam and PSA should be documented. The changing landscape of PSA's use for prostate cancer screening mandates a discussion of the risks of prostate cancer in those men who are at high risk due to their family history. While TRT has not been shown to cause prostate cancer, patients with siblings already diagnosed with prostate cancer should probably be referred to a urologist for education and a prostate biopsy if TRT is in order. In addition, patients with an elevated age specific PSA or abnormal digital rectal exam require a urologic evaluation prior to TRT administration.[13] Despite its safety, historically, testosterone remains tied to prostate cancer due to the dramatic effects of castration on the management of the disease.

A more complete discussion of the specific effects of testosterone on bone, cognitive function, body composition, sexual function and prostate can be found in a recent article published in The Canadian Journal of Urology Supplement in Dec 2007.[13]

Who should be screened for low testosterone levels?

Because almost 20% of men aged 60-69 and 30% of men aged 70-79 have low testosterone levels, screening is to be discouraged. Narrowing our sites to the high risk groups is more likely to uncover clinically significant androgen deficiency and provide physicians with a patient group with improved outcomes due to testosterone supplementation. With the introduction of safe testosterone preparations, physicians have begun to widen their scope and consider androgen deficiency when evaluating men with mild depression, frailty, decreased lean muscle mass, increased central obesity, decreased energy levels and sexual difficulties.

Metabolic syndrome

As mentioned earlier, men with obesity, diabetes and hypertension have an increased likelihood of androgen deficiency. This group of patients should have their testosterone levels assessed even if they exhibit no signs of hypogonadism. The effect of testosterone on body composition includes a decrease in fat mass and an increase in lean muscle mass, along with a decrease in insulin resistance. Testosterone also has been shown to effect the redistribution of adiposity to the viscera and the subcutaneous tissues typical of eugonadal men.[13]

The effect of testosterone supplementation on lipid levels is yet to be fully elucidated, but preliminary evidence suggests a minimal decrease in HDL levels. Population studies have demonstrated an inverse relationship between bioavailable testosterone levels and aortic atherosclerosis.[14] Previously, especially with the older (no longer available) methylated testosterones, there was a potential for significant lipid imbalance that lead to premature atherosclerosis and heart attacks. With the present esterified testosterones that are metabolized through the lymphatics, TRT can actually be cardio-protective.

Erectile dysfunction

In the absence of poor libido, the cost effectiveness of routine T determination in men with erectile dysfunction is questionable. On the other hand, patients who have failed a course of phosphodiesterase 5 inhibitors (PDE5i)) should have their testosterone levels drawn. Approximately 30% of men who fail PDE5i who are found to have low serum T will be improved by testosterone supplementation.[15] It is very safe to use the PDE5i at the same time that the patient is on TRT.

When to refer to an endocrinologist or urologist

Certainly, the majority of men with the signs and symptoms of androgen deficiency can be managed by the primary care physician. In a few instances, a team approach with input from a urologist or endocrinologist is appropriate. Secondary causes of hypogonadism such as hyperprolactinemia require endocrinologic input. Men with a strong family history of prostate cancer, an elevated PSA or abnormal digital exam should be evaluated by a urologist. In addition, significant changes in PSA levels that do not normalize with cessation or alteration of therapy should be investigated.

It has been shown that testosterone therapy does not cause prostate cancer. In men that have had a radical prostatectomy for the curative approach to prostate cancer, there is about a 20% chance for the development of symptomatic hypogonadism. If the patient is miserable with the condition and requests TRT, then he should be referred to the urologist. If the patient is a few years out and has a PSA of zero, after a significant informed consent, some physicians may consider testosterone. Very lengthy and rigid follow-up and monitoring is mandatory.

Treatment

Once the clinical and biochemical diagnosis of androgen deficiency is made, the clinician has a variety of therapeutic options to consider. The route of testosterone administration should be discussed with each patient as there are cost and compliance issues that may determine treatment success. All available preparations can normalize testosterone levels. Present options include injectables, oral preparations and topical gels. The advantages and disadvantages of each route are summarized in Table 1.

Once testosterone supplementation is instituted, patients require regular monitoring for response and safety. Certainly, during the first year of therapy, more frequent assessments of PSA and hemoglobin (q 3 months) might be in order. One should also do baseline and 6 monthly liver function tests, and DREs although the newer preparations are very safe. Patients should be informed that a 3 to 6 month trial of therapy may be necessary before discontinuation for lack of efficacy. Some patients will absorb one preparation better than others, so if one fails at maximum dosage, then switching to another preparation, could salvage some patients.

Compliance is always an issue, particularly in our male patients. In addition to supplementation, the physician can use this diagnosis as an opportunity to discuss the benefits of weight loss and exercise.

TABLE 1. **Advantages and disadvantages of testosterone administration**

Route of administration	Dose	Advantages	Disadvantages
Injectable (delatestryl)	200-400 mg q 3 weeks	Low cost Good compliance	Requires supervised administration May have higher risk of hemoconcentration
(Testosterone Undecoanate-Nebido)	1000 mg q3 months	Increased compliance and steadier blood levels	Costly Not easily reversible because long lasting
Oral (Andriol) (Canada only)	80-120 mg bid	Easy to titrate dose Familiar route for	Must be taken with food Variable absorption most patients
Topical gel (Androgel, Testim)	5-10 gms daily	Once a day dose Reliable absorption	Can be messy Low risk of transference
Patch (Androderm)	1 patch daily	Easy to apply, reliable absorption	Skin irritation in over 30% of patients

Testosterone's effects on body composition (adipose redistribution) and chest to waist ratio will only be augmented by combining your prescription with an exercise program and dietary counseling, if necessary.

Monitoring

Baseline hemoglobin, liver function tests and PSA should be repeated after 3 months of therapy. If within normal range, there is some controversy on the frequency on monitoring necessary, but there is no evidence to suggest that more than twice a year is necessary.

Many patients will have a transient rise in their PSA's, usually to age specific levels. Continued elevations should be investigated and a urologic referral considered.

