

PRIMARY CARE UPDATE IN UROLOGY

Sponsored by the
American Urological Association

Complimentary CME Program
for Primary Care Physicians

MONOGRAPH 2011

TOPICS

LUTS

ERECTILE DYSFUNCTION

PROSTATE CANCER

URINARY TRACT INFECTIONS

GERIATRIC UROLOGY

Support provided by educational grants from Abbott Laboratories;
Astellas Pharma Global Development; Endo Pharmaceuticals;
Ethicon, Inc.; Lilly USA, LLC; Pfizer and Slate Pharmaceuticals

CME CREDIT

Table of Contents

CME Information	1
Preface. <i>Matt T. Rosenberg and Howard N. Winfield</i>	4
Evaluating and Treating Lower Urinary Tract Symptoms. <i>Matt T. Rosenberg, Steven A. Kaplan and David R. Staskin</i>	5
Erectile Dysfunction and Cardiometabolic Risk. <i>Martin M. Miner</i>	9
Prostate Cancer Overview 2011. <i>Howard N. Winfield</i>	13
Urinary Tract Infections and Interstitial Cystitis. <i>C. Lowell Parsons</i>	14
Urinary Tract Infections and Hematuria. <i>Diane K. Newman</i>	17
Geriatric Urology: Demographics, Theories and Physiology of Aging, and Common Clinical Conditions in Older Adults. <i>Tomas L. Griebing and Ted M. Johnson, II</i>	19

Copyright © 2011 by American Urological Association

None of the contents may be reproduced in any form without prior written permission of the publisher. The opinions expressed in this publication are those of the speakers and do not necessarily reflect the opinions or recommendations of their affiliated institutions, the publisher, the American Urological Association or any other persons. Some articles in this publication may discuss unapproved or “off-label” uses of products. Any procedures, medications or other courses of diagnosis or treatment discussed or suggested in this publication should not be used by clinicians without evaluation of their patients’ conditions and of possible contraindications or dangers in use, review of any applicable manufacturers’ product information and comparison with the recommendations of the authorities.

For an Online Webcast of Primary Care Update in Urology

Visit

www.AUA2011.org/PrimaryCare

CME Information

Medium and Method of Participation

This CME enduring material activity consists of a printed overview of the content presented at the 2011 Primary Care Update in Urology program, an online posttest and evaluation. To receive CME credit, participants must read the overview of the program, complete the online posttest, passing with a minimum score of 80%, and submit an evaluation and claim credit by visiting <http://www.auanet.org/pcu11>.

Estimated Time to Complete this Activity: 1.5 hours

Release Date: November, 2011

Expiration Date: October 31, 2012

Minimum Hardware and Software Requirements

- PC/Windows XP, Macintosh/OS X 10.1 or Linux/Mozilla Firefox 3.0
- Processor speed of 800 MHz (1GHz preferred)
- 128 MB of RAM (more preferred)
- Modem speed of at least 56k (broadband preferred)
- Internet browser: Internet Explorer 8.0, Firefox 3.0, Chrome 4.0 or Safari 4.0
- Adobe Acrobat Reader 9

AUA Disclosure Policy

As a provider accredited by the Accreditation Council for Continuing Medical Education (ACCME), the American Urological Association Education and Research, Inc. (AUAER) must ensure balance, independence, objectivity and scientific rigor in all of its activities.

All persons in a position to control the content of an educational activity (ie activity planners and presenters) provided by the AUAER are required to disclose to the provider any relevant financial relationships they have with any commercial interest. The AUAER must determine if an individual's commercial relationships may influence the educational content with regard to exposition or conclusion, and resolve any conflicts of interest prior to the commencement of the educational activity. The intent of this disclosure is not to prevent individuals with relevant financial relationships from serving as planners or presenters, but rather to provide the audience with information on which they can make informed judgments about the material presented.

Disclaimer

The opinions and recommendations expressed by faculty, authors and other experts whose input is included in this CME enduring material activity are their own and do not necessarily represent the viewpoint of the AUAER.

Faculty

Tomas L. Griebing, M.D., MPH

John P. Wolf Masonic Distinguished Professor of Urology
University of Kansas
Vice-Chair, Department of Urology
The Landon Center on Aging
Kansas City, KS

Disclosures: *MEDTRONIC*: Consultant/Advisor, Scientific Study/Trial; *Pfizer*: Scientific Study/Trial, Investigator, Consultant/Advisor

Theodore Johnson II M.D., MPH

Professor of Medicine
Division Director, Geriatric Medicine
Emory University/Atlanta VA
Decatur, GA

Disclosures: *Ferring, Johnson & Johnson, Vantia*: Consultant/Advisor; *Pfizer*: Scientific Study/Trial, Consultant/Advisor

Steven A. Kaplan, M.D.

Professor of Urology
Chief, Institute for Bladder and Prostate Health
Weill Cornell Medical College
New York, NY

Disclosures: *Astellas, Neotract, Pfizer, Watson*: Consultant/Advisor; *NIDDK, NIH*: Scientific Study/Trial

Martin M. Miner, M.D.

Co-Director, Men's Health Center
Chief of Family and Community Medicine, Miriam Hospital
Clinical Associate Professor of Family Medicine
Warren Alpert School of Medicine
Brown University
Providence, RI

Disclosures: *ENDO*: Consultant/Advisor; *GSK, Auxilium*: Investigator

CME Information

▼ Continued from page 1

Diane K. Newman, RNC, MSN

Instructor, School of Medicine

Nurse Practitioner

University of Pennsylvania

Berwyn, PA

Disclosures: *Astellas, GSK*: Meeting Participant/Lecturer

C. Lowell Parsons, M.D.

Professor of Surgery/Urology

School of Medicine

University of California San Diego

San Diego, CA

Disclosures: *O-M Corp, Ortho-McNeil Corp.*: Meeting Participant/Lecturer

Matt T. Rosenberg, M.D.

Director

Mid-Michigan Health Systems

Allegiance Health

Jackson, MI

Disclosures: *Allergan, Ferring, GSK, Roche, Sanofi-Aventis, Schering Plough*: Consultant/Advisor; *Forest, Novartis, Pfizer Inc.*: Meeting Participant/Lecturer

David R. Staskin, M.D.