The occasional patient will develop significant increases in Hgb (> 180). This is usually corrected by reducing the dose of testosterone.[16]

Risks of testosterone supplementation

In general, TRT has minimal risks in the appropriate patient. The biggest concern most patients and physicians have is that of prostate health. A recent publication by the Endogenous Hormones and Prostate Cancer Collaborative Group reviewed 18 studies which included over 3000 men with prostate cancer and 6438 controls. No association with serum concentrations of sex hormones and prostate cancer risk was found. Prudent use of TRT in high risk populations (family history of prostate cancer, previous high grade PIN on prostate biopsy, previous surgery to remove localized prostate cancer) is suggested until better safety data is available.[17]

Another concern is that of testosterone abuse. We have all encountered patients in our practice that are seeking testosterone for performance enhancement. Many confuse what they see in the media (steroids in sports, for example) with the type of preparations used by physicians for TRT. Testosterone has minimal anabolic effects and there is little scientific data to support any athletic performance effect at higher than therapeutic doses. In Canada, testosterone remains a controlled substance and it is extremely difficult for patients to over treat themselves. In my experience, those seeking testosterone for nonmedical purposes obtain it via internet pharmacies without the consent of their physicians.

It is this inherent safety of the newer testosterone preparations, that allows for a trial of therapy. In those patients where one is equivocating over treatment, a 3-month trial of one of the TRTs can be both diagnostic and therapeutic. The issue is the treatment in those patients that are in the "normal" range. What one does not know is what is "normal enough" for that particular individual.

Summary

Androgen deficiency can have a significant impact on the quality of life of our male patients. These effects can be reversed by the administration of testosterone with acceptable risks. The diagnosis of hypogonadism requires appropriate biochemical testing and clinical judgment. There are a number of high risk groups where the prevalence of androgen deficiency warrants consideration of the diagnosis and where treatment may produce significant positive patient outcomes.

The primary care physician should consider directed testosterone determination in these populations (diabetes, obesity, hypertension, sexual dysfunction, frailty syndrome). There are a number of safe treatment options available that will allow the physician to restore normal testosterone levels in a safe and effective manner. Only a small percentage of these patients require specialist consultation.

Disclosure

Dr. Casey has received financial support from Bayer, Eli Lilly and Pfizer. Dr. Barkin has been a clinical investigator for Solvay and Organon and sits on the medical advisory committees for both companies. He has spoken about all drugs for hypogonadism and all testosterone producing pharma-companies for the last 25 years. □

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DISCUSSION

Question (Dr. Rosenberg):
In males that undergo treatment for prostate cancer is there ever a point when one should consider initiating testosterone therapy?

Answer (Dr. Casey):
Symptomatic hypogonadal men who have received curative therapy for their localized prostate cancer can be treated with testosterone replacement therapy. While the amount of clinical data examining the risks in this prostate cancer population is sparse, there is no reason to suggest that restoring patients to eugonadal status increases their cancer morbidity. Men who are being treated with androgen deprivation therapy for locally advanced or metastatic prostate cancer should not be considered for supplementation until there is data supporting its safety. It is my opinion that TRT in this population should be managed by the same physician who is responsible for managing the patient's prostate cancer.

Question (Dr. Laroche):
Please comment about the utilization of testosterone in women to increase libido.

Answer (Dr. Casey):
Decreased libido in our female patients represents a particularly difficult diagnostic and therapeutic dilemma. In the post menopausal woman, with extremely low free testosterone levels, a trial of testosterone therapy might be warranted in addition to estrogen replacement therapy. There seems to be a positive correlation between female sexual functioning index (FSI) and testosterone levels in both pre and postmenopausal estrogen replaced females. However there is little clinical trial data to support its widespread application in the hypoactive sexual desire disorder population. Anectdotal reports of its potential benefits in selective populations has kept the concept of testosterone supplementation alive for HSDD patients.

Question (Dr. Miner):
At which point, if at all, should a patient with history of depression, decreased libido and frailty be considered a candidate for TRT?

Answer (Dr. Casey):
There is some evidence that depressed hypogonadal men might receive significant relief from their illness with TRT despite a poor correlation between depression and testosterone levels. In the eugonadal population there is unlikely a role for TRT as a treatment for depressive illness.

Frailty syndrome is a complex syndrome and requires a multidisciplinary approach to treatment. Certainly, motivated hypogonadal patients can receive significant benefit from TRT and weight bearing exercises. Appropriate attention to prostate health in this elderly population is necessary to insure that an undiagnosed prostate cancer is not present.

Question (Dr. Greenberg):
How clinically useful is getting a baseline Testosterone level on all patients by the time they are 40.

Answer (Dr. Casey):
Until there is more data to support the cost effectiveness of screening for hypogonadism, routine testosterone determinations in the absence of at least some supporting clinical evidence, is to be discouraged.

Uropharmacology for the primary care physician

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Advances in the understanding of the pathophysiology of a variety of urological disorders have resulted in the development of novel medications to manage these diseases. While many disorders such as erectile dysfunction, overactive bladder, hypogonadism and benign prostatic hypertrophy have traditionally been managed primarily by urologists, the use of these newer medications has become commonplace in the primary care setting. For example, symptomatic benign prostatic hyperplasia therapy, while historically treated with primary surgical intervention, is now commonly initially managed with medical therapy. Prostate cancer patients are being treated with newer formulations of long term hormone therapy that range from monthly to yearly administration. Additionally, the open dialogue about erectile dysfunction can be directly traced to the development of oral therapy for this condition. Testosterone replacement therapy can be administered using a variety of oral, transdermal and intramuscular therapies in order to minimize side effects and provide a more consistent dosing pattern. Finally, overactive bladder, which is a significant problem socially, has many new medications available for its treatment. This article will review some of the newer classes of urological medications, provide an understanding of basic uropharmacology that may guide treatment recommendations, and provide insight into the potential adverse side effects and interactions of these useful medications.

Key Words: uropharmacology, urological medications

Introduction

Over the past several decades, improved understanding of the physiology that underlies various urological diseases and conditions has led to the development of many new medications. The use of these medications for the treatment of urological diseases has expanded from the urologist's office to the office of the primary care physician, who may provide both the initial evaluation and treatment. An understanding by primary care physicians of the pathophysiology and pharmacology of common urological diseases is important for the successful and safe management of these patients either as the primary caregiver or in coordination with their urological care. In this review, we focus on the significant advances in the medical management of common urological diseases such as benign and malignant diseases of the prostate, erectile dysfunction, overactive bladder and hypogonadism.

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Symptomatic benign prostatic hyperplasia

Pathophysiology and pharmacology

Benign prostate hyperplasia (BPH) is a term that is commonly, but incorrectly, used for prostatic

obstruction leading to urinary symptoms. BPH is a histologic diagnosis, the precursor to benign prostate enlargement (BPE). BPE can then lead to changes in voiding habits consistent with bladder outlet obstruction (BOO). This article will use symptomatic (sBPH) to encompass BPH, BPE and lower urinary symptoms (LUTS).[1,2] LUTS are constellation of irritative symptoms such as urgency, frequency and nocturia, or obstructive symptoms such as hesitancy, weak stream, intermittency or straining. While traditionally viewed as a disease of "inconvenience", sequelae of sBPH may sometimes include urinary retention, increased post void residual, bladder calculi, renal failure, hematuria, urinary tract infection and irreversible bladder dysfunction. It is important to recognize that the signs and symptoms of sBPH can also overlap with other urological pathology or insults to the central nervous system (e.g., urethral stricture, bladder dysfunction, neurological disorders including Parkinson disease and multiple sclerosis).

sBPH affects more than 50% of men over the age of sixty. The incidence steadily increases to approximately 90% as men reach their ninth decade of life.[1,2] Moderate to severe LUTS occur in 18%, 29%, and 50% of men in their 40's, 50's, and 60's, respectively, with a quarter progressing to require surgical intervention.[1,2]

The smooth muscle tone of the prostate can be the primary cause responsible for symptoms seen with sBPH. The prostate, human vasculature, and central nervous system are responsive to autonomic intervention via the neurotransmitter norepinephrine (NE) which then mediates various adrenoreceptors (AR). Alpha$_1$ AR have an important role in the urinary tract. Within alpha$_1$ AR there are three subtypes that have been identified: alpha$_{1A}$, alpha$_{1B}$, and alpha$_{1D}$.[3] A considerable amount of attention has been placed on the alpha$_{1A}$ subtype because of its high concentration in the prostatic urethra, stroma and bladder neck. By pharmacologically targeting these receptor subtypes, a decrease in tone can be elicited and lead to symptom relief.

sBPH can also be the result of the mechanical impediment of urinary flow from an enlarged prostate gland. Testosterone and dihydrotestosterone (DHT) are the predominant male hormones responsible for virilizaton and growth of the male genitalia. DHT is formed by two isoenzymes, types I and II, 5-α-reductase. Type I, 5-α-reductase is predominantly concentrated in the lung and skin (10% found in the prostate), and type II, 5-α-reductase is present in the stroma and basal epithelial cells of the prostate and is responsible for intraprostatic conversion.[4] The conversion of testosterone to DHT by type II 5-α-reductase is mostly responsible for the growth of the prostate. Interestingly, DHT also indirectly modulates vascular derived endothelial growth factor (VEGF), causing microvascular proliferation, and contributes to the increased vascularity and hematuria occasionally seen in patients with sBPH.[5,6] The management of sBPH today can include surgical debulking of the prostate with standard or newer "minimally invasive" technologies such as lasers or radio frequency ablation. Pharmacological management, which is typically the initial management approach, is based on two concepts: reducing prostatic tone and decreasing the size of the prostate gland, thus leading to less resistance of flow.

Alpha-blockers

Alpha adrenergic antagonists competitively inhibit the alpha AR. Blocking these receptors promotes bladder neck and prostatic urethral relaxation. Alpha AR blocking agents (alpha-blockers) can be subdivided depending on their degree of selectivity for the AR and patient tolerability.[7,8] Correspondingly, there are first generation (phentolamine, phenoxybenzamine), second generation (prazosin [Minipress], doxazosin [Cardura], terazosin [Hytrin]), and third generation (tamsulosin [Flomax CR], alfuzosin [Xatral]) agents. Canadian Urological Association (CUA) guidelines do not recommend first generation alpha-blockers or prazosin in the treatment of sBPH.[9] The alpha-blockers were among the first class of medications approved for the treatment of sBPH.

First generation alpha-blockers are no longer considered in the management of sBPH because of their severe side effect profile, such as non-selectivity toward the alpha$_1$ and alpha$_2$ ARs, and irreversibility found in phenoxybenzamine. This generation of medications historically caused palpitations, dizziness, impaired ejaculation, nasal stuffiness, and visual disturbances. Second and third generation alpha-blockers are more selective by targeting the alpha$_1$ and alpha$_{1A}$ subtypes, respectively. According to the CUA guidelines, second and third generation alpha-blockers are similar in reducing the symptoms of BPH, increasing maximum urinary flow rate, and reducing post void residual, but vary in their degree of side effects and pharmacological profiles.[9]

Second generation alpha-blockers are commonly associated with cardiovascular symptoms such as hypotension, dizziness, fatigue, and first dose syncope, although these actually occur less than with first generation alpha-blockers. These adverse reactions are thought to be due to interactions with alpha$_1$

TABLE 1. **Alpha-blocker medications for symptomatic benign prostatic hyperplasia (sBPH)**

Name	Dosage	Side effects
Second generation		
Terazosin (Hytrin)	1 mg-10 mg daily*	First dose syncope; dizziness; tachycardia; hypotension; headache; asthenia; rhinitis
Doxazosin (Cardura)	1 mg-8 mg daily*	Same as above
Third generation		
Alfuzosin (Xatral)	10 mg daily with food	Dizziness; headache; minimal cardiovascular effect; less ejaculatory dysfunction then tamsulosin
Tamsulosin (Flomax CR, generic capsules)	Flomax CR: 0.4 mg daily (with or without food) Generic capsules: 0.4 mg-0.8 mg daily with food	Ejaculatory dysfunction; rhinitis

*Dose titrated weekly to desired response.

receptors that control the tone of systemic blood vessels and those in the central nervous system (CNS).[2] However, it is cautioned that alpha-blockers should not be used as the primary treatment for blood pressure management.[10] Second generation alpha-blockers require titration over several weeks until maximum dosages are obtained. Individually, these medications differ somewhat in their side effect profiles. Terazosin has a peak plasma concentration that is delayed with fatty meals. Doxazosin is hepatically metabolized, so caution should be used in patients with liver pathology.[11]

The third generation alpha-blockers tamsulosin and alfuzosin have been found to have minimal cardiovascular effects while exerting the desired effect of decreasing the symptoms associated with BPH. Unlike their second generation counterparts, both medications do not need to be titrated. Alfuzosin is noted to be pharmacologically similar to the second generation but clinically it is has been found to be more uroselective, exhibiting minimal cardiovascular side effects. Tamsulosin selectively targets the bladder and prostatic urethra, having a high affinity for the $alpha_{1A}$ AR. Alfuzosin and tamsulosin exhibit similar side effects, such as dizziness, but tamsulosin has been found to have higher rates of ejaculatory dysfunction (10%) (anejaculation and/or retrograde ejaculation), which may be attributed to an affinity toward 5HT1A and D2 receptors centrally.[12] To improve absorption, alfuzosin and tamsulosin (generic capsules) should be taken after the same meal daily. (Flomax CR tablets may be taken with or without food.)