Associate Professor of Urology

Director, Female Urology and Male Voiding Dysfunction

St Elizabeth's Medical Center

Tufts University School of Medicine

Boston, MA

Disclosures: *Allergan, AMS, Astellas, GSK, Pfizer, Uroplasty*: Consultant/Advisor

Howard N. Winfield, M.D.

West Alabama Urology Associates

Director of Robotic Surgery

Regional Medical Center

Tuscaloosa, AL

Disclosures: Nothing to disclose

Learning Objectives

At the conclusion of this CME enduring material activity, the participant will be able to:

- differentiate normal and abnormal function as it pertains to the genitourinary system
- identify and perform the initial evaluation of urological diseases in accordance with AUA guidelines
- evaluate when treatment in the primary care setting is appropriate and when to refer to a specialist
- discuss the treatment options for various urological diseases
- identify refractory symptoms of all urological conditions

Statement of Need

In providing first line of care, primary care providers need a thorough knowledge of the most recent developments and techniques in urology to ensure the highest standards of patient care and safety. This CME enduring material activity is designed to provide the latest research from expert urologists and primary care physicians to enhance knowledge and improve patient care. Topics to be addressed include lower urinary tract symptoms, overactive bladder/benign prostatic hyperplasia/other causes; erectile dysfunction/hypogonadism and cardiometabolic syndrome; prostate cancer; interstitial cystitis/urinary tract infection; and geriatrics in urology.

Target Audience

Primary Care Providers

Accreditation

The American Urological Association Education and Research, Inc. is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The AUAER takes responsibility for the content, quality and scientific integrity of this CME enduring material activity.

CME Information

▼ Continued from page 2

Credit Designation

The American Urological Association Education and Research, Inc designates this CME enduring material activity for a maximum of 1.5 AMA PRA *Category 1 Credits*[™]. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This activity has been reviewed and is acceptable for up to 1.5 Prescribed credits by the American Academy of Family Physicians (AAFP). AAFP accreditation begins 11/1/2011. Term of approval is for one year(s) from this date, with option for yearly renewal.

Commercial Support

This CME enduring material activity is supported by educational grants from Abbott Laboratories; Astellas Pharma Global Development; Endo Pharmaceuticals; Ethicon, Inc.; Lilly USA, LLC; Pfizer and Slate Pharmaceuticals.

Statement of Evidence-Based Content

As a provider of continuing medical education accredited by the ACCME, it is the policy of the AUAER to review and

certify that the content contained in this CME enduring material activity is valid, fair, balanced, scientifically rigorous and free of commercial bias.

Off-Label or Unapproved Use of Drugs or Devices

It is the policy of the AUAER to require the disclosure of all references to off-label or unapproved uses of drugs or devices prior to the presentation of educational content. The audience is advised that this CME enduring material activity may contain reference(s) to off-label or unapproved uses of drugs or devices. Please consult the prescribing information for full disclosure of approved uses.

AUA Privacy and Confidentiality Policy

<http://www.aunet.org/cme/onlineeduconf.cfm>

Copyright © 2011 by the American Urological Association

Contact Information

For all inquiries regarding CME credit please contact CME@AUANet.org

Preface

The continuum of medical care requires multiple providers working together in a seamless manner. The primary care provider (PCP) is the gatekeeper and, as such, must be prepared to deal with any condition that comes their way. The American Urological Association (AUA) realizes the important role of the PCP in dealing with patients who may be afflicted by genitourinary disorders and also recognizes their responsibility in providing education and assistance to their primary care colleagues. The magnitude of genitourinary diseases undoubtedly impacts the PCP on a daily basis, and the ability to screen for and identify these issues is crucial. In an effort to assist in patient care, the AUA Office of Education has designated educational events to be held as part of the AUA Annual Meeting and satellite symposia across the country. To achieve balance as to what is important and practical for the PCP, various genitourinary disorders are discussed by acknowledged thought leaders in urology as well as primary care.

In this 2011 issue we have chosen several disease entities commonly encountered by the PCP in daily practice. Lower urinary tract symptoms affect 15% to 60% of patients older than 40 years in the form of overactive bladder with incontinence, stress urinary incontinence and/or bladder outlet obstruction, and yet this population is grossly under diagnosed and under treated. Is there a week that goes by that a patient does not present with symptoms of a urinary tract infection? However, is it always an infection or a sign of something else? Interstitial cystitis, once thought to have a low prevalence, in fact, is highly common. This debilitating disease can be evaluated in the PCP office without extensive diagnostics and, if identified and treated early, the outcomes are markedly improved.

Erectile dysfunction (ED) is not only common, but is now considered a marker of cardiovascular disease. Treating ED is a patient's choice but identification of the process is essential as it can be lifesaving. Likewise, hypogonadism is strongly connected with cardiometabolic syndrome and treatment should be considered on an individual basis.

Prostate cancer is the most frequently diagnosed malignancy in men and the second most common cause of death. Primary care physicians have been exposed to a considerable amount of conflicting literature with respect to prevention, screening and treatment modalities of this disease.

An additional concern with these urological diseases is the effect on the geriatric population. This group tends to have more medical problems and subsequently takes more medications than younger groups. Thus, the elderly pose unique challenges on how multiple diseases and treatments interact.

It is our hope that the perspectives from the primary care and urology faculty in this Monograph allow a balanced overview and discussion. Such an approach will allow the primary care physician to better serve their patients and improve the overall quality of genitourinary care.

Matt T. Rosenberg, M.D.

Mid-Michigan Health Systems
Allegiance Health
Jackson, Michigan

Howard N. Winfield, M.D.

West Alabama Urology Associates
Robotic Surgery
Regional Medical Center
Tuscaloosa, Alabama

Evaluating and Treating Lower Urinary Tract Symptoms

Matt T. Rosenberg, M.D., Mid-Michigan Health Systems, Allegiance Health, Jackson, Michigan

Steven A. Kaplan, M.D., Institute for Bladder and Prostate Health, Weill Cornell Medical College New York, New York

David R. Stakin, M.D., Female Urology and Male Voiding Dysfunction, St Elizabeth's Medical Center, Tufts University School of Medicine, Boston, Massachusetts

Lower urinary tract symptoms (LUTS) affect 15% to 60% of patients older than 40 years and can have a significant impact on their lives.^{1,2} LUTS can result in decreased quality of life, impaired activities of daily living, depression, increased risk of falls and prostatic obstruction requiring medical or surgical intervention.^{1,2} We tend to implicate the outlet (overactive outlet/prostatic obstruction) in males with LUTS and the bladder (overactive bladder, OAB) in females.

We classify the problems urologically as the ability to hold (store) or void (empty) urine. In addition to urological based symptom assessment (bladder and/or outlet dysfunction affecting storage or emptying), the causes of LUTS can be medically based (disorders of fluid intake or output), and these varied etiologies often present in combination. Thus, the role of the primary care provider (PCP) is to elucidate the cause, which may often be multifactorial, and treat accordingly. In summary, LUTS may be secondary to a disorder of storage or emptying due to dysfunction of the bladder and/or bladder neck with or without an abnormal fluid intake or metabolism.

Before we can diagnose an abnormal function of the genitourinary system, we need to understand the basics of normal function. The bladder stores and empties urine.³ The storage capacity of the bladder is 300 to 500 ml stored at low pressure with a competent outlet. Following the sensation motivating voluntary micturition, an adequate bladder contraction with an unobstructed outlet is required. In summary, the bladder stores at low pressures and develops an adequate contraction for emptying while the outlet maintains the appropriate resistance during the storage phase and provides no obstruction during emptying.

Abnormal storage is when voiding occurs frequently with small or below capacity amounts, generally after an uncontrollable compelling need (urgency) to empty which may result in urgency incontinence. Abnormal storage is also considered as leakage from inadequate outlet resistance. Abnormal emptying results from obstruction causing hesitancy, a poor stream, a feeling of incomplete voiding or an inadequate bladder contraction. The normal function of the prostate is to produce fluid for seminal emission. It does not have a role in voiding until it enlarges into the urethra, thus causing obstructed flow.³ The obstruction can be partial, resulting in flow

abnormalities, or complete, causing retention. Surgery on the prostate (more commonly radical surgery for cancer) can also cause sphincteric damage which results in loss of urine with effort or activity (stress incontinence, SI). Appendix 1 lists the symptoms a patient may have when LUTS are related to the bladder or prostate.^{4,5}

The symptoms can be the key to the problem. The bladder that cannot store well is considered overactive, and the symptoms are frequency, urge, nocturia and urge incontinence. The bladder that does not empty is considered underactive, and the symptoms are hesitancy, straining, incomplete voiding and overflow incontinence. The underactive outlet does not provide enough resistance and the symptom is leakage of urine with movement, laughing, coughing or sneezing. The overactive outlet provides too much resistance and the symptoms are hesitancy, straining, incomplete emptying and overflow incontinence.³

Understanding the functions of the genitourinary tract helps make sense of the common terminology used to describe LUTS. OAB is defined by the International Continence Society (ICS) as a syndrome of urinary urgency (intense, sudden desire to void) with or without incontinence, urinary frequency (voiding too often during the day) and nocturia (wakening at night to void).⁴ SI is involuntary leakage upon effort, exertion, sneezing or coughing.⁴ Benign prostatic hyperplasia (BPH) refers to the asymptomatic microscopic detection of prostatic hyperplasia, the benign proliferation of the prostatic stroma and epithelium. Benign prostatic obstruction (BPO) occurs when hyperplasia is caused by LUTS (specifically, impaired urinary flow).^{6,7} It is important to remember that these problems are not mutually exclusive and can coexist.⁸

Given the fact that the symptoms overlap, is it possible to differentiate the cause of LUTS based on patient history? Although it is not a perfect science, we advocate that if the patient has a weak flow, think prostate or anatomical obstruction; if the patient is voiding small amounts, think bladder; if there is leakage of urine, it is likely a result of the overactive bladder or sphincter; and if there is good flow and normal volume of urine, it is likely too much fluid production. The reality is that having information on volume voided, urine flow and

Evaluating and Treating LUTS

▼ Continued from page 5

fluid intake-output can obviate the need for further testing. After obtaining a good history from the patient, the next step in the evaluation of LUTS is to look for causes other than the urinary tract. An advantage for the PCP evaluating the patient for LUTS is that he/she generally has this information on file and a quick review may be all that is needed.

The medical and surgical history, medications, focused physical examination, voiding diary and certain laboratory values all have a role in this next step.⁸⁻¹¹ A few examples of comorbid conditions causing LUTS include diabetes (polyuria, polydipsia), immobility (slowing ability to get to bathroom), constipation (causing bladder irritation) or congestive heart failure (nighttime diuresis.) Surgery can affect mobility or cause urethral irritation if a bladder catheter was placed. Various medications can have an effect such as diuretics (affecting voided volume), opioids (constipation) or allergy medications (sphincter control) (Appendix 2).^{10,12-15} The key point is that a recent onset of symptoms may provide a clue to the etiology.^{16,17}

The history and physical examination (HPE) can be focused on the established patient if he/she has had a recent evaluation. Abdominal tenderness, masses or distension should be noted. A normal meatus, testis and prostate in the male should be confirmed. Although a large prostate does not mean obstruction, it is true the likelihood of BPO increases with size. In the female the PCP should evaluate for vaginal mucosal integrity, urethral mobility or bladder prolapse. A neurological assessment is important to understand mental and ambulatory status as well as neuromuscular function.^{8,18,19}

The voiding diary is a useful part of this evaluation. The information needed is centered on the voiding frequency, volumes and timing. It can help differentiate behavioral vs pathological causes of LUTS. For example, voiding frequently after drinking a 40 ounce beverage is generally a behavioral issue as is voiding small amounts because of always being in a rush. On the other hand, voiding frequently of small amounts because of urgency is likely a sign of OAB. Given this information, the diary can alert the patient to their habits and provide opportunities to modify them as well as monitor treatment effects.¹⁴

The suggested laboratory tests include urinalysis (UA), blood sugar (BS) and prostate specific antigen (PSA). UA is evaluated for infection, blood or crystals and is not an adequate screen for diabetes since the blood sugar must be greater than 180 mg/dl before it spills into the urine. A random or fast-

ing BS checks for possible diabetes. The PSA is useful for the information it offers. It is prostate specific not cancer specific, but can be used for screening. It is excellent as a surrogate marker for prostate size and is more accurate than a digital rectal examination in this regard. A PSA of 1.5 ng/ml equates to a prostate volume of at least 30 gm (ml).¹⁹⁻²¹ An important part of the evaluation for LUTS is when the findings warrant a referral to a specialist (Appendix 3).⁸