An uncommon side effect of alpha-blockers is intraoperative floppy iris syndrome (IFIS), a condition that occurs during phacoemulsification cataract surgery and was first described in 2005.[13] The syndrome is characterized by a triad of events that may lead to a more difficult cataract operation and an increased risk of surgical complications of up to 49%.[14] The cause of IFIS is thought to be due to the interaction between alpha-blockers and the heavily dominated $alpha_{1A}$ receptors in the iris. Tamsulosin has been implicated in several case reports of causing IFIS.[13,14] In anecdotal studies, terazosin, doxazosin, and alfuzosin have also been implicated as culprits, but to a lesser degree.[15,16] Currently, it is recommended that one discontinue tamsulosin therapy for 1 to 2 weeks prior to cataract surgery.[13,17] Table 1.

5-alpha-reductase inhibitors

An enlarged prostate gland, although not directly correlated with degree of prostatic obstruction, can be a cause of sBPH. Finasteride [Proscar] and dutasteride [Avodart] are the two agents in the category of 5-alpha-reductase inhibitors (5-ARI). Finasteride is also available in a lower dosage to treat alopecia [Propecia].

Both finasteride and dutasteride act by blocking the conversion of testosterone to DHT. Decreases in DHT have been shown to induce prostatic epithelial apoptosis and atrophy.[18] Finasteride is a type II 5-ARI that has been found to decrease serum DHT by 70%-90% within the prostate, causing a reduction in prostate size by 20%-30% over a 6-12 month period.[18,19] The loss of glandular tissue is responsible for a decrease in prostate-specific antigen (PSA) by

TABLE 2. **5-alpha-reductase inhibitor medications for symptomatic benign prostatic hyperplasia (sBPH)**

Name	Dose	Half-life	Mechanism	Side effects
Finasteride (Proscar)	5 mg daily	6-8 hours	Inhibits type II 5-AR	Decreased libido, sexual dysfunction, gynecomastia, and breast tenderness
Dutasteride (Avodart)	0.5 mg daily	3-5 weeks	Inhibits types I and II 5-AR	Same as above

42% and 50% at 3 and 6 months, respectively.[19] This PSA change should be considered when screening for prostate cancer in patients that have been prescribed a 5-ARI. Dutasteride, unlike finasteride, impedes both type I and type II 5-alpha enzymes and leads to almost total elimination of DHT in the serum. Both dutasteride and finasteride have been shown to have similar efficacy and tolerability, but differ in that dutasteride has a half life of several weeks, however this has not been shown to have any adverse consequences.[20,21] Table 2.

Data suggest that 5-ARI can be utilized as a chemoprevention agent against prostate cancer (not currently approved by Health Canada or in the United States for this indication). The Prostate Cancer Prevention Trial (PCPT) examined the effects of finasteride on prostate cancer.[22] The results demonstrated a decreased incidence of prostate cancer, initially reported an increase in the incidence of high grade prostate cancer when compared to placebo. The latest evidence suggests that the observed increase in high grade cancers was influenced by the smaller post treatment prostate volumes that improved the sensitivity of PSA, digital rectal exam and prostate biopsies. There is speculation that there is also a selective inhibition of low grade cancer.[23,24]

To date, finasteride is the only medication in a prospective randomized trial to reduce the incidence of prostate cancer. A study is currently ongoing to determine if dutasteride can also reduce the risk of prostate cancer.[25]

The side effects of the 5-ARI family include decreased libido, sexual dysfunction, gynecomastia, and breast tenderness. Blood donations should be delayed by 6 months in men taking dutasteride due to the extended half life. The inhibition of DHT also has the added advantage of decreasing bleeding from the prostate by indirectly inhibiting microvascular proliferation.[5] Both medications are considered to be teratogenic and should not be handled by women of childbearing age.

Combination sBPH therapy

Concomitant therapy with alpha-blockers and 5-ARI should be considered in patients who have an enlarged prostate gland and symptoms consistent with bladder outlet obstruction. The Medical Therapy of Prostatic Symptoms (MTOPS) trial was a landmark study whose goal was to determine if clinical disease progression could be reduced by doxazosin and finasteride as mono- or combination therapy.[21] Combination therapy was found to be superior to both doxazosin and finasteride individually in preventing disease progression. In addition, the need for surgical therapy was found to be significantly reduced with finasteride and combination therapy, but not with doxazosin as monotherapy. Similarly the CombAT trial demonstrated that combination treatment with dutasteride and tamsulosin provides significantly greater urinary symptom improvement for men with an enlarged prostate than either dutasteride or tamsulosin monotherapy over 24 months.[26] This combination of dutasteride with tamsulosin was approved in 2008 in the United States by the FDA for sBPH.

Erectile dysfunction

Pathophysiology and pharmacology

Erectile dysfunction (ED) is the consistent inability to achieve and maintain an erection sufficient for sexual intercourse.[6] ED can have complex implications on the psychosocial well-being of patients. Additionally, ED may be the presenting symptom of cardiovascular or endocrine abnormalities. Approximately 50% of men over age 40 are affected by ED.[27-29] Multiple factors may be attributed to ED, including neurogenic, hormonal, arterial, cavernosal, and drug induced; collectively, these are classified as organic or psychogenic and/or a combination of the two.

A symphony of well-correlated psychological, neurovascular, muscular and chemical events are necessary to obtain an adequate erection. Simply put, during sexual stimulation, impulses from the

parasympathetic nerve fibers lead to a release of nitric oxide from endothelial cells. Nitric oxide then enters smooth muscle cells stimulating guanylyl cyclase and converts cyclic guanine triphosphate (cGTP) to cyclic guanosine monophosphate (cGMP). This in turn, activates protein kinase and stimulates phosphorylation of proteins and opening of ion channels that eventually cause an increase in smooth muscle tone and blood flow to the corporal sinusoids. A net decrease in venous outflow occurs due to occlusion of subtunical venular plexuses that are compressed against the wall of the tunica albuginea, resulting in an erection. Detumescence occurs when cGMP is hydrolyzed to GMP by phosphodiesterase type 5 isoenzyme (PDE5).[30] Eleven isoenzymes of PDE have been identified in human tissue.[13] PDE5 is found primarily in the corpus cavernosum, platelets, and vascular and visceral smooth muscle.