If no identifiable etiology or reversible causes have been uncovered on initial evaluation, then treatment is considered. A question for the patient is how much is he/she bothered by LUTS. Many patients truly want to understand that the symptoms are not a result of something more pathological or life threatening. If they are satisfied with that, they may opt for a “watchful waiting” program. However, if they desire treatment then it should be offered. Most specialists will agree that symptom bother drives treatment and watchful waiting requires education as to what to expect. The reality is that OAB symptoms may worsen and subsequently affect quality of life. For example, increasing nocturia episodes increase the risk for falls, and the resultant morbidity and mortality after a hip fracture are high.²² Skin irritation and urinary infections are risks of incontinence in addition to the effects on activities of daily living.²² Since the prostate continues to grow as the male ages, BPH can be a progressive disease and those patients with large prostates are more at risk for decreased flow, increased incidence of acute urinary retention (AUR) and increased need for surgical intervention.²³

The reality is that not all PCPs will be comfortable treating the complex presentation of LUTS, but following this evaluation they should be more comfortable about when to refer. An algorithm for which the PCP can refer to in the process is provided in the figure.⁸ A summary of this process would be weak flow – think prostate, poor voiding volumes – think bladder and if incontinent – think bladder or outlet. Let us first consider the patient with BPH. The treatment options for BPH are behavioral, α -blockers (ABs), 5 α -reductase inhibitors (5ARIs), combination of ABs and 5ARIs, and surgery.¹⁹ Since PCPs do not offer surgery this will not be discussed further.

BPH is truly no different from other disease states in that behavioral therapy can be the backbone of treatment. Advocating good micturition hygiene includes teaching the patient how to relax while voiding, take appropriate time in doing so and make sure to empty to completion. In addition, restriction of fluid intake, especially at night, and moderate daily exercise

▼ Continued on page 7

Evaluating and Treating LUTS

▼ Continued from page 6

have been shown to help.²⁴ Knowing when to followup is just as important as the initial treatment. We know that ABs are likely to provide response within 2 to 4 weeks, whereas 5ARIs may take 3 to 6 months. This information shared with the patient may alleviate significant concerns by aligning expectations. A good response requires only periodic followup and patient awareness of potential symptoms of progression. Since prostate size decreases with the use of the 5ARI, so should the PSA. However, most importantly, is that PSA should never increase after treatment is initiated and if it does then a referral is warranted.

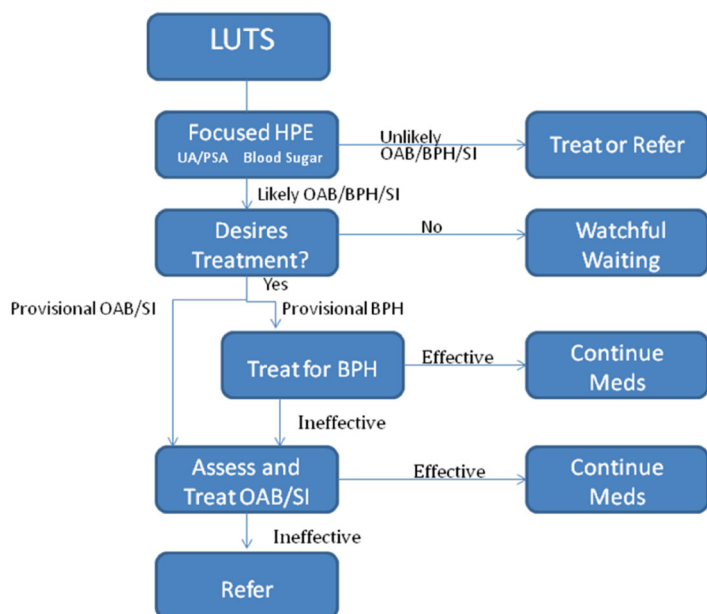
What should the provider do if no, or minimal, response is noted within a reasonable time? The possibilities now include a prostate that is refractory to therapy, OAB or some other anatomical or physiological problem. Some providers may be most comfortable referring the patient at this time which is acceptable and appropriate when all of the aforementioned possibilities have been considered. OAB is nearly as common as BPH in males⁸ but there are concerns when considering OAB in a male as prior thinking was that retention would occur if an antimuscarinic was administered. Expert opinion is that if the urine flow is good, obstruction is unlikely. Data show that if the post-void residual (PVR) is less than 50 ml, causing retention when treating OAB is extremely unlikely. While it is true that most PCPs will not have a bladder scanner or want to catheterize a patient, they will have access to an ultrasound unit and can order a PVR.⁸ Common sense can also be useful. If a patient is treated for OAB and has not voided in 6

to 8 hours or has a sense to void but cannot, he should be instructed to contact the provider.²⁵

Treatment options for OAB are the same for both genders and in the primary care setting they consist of behavioral modifications, pharmacological management or referral to specialist management/surgery.^{26,27} Similar to therapy for the prostate, behavioral modification is the cornerstone of treatment and should be offered to every patient. Included in behavioral therapy is education, voiding diaries, fluid and dietary management, timed voids, pelvic floor exercises and biofeedback.^{24,28-31} Antimuscarinics are the first line option in pharmacological management of OAB. There are many medications to choose from and all have been proven to be effective. Choice should be based on efficacy, dose flexibility, adverse event profiles and drug interactions. It is also considered appropriate to try several medications before referral for lack of any 1 medication response.

Followup evaluation for the patient treated for OAB varies among specialists. We recommend a followup visit after 2 to 4 weeks. If the patient is satisfied then nothing further needs to be done. If he/she is not getting enough effect, then titrating the dose or trying a different medication is appropriate. Studies have shown that greater than 50% of patients will agree to increase the dose if given the option.³² As a safety measure in males, it is recommended to check the PVR to ensure that the volume is not increasing. Studies on antimuscarinic use in males indicate safety and a minimal increase in PVR during followup.⁸ However, the risk of urinary retention (although low) is highest during the first 30 days of treatment.³³

In summary, LUTS is common and the PCP will frequently see patients with one form or another. It is essential for the provider to understand normal function of the urinary tract so that he/she can identify abnormal. Flow and volume voided are important components of the patient history. A poor flow is more consistent with prostate problems (voiding), whereas decreased volumes are more consistent with bladder problems (storage). Using a logical, conscientious approach will ensure patient safety and allow LUTS to be treated effectively in the PCP setting.



Evaluating and Treating LUTS

▼ Continued from page 7

Appendix 1

Storage (bladder)	Voiding (prostate)
Urgency	Hesitancy
Frequency	Poor flow/weak stream
Nocturia	Intermittency
Urge incontinence	Straining to void
Stress incontinence	Terminal dribble
Mixed incontinence	Prolonged urination
Overflow incontinence	Urinary retention

Appendix 2

Sedatives	Confusion, secondary incontinence
Alcohol, caffeine, diuretics	Diuresis
Anticholinergics	Impair contractility, voiding difficulty, increase overflow
α -Agonists	Increase outlet resistance, voiding difficulty
β -Blockers	Decrease urethral closure, stress incontinence
Calcium channel blockers	Reduce bladder smooth muscle contractility
Angiotensin converting enzyme	Induce cough, stress urinary incontinence
First generation antihistamines	Increase outlet resistance
Cholinesterase inhibitors	Precipitate urge incontinence
Opioids	Constipation

Appendix 3: Indications for referral

<ul style="list-style-type: none"> • Microscopic or gross hematuria • Prior genitourinary surgery • Elevated prostate specific antigen • Abnormal genital exam • Suspicion of neurological cause of symptoms • History of genitourinary trauma • Meatal stenosis • Pelvic pain • Uncertain diagnosis or patient choice

1. Parsons JK, Palazzi-Churas K, Bergstrom J et al: Prospective study of serum dihydrotestosterone and subsequent risk of benign prostatic hyperplasia in community dwelling men: the Rancho Bernardo Study. *J Urol* 2010; **184**: 1040.
2. Roehrborn CG, Siami P, Barkin J et al: The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4 year results from the CombAT study. *Eur Urol* 2010; **57**: 23.
3. Wein AJ: Pathophysiology and categorization of voiding dysfunction. In: Campbell's Urology, 9th ed. Edited by AJ Wein, LR Kavoussi, AC Novick et al. Philadelphia: WB Saunders Elsevier, 2007; pp 1973-1985.
4. Abrams P, Cardoza L, Fall et al: The standardization of terminology of lower urinary tract function: report from the Standardization Subcommittee of the International Continence Society. *Neurourol Urodyn* 2002; **21**: 167.
5. Chapple CR and Roehrborn CG: A shifted paradigm for the further understanding, evaluation, and treatment of lower urinary tract symptoms in men: focus on the bladder. *Eur Urol* 2006; **49**: 651.
6. Dennis L, Griffiths K, Khoury S et al: Proceedings of the Fourth International Consultation on Benign Prostatic Hyperplasia. London: Health Publications, Ltd., 1998; pp 669-684.
7. Lee C, Cockett A, Cussenot K et al: Proceedings of the Fifth International Consultation of Benign Prostatic Hyperplasia. London: Health Publications, Ltd., 2001; pp 79-106.
8. Rosenberg MT, Staskin DR, Kaplan SA et al: A practical guide to the evaluation and treatment of male lower urinary tract symptoms in the primary care setting. *Int J Clin Pract* 2007; **61**: 1535.
9. Hashim H and Abrams P: Drug treatment of overactive bladder: efficacy, cost and quality-of-life considerations. *Drugs* 2004; **64**: 1643.
10. Lavelle JP, Karram M, Chu FM et al: Management of incontinence for family physicians. *Am J Med, suppl.*, 2006; **119**: 37.
11. Rosenberg MT and Dmochowski RR: Overactive bladder: evaluation and management in primary care. *Cleve Clin J Med* 2005; **72**: 148.
12. DeBeau CE: The aging lower urinary tract. *J Urol* 2006; **175**: S11.
13. Gill SS, Mamdani M, Naglie G et al: A prescribing cascade involving cholinesterase inhibitors and anticholinergic drugs. *Arch Intern Med* 2005; **165**: 808.
14. Wyman JF, Burgio KL and Newman DK: Practical aspects of lifestyle modification and behavioral changes in the treatment of overactive bladder and urinary incontinence. *Int J Clin Pract* 2009; **63**: 1177.
15. Newman DK: Talking to patients about bladder control problems. *Nurse Pract* 2009; **34**: 33.
16. Haidinger G, Temmi C, Schatzl G et al: Risk factors for lower urinary tract symptoms in elderly men. For the Prostate Study Group of the Austrian Society of Urology. *Eur Urol* 2000; **37**: 413.
17. Gades NM, Jacobsen DJ, Girman CJ et al: Prevalence of conditions potentially associated with lower urinary tract symptoms in men. *BJU Int* 2005; **95**: 549.
18. Rosenberg MT, Newman DK, Tallman CT et al: Overactive bladder: recognition requires vigilance for symptoms. *Cleve Clin J Med* 2007; **74**: S21-S29.
19. Rosenberg MT, Miner MM, Riley PA et al: STEP: simplified treatment of the enlarged prostate. *Int J Clin Pract* 2010; **64**: 488.
20. Bosch J, Bohnen AM and Groeneveld FP: Validity of digital rectal examination and serum prostate specific antigen in the estimation of prostate volume in community-based men aged 50 to 78 years: the Krimpen Study. *Eur Urol* 2004; **46**: 753.
21. Roehrborn, CG, Boyle P, Gould AL et al: Serum prostate-specific antigen as a predictor of prostate volume in men with benign prostatic hyperplasia. *Urology* 1999; **53**: 581.