Androgens are also instrumental for normal sexual function and erections. They have direct effects on libido, and also have a role in the regulation of cGMP, PDE5 and nitric oxide synthase expression.[31-33]

Oral therapy for erectile dysfunction

Erectile dysfunction can be managed by medical therapy, intracavernosal injections, mechanical enhancements such as vacuum tumescence devices and penile prosthesis, with the oral agents having the biggest market share today. Sildenafil [Viagra], vardenafil [Levitra] and tadalafil [Cialis] are oral phosphodiesterase-5 inhibitors (PDE5i). PDE5i function by slowing the degradation of cGMP, enhancing the effect of nitric oxide and amplifying the relaxation of the cavernosal smooth muscles. The PDE5i are comparable in their efficacy but differ in their pharmacokinetic and side effect profiles. Many of their adverse reactions can be attributed to interactions with other PDE isoenzymes. Sildenafil, for example, has a high affinity towards the PDE6 isoenzyme, which is concentrated in the eye. This particular interaction may lead to blue tinged vision, a side effect that is rarely seen with vardenafil or tadalafil. Vardenafil has been found to prolong the QT interval, and tadalafil has a high rate of muscle pain (up to 9% of users).[34]

Sildenafil and vardenafil have a serum half life of approximately 4 hours while tadalafil exhibits a half life of approximately 17.5 hours.[13] The longer half life of tadalafil has not been correlated with significant side effects. Additionally, sildenafil and vardenafil interact with fatty meals which can slow the time of onset. All three PDE5i may exhibit symptoms of facial flushing, headache and rhinitis. Recently, tadalafil has been approved for a daily dosing regimen to theoretically avoid the need for "on-demand" dosing.

PDE5i are contraindicated with concurrent use of nitrates because of excessive systemic vascular smooth muscle relaxation causing pronounced hypotension and possible death. Patients with cardiac risk factors should be screened and grouped prior to initiation of treatment.[35] Current guidelines from the Princeton Consensus Conference have categorized patients into low, intermediate, and high risk based on their cardiovascular disease. Low risk typically implies the ability to perform exercise of modest intensity without symptoms; intermediate risk indicates the need for further evaluation to reclassify risk as low or high; and high risk indicates that patients should defer sexual activity until cardiac assessment and/or treatment has been implemented.[36,37]

Non-arteritic anterior ischemic optic neuropathy (NAION) is an adverse effect that has been recognized in patients taking PDE5i. It has classically been described as a sudden, painless, and unilateral irreversible ischemic event of the intraocular optic nerve.[38] Interestingly, 10% of patients have been reported to experience ocular pain. On ocular examination, visual acuity is very often decreased to no light perception, and there may be a variety of visual field defects. Physical examination may reveal disc edema and a small cup to disc ratio, or absence of the cup entirely. The incidence occurs in 10/100,000 persons and is significantly more common in Caucasians. Several cases have been reported since 2005.[39,40] Some risk factors of NAION include prolonged surgical procedures, hypovolemia, hemodilution through volume expansion, hypotension, and underlying vasculopathic diseases such as hyperlipidemia, hypertension, diabetes, and prothrombotic disorders.[41] Currently, the World Health Organization (WHO) and Health Canada have concluded that there is no definitive evidence connecting NAION and PDE5i, but patients should be advised to call a physician and stop the medication if any visual difficulties occur.[42] Physicians should also be aware of the symptoms of NAION and try to elicit a history of visual loss or NAION prior to prescribing PDE5i. Table 3.

Oral PDE5i combined with androgen replacement therapy have a role in the treatment of a select number of ED patients. A threshold of testosterone is known to be necessary for normal erections. Patients that are hypogonadal and do not initially respond to PDE5i have been found to have sustainable erections after testosterone levels have been normalized and PDE5i are continued.[43,44]

Intraurethral therapy for erectile dysfunction

In the event that oral therapy is unsuccessful, other pharmacological options are available for patients

TABLE 3. **Oral phososphodiesterase-5 inhibitors medications for erectile dysfunction**

Name	Dosage	Time to maximum plasma concentration	Serum half life (hrs)	Affected by food	Notable side effects (other than headache, flushing, rhinitis, dyspepsia)
Sildenafil (Viagra)	25 mg-100 mg 30-60 minutes before sexual activity Max 1x day	60 minutes	4	Yes Delays onset	Visual disturbances
Vardenafil (Levitra)	5 mg-20 mg 25-60 minutes before sexual activity Max 1x day	60 minutes	4	Yes Delays onset	Increase in QT interval. Avoid use with other medications that prolong QT interval
Tadalafil (Cialis)	On-demand dosing: 10 mg-20 mg Effective within 30 minutes Max 1x day Daily dosing: 2.5 mg-5 mg daily	120 minutes	17.5	No	Myalgia, back pain

with ED. Prostaglandin E1 (PGE1) stimulates adenyl cyclase to increase levels of cAMP; this stimulates adenylate cyclase, which ultimately causes arteriolar vasodilatation and increased arterial blood flow leading to erection. Alprostadil [MUSE] is a synthetic PGE1 that is inserted into the urethra and is then absorbed by the corpora cavernosum and spongiosum. Efficacy is approximately 60%, with lower reports in patients who are either post prostatectomy or have suffered a spinal cord injury.[20] One of the advantages of using intraurethral alprostadil is local absorption, and thus minimal systemic side effects and drug interactions. Intraurethral alprostadil may cause penile pain, warmth and burning, vaginal discomfort in partners, and hypotension. First-use office administration is advised. Table 4.

TABLE 4. **Transurethral (TU) and intracavernosal (IC) medications for erectile dysfunction**

Name	Dosage	Mechanism of action	Side effects
Alprostadil TU (MUSE)	250 mcg-1000 mcg Max 2 administrations per 24 hrs	Synthetic PGE1 stimulates adenyl cyclase to increase cAMP	Painful erection, urethral pain and bleeding; can be delivered to partner; priapism (rare)
Alprostadil IC (Caverjet)	2.5 mcg-20 mcg* Max 1x daily and 3x weekly	Same as Alprostadil TU	Penile pain, fibrosis hematoma; priapism (rare)
Papavarine IC†	15 mg-60 mg (monotherapy) 5 mg-20 mg (used in combination)	Non-selective PDE inhibitor increases cAMP and cGMP	Priapism; corporal fibrosis
Phentolamine IC†	0.5 mg-1 mg (used in combination)	Alpha-blocker inhibits sympathetic tone to penis	Hypotension; reflex tachycardia

*Neurogenic ED may require lower starting dose. Severe vascular ED may require greater doses.
†Not approved by Health Canada for this use.