▼ Continued on page 9

Evaluating and Treating LUTS

▼ Continued from page 8

22. Vaughn CP, Johnson TM, Ala-Lipasti MA et al: The prevalence of clinically meaningful overactive bladder: bother and quality of life results from the population-based FINNO study. *Eur Urol* 2011; **59**: 629.
23. Roehrborn CG: Etiology, pathophysiology, epidemiology, and natural history of benign prostatic hyperplasia. In: *Campbell's Urology*, 8th ed. Edited by PC Walsh, AB Retik, ED Vaughan et al. Philadelphia: WB Saunders; 2002; pp 1297-1336.
24. Soda T, Masui K, Okuno H et al: Efficacy of nondrug lifestyle measures for the treatment of nocturia. *J Urol* 2010; **184**: 1000.
25. Rosenberg MT: The treatment of overactive bladder: a primary care provider's perspective. *Curr Urol Rep* 2008; **9**: 428.
26. Kirby M, Artibani W, Cardozo L et al: Overactive bladder: the importance of new guidance. *Int J Clin Pract* 2006; **60**: 1263.
27. Burgio KL, Locher JL and Goode PS: Combined behavioral and drug therapy for urge incontinence in older women. *J Am Geriatr Soc* 2000; **48**: 370.
28. Burgio KL: Influence of behavior modification on overactive bladder. *Urology*, suppl., 2002; **60**: 72.
29. Burgio KL, Goode PS, Locher JL et al: Behavioral training with and without biofeedback in the treatment of urge incontinence in older women: a randomized controlled trial. *JAMA* 2002; **288**: 2293.
30. Fantl JA, Wyman JF, McClish DK et al: Efficacy of bladder training in older women with urinary incontinence. *JAMA* 1991; **265**: 609.
31. Ouslander JG: Management of overactive bladder. *N Engl J Med* 2004; **350**: 786.
32. Chapple CG, Rosenberg MT and Brenes FJ: Listening to the patient: a flexible approach to the use of antimuscarinic agents in overactive bladder syndrome. *Brit J Urol* 2009; **104**: 960.
33. Martín-Merino E, García-Rodríguez LA, Massó-González EL et al: Do oral antimuscarinic drugs carry an increased risk of acute urinary retention? *J Urol* 2009; **182**: 1442.

Erectile Dysfunction and Cardiometabolic Risk

Martin M. Miner, M.D., Men's Health Center, The Miriam Hospital, Family Medicine and Urology, Warren Alpert School of Medicine, Brown University, Providence, Rhode Island

Erectile dysfunction (ED) is defined as the inability to reach or maintain erection sufficient for satisfactory sexual performance.¹ Evidence suggests that ED is predominately a vascular disorder in patients older than 30 years.² Seftel et al used a nationally representative managed care claims database that covered 51 health plans with 28 million lives for 1995 through 2002 to examine this possibility.³ They noted that hypertension, hyperlipidemia, diabetes mellitus (DM) and depression were prevalent in patients with ED, which supported the notion that ED shares common risk factors with these 4 concurrent conditions. Therefore, as a pathophysiological event, ED could be viewed as a potential observable marker for these diseases. Based on the results of a retrospective cohort study comparing the prevalence rates of DM between men with and without ED, Sun et al found that those with ED were more than twice as likely to have DM (20%) than those without ED (7.5%).⁴

Building upon these data, the presence of ED has now emerged as a potential predictor of subsequent cardiovascular disease (CVD). Men 55 years old or older randomized to the placebo group in the Prostate Cancer Prevention Trial were evaluated every 3 months for CVD and ED between 1994 and 2003.⁵ Proportional hazards regression models were used to evaluate the association of ED and CVD. A total of 3,816 (47%) men with ED at study entry had no CVD. Of the 4,247 men without ED at study entry 2,420 (57%) reported incident

ED after 5 years. For subsequent cardiovascular (CV) events, the unadjusted risk of an incident CV event was 0.015 per person-year among men without ED and 0.024 for men with ED at study entry. This association was in the range of risk associated with current smoking or a family history of myocardial infarction. The authors concluded that ED is a harbinger of CV clinical events.

ED as a Risk Factor for CVD in the Diabetic Population

Gazzaruso et al expanded upon the diabetes-ED paradigm looking at the potential for ED as a risk factor for future CVD.⁶ Of 291 type 2 diabetic men with ED and silent coronary artery disease (CAD) angiographically documented 49 experienced major adverse cardiac events (MACE) during followup of 47.2 ± 21.8 months (range 4 to 82). The difference in ED prevalence between patients with and without MACE was significant (61.2% vs 36.4%, $p = 0.001$). Among patients with CAD and ED the Kaplan-Meier method showed that statin (Mantel log-rank test 3.921, $p = 0.048$) and phosphodiesterase type 5 (PDE-5) inhibitor use (Mantel log-rank test 4.608, $p = 0.032$) were associated with a lower rate of MACE. These data were the first to indicate that ED is a predictor of CV morbidity and mortality in diabetic patients with silent CAD, and treatment with statins and PDE-5 inhibitors might decrease the occurrence of MACE.

▼ Continued on page 10

Erectile Dysfunction and Cardiometabolic Risk

▼ Continued from page 9

Ma et al studied a consecutive cohort of men with no clinical evidence of CVD who underwent comprehensive assessment for diabetic complications.⁷ The incidence of coronary heart disease (CHD) events was higher in men with than without ED (19.7/1,000 person-years, 95% CI 14.3 to 25.2 person-years vs 9.5/1,000 person-years, 95% CI 7.4 to 11.7 person-years). Men with CHD events were older, and had a higher frequency of ED and microvascular complication, longer duration of diabetes, higher blood pressure, total cholesterol, low-density lipoprotein cholesterol and urinary albumin/creatinine ratio but lower high-density lipoprotein cholesterol (HDL-C) and estimated glomerular filtration rate. ED remained an independent predictor of CHD events after adjustment for other covariates along with age, duration of disease, use of antihypertensive agents and albuminuria. The authors concluded that in type 2 diabetic men without clinically overt CVD the presence of ED predicted a new onset of CHD events and recommended that symptoms of ED be independently sought to identify high risk subjects for comprehensive CV assessments.⁷

ED Precedes CVD by 2 to 5 Years

Montorsi et al studied patients with CAD and found that ED prevalence differed across subsets of patients and was related to coronary clinical presentation and extent of CAD.⁸ In logistic regression analysis age, multiple vessels vs single vessel and chronic coronary syndrome vs acute coronary syndrome were independent predictors of ED. In patients with established CAD, ED preceded CAD by an average of 2 to 3 years.

ED Predicts CVD in a Nondiabetic Population: The Middle Aged Male

Inman et al screened biennially for ED a random sample of more than 1,400 community dwelling men who had regular sexual partners and no known CAD.⁹ The prevalence of ED was 2% for ages 40 to 49 years, 6% for 50 to 59 years, 17% for 60 to 69 years and 39% for 70 years or older. The CAD incidence densities per 1,000 person-years for men without ED in each age group were 0.94, 5.09, 10.72 and 23.30, respectively. For men with ED, the incidence densities of CAD for each age group were 48.52, 27.15, 23.97 and 29.63, respectively. The authors concluded that ED and CAD may represent different manifestations of a common underlying vascular pathology.

When ED occurs in a younger man it is associated with a marked increase in the risk of future cardiac events, whereas in older men ED appears to be of little prognostic importance. Therefore young men with ED may be ideal candidates for CV risk factor screening and medical intervention.¹⁰

Overall, these data strongly suggest that ED is a clear signal for future CV events. However, given the high prevalence of ED in the middle-aged population, systematic cardiologic screening of all men with ED may not be cost-effective. Acknowledging the potential CV benefits and risks of sexual activity, and a need for guidelines regarding use of PDE-5 inhibitors in select patients with CV risk factors, a second consensus conference on sexual activity and cardiac risk (Princeton II) clarified the importance of risk factor evaluation and treatment for all patients with ED, and emphasized the safety of the oral PDE-5 inhibitors in men with CVD.¹¹ Men at intermediate risk whose cardiac conditions are uncertain as well as those with multiple risk factors require further testing or evaluation. Through consensus in Princeton III we hope to evaluate the relative and absolute risk of a CV event in the next 10 years of the younger patient (age 30 to 60 years) using one of several risk assessment office based approaches.

Endothelial Dysfunction and ED

Endothelial dysfunction is a contributing factor in the genesis of myocardial ischemia and acute coronary syndrome in patients with either angiographically proven CAD or angiographically normal coronary vessels.¹² Moreover, it has been shown to be an independent predictor of future CV events providing valuable prognostic information in addition to that derived from traditional risk factors.¹³ Because endothelial tests for coronary circulation are invasive and thus impractical to use on a wide scale, noninvasive evaluation of endothelial function has been advocated.¹⁴⁻¹⁶ Results similar to those obtained from invasive studies have been reported, confirming endothelial dysfunction as a systemic disorder.^{14, 15}

To date 4 studies addressing endothelial function in asymptomatic ED subjects have been published.¹⁶⁻¹⁹ Despite differences in the clinical characteristics of the patient populations, results consistently showed a blunted endothelium dependent vasodilatation response in patients with ED compared to controls. Kaiser et al reported an impaired vascular response in patients with ED and no CVD without major risk factors or

Erectile Dysfunction and Cardiometabolic Risk

▼ Continued from page 10

detectable cardiac and vascular abnormalities.¹⁸ In 3 of the 4 studies an impairment of endothelium independent vasodilatation was detected, suggesting a systemic disorder of vascular smooth muscle cells.^{19,20} However, endothelium independent impairment has not been found to predict long-term coronary events.²¹

It has been proposed that ED and CAD may be different manifestations of the same underlying vascular pathology and that new onset ED is likely to precede symptoms of CAD in younger men. Montorsi et al proposed that this phenomenon relates to the caliber of the blood vessels.² The penile artery has a diameter of 1 to 2 mm, whereas the proximal left anterior descending coronary artery is 3 to 4 mm in diameter. An equally sized atherosclerotic plaque burden in the smaller penile arteries would more likely compromise flow earlier and cause ED compared to the same amount of plaque in the larger coronary artery causing angina.

Another plausible explanation by multiple authors suggests greater impairment in arterial endothelial cell function with age.²²⁻²⁴ The repetitive pulsations that the large central arteries are subjected to over their lifespan lead to fatigue and fracture of the elastic lamellae resulting in increased stiffness.²⁵ Ultimately small arteries such as the pudendal and penile arteries begin to degenerate and end organ ischemia results. Even in the absence of plaque, in the younger male impaired vasodilatation of a penile artery is more likely to lead to ED than will impaired vasodilatation of coronary arteries lead to cardiac symptoms. More than 1 mechanism may exist.

It is possible that the increased dilatation required for full erection is like a vascular “stress test” for the penis in a functional more than anatomical sense. It may be a combination of anatomical and functional mechanisms that lead to the appearance of ED before CAD. Regardless of mechanism, if a readily available test of endothelial function or measure of vascular stiffness existed, it would be of interest for our patient with ED at potential risk for CVD as an early identifier, leading to aggressive management of CV risk and potential CV prevention.

Back to Basics: The Limitations of Framingham Risk Scores to Stratify the High Risk ED Patient

The Framingham risk score (FRS) is unique because it is dominated by chronologic age, systolic blood pressure, total cholesterol, HDL-C and cigarette smoking. We also know its

limitations as it assesses the 10-year risk of nonfatal myocardial infarction or coronary heart disease death rather than a longer term risk, potentially depriving younger men and women of more intensive therapies. The Framingham study involved only 5,200 patients but it is unclear whether this population is generalizable to other, particularly non-Caucasian populations.²⁶ In addition, Framingham risk score does not include family history of premature CHD and concepts of exercise and diet, which may be of great importance for future CVD risk. It also does not consider some of the novel biomarkers, such as C-reactive protein.

In a systemic review of 27 studies using the FRS, the predicted-to-observed ratios ranged from an under prediction of 0.43 in a high risk population to an over prediction of 2.87 in a low risk population.²⁷ Therefore, we are concerned that the FRS underestimates CHD risk in patients with ED younger than 60 years.²⁷ In 1 study the answer to a single question regarding ED asked of 1,248 men with no CVD at baseline revealed that 22.8% had reduced erectile rigidity and 8.7% had severely reduced erectile rigidity.²⁸ During an average of 6.3 years of followup a hazard ratio of 1.6 was found for increased CV events after adjusting for age and CVD risk score. The answer “yes” to the presence of ED proved to be a predictor of the outcomes of acute myocardial infarction, stroke and sudden death independent of the Framingham risk factors. These findings led to the proposal of other risk scores that factor in additional variables such as family history and lower socioeconomic status.^{29,30} However, none of these scoring systems appears clearly superior to the FRS.

The National Cholesterol Education Program and the American Heart Association recommend consideration of lifetime risk estimates in primary prevention but without specific guidance as to incorporate the 2 risk prediction scores currently accepted, eg the Framingham 10-year risk and the previously published lifetime risk algorithm by Lloyd-Jones et al.³¹ They suggest incorporating a stepwise approach to CV risk stratification with the Framingham criteria used for all patients and the lifetime analysis added for those predicted to be at low 10-year risk. Present screening methodology including the standardized Framingham coronary risk may be misleading for men younger than 60 years.