Intracavernosal therapy for erectile dysfunction

There are three intracavernosal (IC) injection therapies used for the treatment of ED. Alprostadil [Caverject] is a PGE1 that can be used safely and effectively in up to 70%-88% of non responders to oral agents and is the only officially approved intracavernosal agent.[45-47] Although the dose used is significantly lower than intraurethral therapy, the mechanism of action is identical. Side effects include pain at the injection site, fibrosis, hematoma, prolonged erection, and priapism. Papaverine is a nonselective PDEI that increases cAMP, which causes relaxation of corporal sinusoids. Papaverine has been found to be 55% effective when used as monotherapy. Bothersome side effects include a significantly high incidence of priapism (up to 35%), fibrosis of the corpora cavernosum (up to 33%), and occasional increases in serum aminotransferase.[20] Phentolamine is an alpha-blocker that, when used alone, does not produce rigid erections, but is thought to have an effect on corporal smooth muscle cells which may increase the supply of nitric oxide to the cells and potentiate the effects of the IC medications previously mentioned.

Although not approved by Health Canada, combining IC medications has also been found to be effective in the treatment of ED, with high rates of success and a lower risk of side effects, since lower doses of each agent can be used. Phentolamine and papaverine in combination have been shown to be highly successful. Success rates up to 87% have been reported, and with the addition of alprostadil (Tri-mix), success can increase to 92% in patients who were otherwise refractory to other medications.[48-50] Table 4.

Hypogonadism

Pathophysiology and pharmacology

A patient with ED will sometimes have concurrent hypogonadism. Male serum testosterone begins to gradually decline toward the end of the third decade of life, after a surge in mid-teen years. The rate of decline continues at approximately 1% per year or approximately 10% per decade after the age of 40.[51,52] Common symptoms of hypogonadism include ED, diminished libido, depressed mood, fatigue, decreased lean body mass, anemia, and osteoporosis.

The diagnosis of hypogonadism should be suspected based on clinical findings and laboratory examination. The work-up of the patient presenting with signs and symptoms of hypogonadism is beyond the scope of this article, but the laboratory examination should begin with a morning total serum testosterone. In the normal male blood, testosterone exists in three forms: 2% of testosterone is active and is unbound (free); 30% is bound to sex hormone binding globulin (SHBG) and is inactive; and the remainder is bound to albumin and is bioavailable.[31] The realm of hypogonadism includes primary and secondary etiologies. Primary hypogonadism occurs when there is failure of the testes to produce testosterone, and secondary hypogonadism is due to insufficient production of LH and FSH by the pituitary gland. If discovered, the underlying causes for the hypogonadism should be investigated by a specialist.

Testosterone replacement therapy

Testosterone replacement therapy (TRT) represents the primary therapy for patients with hypogonadism. Treatment may benefit sexual dysfunction and have positive effects on lean body mass, bone density, and mood.[53-55] Thus, men with the stigmata and laboratory findings of hypogonadism, even in the absence of sexual dysfunction, may benefit from treatment. There are several methods by which testosterone can be administered. These include oral, intramuscular injection, and topical formulations.

Oral alkylated androgens (fluoxymesterone, methyltestosterone, etc.) are administered daily, and undergo rapid hepatic metabolism, oftentimes failing to achieve consistent therapeutic ranges in the serum. Inconsistent levels may lead to mood swings and sexual side effects. Liver toxicity, including hepatocellular adenomas, hemorrhagic cysts, and cholestatic jaundice have been associated with oral alkylated androgens.[31,56] Testosterone replacement with oral alkylated androgens has lost popularity for other administration routes in the United States, however the use of other oral medications, like testosterone undecanoate [Andriol], is popular in other countries such as Canada.

Testosterone undecanoate is the only oral form of testosterone available in Canada. Liver toxicity is not observed with testosterone undecanoate which avoids the first pass effect.[57] Oral testosterone undecanoate is administered daily and must be taken with food for optimal absorption.

Injectable esters of testosterone, such as testosterone cypionate [Depo-Testosterone] and testosterone enanthate [Delatestryl] represent another alternative in testosterone administration. These medications are more conveniently dosed every 2-4 weeks, as opposed to the daily dosing of oral or topical formulations. However, they can be associated with supraphysiologic levels of testosterone and low nadirs, especially with extended dosing intervals.[31] These fluctuations may

TABLE 5. **Medications for hypogonadism**

Name	Route	Dosage
Testosterone undecanoate (Andriol)	Oral	40 mg-160 mg daily
Testosterone cypionate (Depo-Testosterone)	IM injection	200 mg-400 mg q 3-4 weeks (100 mg-150 mg q 2 weeks preferred)
Testosterone enanthate (Delatestryl)	IM injection	100 mg-400 mg q 4 weeks (100 mg-150 mg q 2 weeks preferred)
Testosterone gel (Androgel 1%)	Topical	5 g-10 g daily
Testosterone gel (Testim 1%)	Topical	5 g-10 g daily
Testosterone patch (Androderm)	Transdermal patch	2.5 mg-7.5 mg daily

result in alterations in mood, and high levels of testosterone can lead to infertility through negative feedback suppression of LH and FSH.

Transdermal patches [Androderm] and gels [Androgel, Testim] have been found to more closely mimic the circadian cycle of testosterone levels.[31] The patch and the gel can be directly applied to the skin. (Transdermal formulations available in Canada should not be applied to the scrotum.) When compared to injectable formulations, the transdermal patch shows less of an effect on LH and FSH levels, reducing chances of infertility. The most annoying side effects of these formulations are skin irritation and rash, which seems to be less common with the use of gels.[58]

New buccal preparations have been found to have favorable results, exhibiting adequate serum testosterone levels. These formulations have also demonstrated a low side effect profile, consisting mostly of buccal irritation and a bitter taste and are not yet available in Canada.[59]

Testosterone therapy is contraindicated in patients with a history of prostate cancer. However, there is increasing interest in using testosterone supplementation in the hypogonadal man who has been rendered disease free following radical prostatectomy.[59] Some side effects reported with testosterone therapy include gynecomastia, erythrocytosis, testicular atrophy, and skin reactions (with topical formulations).[60] Table 5.

Overactive bladder

Pathophysiology and pharmacology

The bladder functions as a reservoir for the storage and emptying of urine. These actions depend on the complex interplay between the brain, spinal cord, autonomic nervous system and organs of the genitourinary system. During filling, the bladder maintains a low intravesical pressure.[61,62] This low pressure protects against urinary reflux, incontinence, and the deleterious effects of bladder dysfunction. Normal voiding is initiated by a coordinated bladder contraction, a decrease in urethral resistance, and relaxation of the external striated sphincter. In general, relaxation of the bladder during filling is moderated by the sympathetic pathway, in which NE is released and stimulates beta-adrenergic receptors that interact with adenlyate cyclase, eventually leading to smooth muscle relaxation of the bladder detrusor muscle.

Parasympathetic stimulation is responsible for voiding and leads to the contraction of detrusor smooth muscle and inhibition of sympathetic input from the bladder neck. It also causes inhibition of the somatic nerves to the striated sphincter.[63] Muscarinic (M) receptors are found within the bladder and throughout the body. The dominant subtype found in the detrusor muscle is the M2 receptor. The M3 subtype is also found in the bladder, as well as the salivary glands, brain, colon, and eye. During voiding, the neurotransmitter acetylcholine interacts with M2 and M3 receptors in the bladder detrusor, leading to contraction of bladder smooth muscle.[63]

Overactive bladder (OAB) is a medical condition characterized by symptoms of urgency, with or without urinary incontinence, accompanied by frequency and nocturia.[64] It should be diagnosed only after other conditions such as urinary tract infection, bladder cancer or neurological disorder have been ruled out. OAB is thought to be caused primarily by abnormal detrusor activity from acetylcholine interaction with M3 receptor subtypes. OAB affects an estimated 1 in 5 Canadian adults and increases in prevalence with aging.[65-67] The cost of OAB has been estimated to be $12 billion (US) per year. The symptoms of OAB are commonly caused by uninhibited contractions of the detrusor muscle from altered innervation due to BPE,

neurological conditions (e.g., stroke), as well as many idiopathic conditions.[62] OAB is also associated with a significant decrease in quality of life, an increased propensity for falls, dermatological conditions, and an increase in urinary tract infections.[68-71]

Antimuscarinics

The medications primarily used in OAB are antimuscarinic agents. This group acts by blocking acetylcholine from interacting with the M receptor, and resulting in a decrease in uninhibited bladder contractions and a decrease in the force of contraction, leading to a reduction in both urgency and urge incontinence.[72] Side effects observed with this class of medications are attributed to interactions with the M receptor subtypes outside the bladder and are anticholinergic in nature. Dry mouth, constipation, gastroesophageal reflux, cognitive impairment, blurred vision, sedation, and tachycardia are not uncommon. Antimuscarinics are contraindicated in patients with narrow angle glaucoma and/or urinary retention.[61]

A naturally occurring antimuscarinic that has been in use for several years is hyoscyamine [Levsin]. It is a more general antimuscarinic that can have several systemic side effects, such as dry mouth, somnolence, urinary retention, and more seriously, tachycardia and psychosis. Its use, however, has decreased with the advent of newer, more specific medications.

Oxybutynin [Ditropan, Oxytrol, Uromax] and tolterodine [Detrol] are antimuscarinic agents that have been used traditionally in the United States and Canada. Newer medications, such as trospium [Trosec], darifenacin [Enablex], and solifenacin [Vesicare] have recently been introduced, and boast similar rates of efficacy. Both oxybutynin and tolterodine are available in short acting and extended release oral formulations, and oxybutynin is also available in a transdermal application. When comparing the extended release to the short acting forms of oxybutynin and tolterodine, the extended release formulations have demonstrated similar efficacy and improved tolerability.[73] Tolterodine has greater affinity for M3, and oxybutynin has additional antispasmodic properties not seen with other antimuscarinic agents.

Trospium has been available in Europe for more than 20 years and exhibits proven effectiveness. Advantages seen with this medication include lower rates of dry mouth, and few CNS side effects secondary to its inability to cross the blood brain barrier.[74] Solifenacin and darifenacin have M3 selectivity. Both of these medications have been found to have high rates of constipation likely due

TABLE 6. **Medications for overactive bladder**

Antimuscarinics		
Name	**Dosage**	**Notes**
Oxybutynin (Ditropan, Ditropan XL, Oxytrol [patch], Uromax)	5 mg BID - QID (short acting); 5 mg-30 mg daily (extended release); Apply patch twice weekly – 1 patch delivers 3.9 mg/day (transdermal patch)	Antispasmodic properties
Tolterodine (Detrol, Detrol LA)	1 mg-2 mg BID (short acting) 2 mg-4 mg daily (long acting)	Special dosing for patients with hepatic dysfunction
Trospium (Trosec)	20 mg BID Take on empty stomach	Renal dosing; does not cross BBB (fewer cognitive side effects)
Solifenacin (Vesicare)	5 mg-10 mg daily	Renal and hepatic dosing; M3 selective
Darifenacin (Enablex)	7.5 mg-15 mg daily	M3>M2
Hyoscyamine (Levsin)		Less specific than newer medications, greater incidence of side effects. (rarely used)

BBB = Blood brain barrier; M = muscarinic receptor type

to interaction with M3 receptors in the colon.[75,76] In patients with renal impairment, trospium and solifenacin doses should be adjusted according to creatinine clearance. Table 6.

Hormonal therapy for prostate cancer

Pathophysiology and pharmacology

The treatment for prostate cancer varies depending on a multitude of factors related to the Gleason score, PSA, pathological stage, age of the patient, and the presence of symptoms. The treatment for low grade prostate cancer in a healthy young patient usually is monotherapy either via radical prostatectomy or radiation therapy. The need for hormonal therapy arises in conditions including local recurrence of prostate cancer, neoadjuvant or adjuvant treatment for high-risk disease, and in metastatic disease with or without symptoms.[77]

Normal prostate cells and malignant prostate cancer cells at least initially rely on androgen stimulation via androgen receptors for growth and vascular proliferation. Androgen withdrawal causes a retardation of prostate cell growth, thought to be from programmed cell death and ischemic injury from anoxia.[78,79] Thus, manipulation of the hormonal milieu plays a role in the treatment of prostate cancer, and decreases morbidity and increases survival.[80-82]

Androgen production relies on the interplay of the hypothalamic-pituitary axis and the testes to produce testosterone.[83] Androgen homeostasis is achieved by pulsatile release of gonadotropin releasing hormone (GnRH) by the hypothalamus to the anterior pituitary gland every 90-120 minutes. The interaction between GnRH and LH receptors in the pituitary gland promotes the release of LH into the systemic blood circulation. LH induces testosterone production by binding to receptors on Leydig cells in the testes. Negative feedback of GnRH is exerted by testosterone through androgen receptors on the hypothalamus and pituitary glands. Currently there are three forms of pharmacological agents to induce the androgen deprived state for the treatment of prostate cancer: LHRH agonists (LHRHA); LHRH antagonists (LHRHAN); and androgen receptor blockers (antiandrogens).[84]

LHRH manipulation

LHRHA exert a non-pulsatile, constant stimulation on the anterior pituitary, which in turn decreases LH and testosterone production. During treatment, LH release is transiently increased up to 2 weeks after the initial dose, which is referred to as hormonal surge. LH receptors are then down-regulated and testosterone production is inhibited. Hormonal surge can sometimes be dangerous, such as with severe bone pain from bone metastasis, ureteral or bladder outlet obstruction, and when neurological compromise is imminent from metastatic disease. Blockade with the initial use of an antiandrogen can be useful.

LHRHA are found in a variety of formulations, and depending on the medication can be administered every 1 to 6 months. The available medications include leuprolide [Lupron, Eligard], goserelin [Zoladex] and triptorelin [Trelstar]. Associated side effects include hot flashes, decreased libido, erectile dysfunction, loss of bone mineral density, anemia, and mood changes.

Abarelix [Plenaxis] is a LHRHAN that inhibits binding onto the LH receptor in the pituitary gland. This drug that was taken off the US market due to financial considerations and but may still be used in men who were treated before the May 2005 action. It has limited availability outside of the United States but is not available in Canada. Unlike LHRHA, there is no hormonal surge. However, the use of this medication is limited by a 3.7% chance of anaphylaxis and the possibility of an increased QT interval.[85]

Antiandrogens

Antiandrogen therapy is used to block the androgen receptor. The two classes of antiandrogens are non-steroidal (flutamide [Euflex], nilutamide [Anandron] and bicalutamide [Casodex]), and steroidal (cyproterone acetate [Androcur]). In many cases, antiandrogens are administered for 2 weeks prior to beginning LHRHA in order to reduce any adverse effects of the hormonal surge. The role of antiandrogen therapy before initiating LHRHA or use long term in combination with LHRHA (known as total androgen blockade) has been debated and may be determined by patient risk factors and cost benefit ratios.[86] All antiandrogens are metabolized by the liver and induce cytochrome P450, which can result in liver toxicity, therefore liver function tests must be monitored periodically. Also, gynecomastia and mastodynia are not uncommon. Individual medications have different pharmacological properties. Flutamide may cause an increase in gastrointestinal symptoms and has a half life of up to 6 hours while nilutamide has a half life of up to 1 week and may cause impaired dark adaptation and interstitial pneumonitis.[84] All of these agents can cause gynecomastia. Table 7.

TABLE 7. **Medications for prostate cancer**

Medications	Class	Administration	Notes
LHRH manipulation			
Leuprolide (Lupron Depot 1 month, Lupron Depot 3 month, Lupron Depot 4 month)	LHRH agonists	7.5 mg IM monthly 22.5 mg IM q 3 months; 30 mg IM q 4months (16 weeks)	Can cause initial hormonal surge
Leuprolide (Eligard 7.5 mg, Eligard 22.5 mg, Eligard 30 mg, Eligard 45 mg)	LHRH agonist	7.5 mg SC monthly; 22.5 mg SC q 3 months; 30 mg SC q 4 months; 45 mg SC q 6 months	Can cause initial hormonal surge
Goserelin acetate (Zoladex 3.6, Zoladex LA 10.8)	LHRH agonist	3.6 mg SC monthly (28 days); 10.8 mg SC q 3 months (13 weeks)	Can cause initial hormonal surge
Triptorelin (Trelstar, Trelstar LA)	LHRH agonist	3.75 mg IM monthly 11.25 mg IM q 3 months (LA)	Can cause initial hormonal surge
Androgen receptor blockade			
Flutamide (Euflex)	Nonsteroidal antiandrogen	250 mg PO q8h w/LHRH analog	Follow LFTs
Nilutamide (Anandron)	Nonsteroidal antiandrogen	Start: 300 mg PO daily x30 days, then 150 mg PO daily w/LHRH analog or orchiectomy	Follow chest x-ray and consider baseline PFTs; Follow LFTs
Bicalutamide (Casodex)	Nonsteroidal antiandrogen	50 mg PO daily w/ LHRH analog	Follow LFTs
Cyproterone acetate (Androcur)	Steroidal antiandrogen	100 mg-300 mg daily, divided into 2-3 doses (take after meals)	Follow LFTs

LFTs = liver function tests; PFTs = pulmonary function tests

Conclusions

Overall, the treatment of urological disease and dysfunction can be complicated and somewhat overwhelming to the patient. A basic understanding of medications and their inherent properties is important for successful treatment that may be supervised by the primary care physician. Also, the primary care physician should be aware of the contraindications and interactions of pharmacological interventions and have an understanding of when further urological consultation is warranted. In this common but potentially complicated area of clinical medicine, a successful working partnership between the primary care physician and urologist is important.

Disclosure

Dr. Leonard Gomella is a consultant for GlaxoSmithKline and TAP Pharmaceuticals. He is a member of the Speakers' Bureau for Astra Zeneca. □

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DISCUSSION

Question (Dr. Rosenberg):
What are the consequences of using antimuscarinic agents that cross blood brain barrier?

Answer (Dr. Gomella):
This class of agents is commonly used to treat overactive bladder, a condition characterized by urgency, with or without urinary incontinence, frequency and nocturia. These agents can have central nervous system side effects that may include cognitive impairment, sedation and rarely frank psychosis. Some of the later more selective forms of antimuscarinic agents such as trospium may have less central effects due to its reduced ability to cross the blood-brain barrier.

Question (Dr. Laroche):
Please discuss the use of antimuscarinics in terms of their impact on QT abnormalities (i.e. Canadian and US guidelines and possible contraindications)?

Answer (Dr. Gomella):
We have an increased appreciation of the potential effects of drugs on the myocardium including agents with antimuscarinic activity. This has increased the need for the evaluation of new drugs for cardiac safety issues. Due to the potential of these medications inducing QT abnormalities they should be cautiously prescribed in patients with a known history of QT prolongation or in patients using antiarrhythmic agents that affect the QT interval.