In the most recent study 56% of Americans had a low 10-year risk but a high lifetime risk of a cardiovascular event.³² A disproportionate increase was noted in short-term predicted risk with older age, such that after age 60 years nearly 90% of

▼ Continued on page 12

Erectile Dysfunction and Cardiometabolic Risk

▼ Continued from page 11

men were at high risk. Notably, of the 40 to 59-year age group, of particular interest for clinical prevention, 80% had a low 10-year coronary risk but three-fourths of them had a high lifetime risk of CV events. It is in this population that the Olmsted study demonstrated that ED may be particularly useful in predicting CHD events and where the FRS may underestimate the risk by examining forward only 10 years.

In a recent prospective population based study of 1,709 men followed for 15 years Araujo et al examined the association of ED with all-cause mortality and cause specific mortality.³³ Mortality was examined due to all causes including CVD, malignant neoplasms and others. After adjustment for age, body mass index, alcohol consumption, physical activity, cigarette smoking, self-assessed health, self-reported heart disease, hypertension and diabetes, ED was associated with hazard ratios of 1.26 (95% CI 1.01-1.57) for all-cause mortality and 1.43 (95% CI 1.00-2.05) for CVD mortality. These findings suggest that ED is significantly associated with an increased incidence of all-cause mortality, primarily through its association with CVD mortality. In the same population group the authors determined that ED was associated with CVD incidence controlling for age, age and traditional CVD risk, and age and FRS.³⁴ After adjusting for age, adding ED to the FRS yielded a reclassification of 8% of men or 1 in 12. These findings were replicated in a recent study of 1,549 cardiac patients randomized to receive telmisartan and/or ramipril.³⁵ The authors concluded that ED is a potent predictor for all-cause death and the composite of cardiovascular death, myocardial infarction, stroke and heart failure in men with CVD.

1. Impotence: NIH Consensus Development Panel on Impotence. *JAMA* 1993; **270**: 83.
2. Montorsi P, Montorsi F and Schulman CC: Is erectile dysfunction the "tip of the iceberg" of a systemic vascular disorder (editorial)? *Eur Urol* 2003; **44**: 352.
3. Seftel AD, Sun P and Swindle R: The prevalence of hypertension, hyperlipidemia, diabetes mellitus and depression in men with erectile dysfunction. *J Urol* 2004; **171**: 2341.
4. Sun P, Cameron A, Seftel A et al: Erectile dysfunction—an observable marker of diabetes mellitus? A large national epidemiological study. *J Urol* 2006; **176**: 1081.
5. Thompson IM, Tamgen CM, Goodman PJ et al: Erectile dysfunction and subsequent cardiovascular disease. *JAMA* 2005; **294**: 2296.
6. Gazzaruso C, Solerte SB, Pujia A et al: Erectile dysfunction as a predictor of cardiovascular events and death in diabetic patients with angiographically proven asymptomatic coronary artery disease: a potential protective role for statins and 5-phosphodiesterase inhibitors. *J Am Coll Cardiol* 2008; **51**: 2040.
7. Ma RC, So WY, Yang X et al: Erectile dysfunction predicts coronary artery disease in type 2 diabetics. *J Am Coll Cardiol* 2008; **51**: 2045.
8. Montorsi P, Ravagnani PM, Galli S et al: Association between erectile dysfunction and coronary artery disease. Role of coronary clinical presentation and extent of coronary vessel involvement: the COBRA Trial. *Eur Heart J* 2006; **27**: 2632.
9. Inman BA, St. Sauver JL, Jacobson DJ et al: A population-based longitudinal study of erectile dysfunction and future coronary artery disease. *Mayo Clin Proc* 2009; **84**: 108.
10. Miner M: Erectile dysfunction and the "window of curability:" a harbinger of cardiovascular events (editorial). *Mayo Clin Proc* 2009; **84**: 102.
11. Kostis JB, Jackson G, Rosen R et al: Sexual dysfunction and cardiac risk [the Second Princeton Consensus]. *Am J Cardiol* 2005; **96**: 313.
12. Sonetti PO, Lerman LO and Lerman A: Endothelial dysfunction. A marker of atherosclerotic risk. *Arterioscler Thromb Vasc Biol* 2003; **23**: 168.
13. Halcox JPJ, Schenke WH, Zalos G et al: Prognostic value of coronary vascular endothelial dysfunction. *Circulation* 2002; **106**: 653.
14. Anderson TJ, Uehata A, Gerhardt MD et al: Close relation of endothelial function in the human coronary and peripheral circulations. *J Am Coll Cardiol* 1995; **26**: 1235.
15. Neunteufl T, Hgeher S, Katzenschlager R et al: Late prognostic value of flow-mediated dilation in the brachial artery of patients with chest pain. *Am J Cardiol* 2000; **86**: 207.
16. Yavuzgil O, Altay B, Zoghi M et al: Endothelial function in patients with vasculogenic erectile dysfunction. *Int J Cardiol* 2005; **103**: 19.
17. Kaya C, Uslu Z and Karaman I: Is endothelial function impaired in erectile dysfunction patients? *Int J Impot Res* 2006; **18**: 55.
18. Kaiser DR, Billups K, Mason C et al: Impaired brachial artery endothelium-dependent and -independent vasodilation in men with erectile dysfunction and no other clinical cardiovascular disease. *J Am Coll Cardiol* 2004; **43**: 179.
19. Chiurlia E, D'Amico R, Ratti C et al: Sub-clinical coronary artery atherosclerosis in patients with erectile dysfunction. *J Am Coll Cardiol* 2005; **46**: 1503.
20. Montorsi P, Ravagnani P, Galli S et al: Association between erectile dysfunction and coronary artery disease: matching the right target with the right test in the right patient. *Eur Urol* 2006; **50**: 721.
21. Halcox JPJ, Schenke WH, Zalos G et al: Prognostic value of coronary vascular endothelial dysfunction. *Circulation* 2002; **106**: 653.
22. Billups KL, Blank AJ, Padma-Nathan H et al: Erectile dysfunction is a marker for cardiovascular disease: results of the Minority Health Institute Expert Advisory Panel. *J Sex Med* 2005; **2**: 40.
23. Guiliano F: New horizons in erectile and endothelial dysfunction research and therapies. *Int J Imp Res* 2008; **20**: S2.
24. Guay AT: ED2: erectile dysfunction = endothelial dysfunction. *Endocrinol Metab Clin North Am* 2007; **36**: 453.
25. O'Rourke MF and Hashimoto J: Mechanical factors in arterial aging: a clinical perspective. *J Am Coll Cardiol* 2007; **50**: 1.
26. D'Agostino RB, Grundy S, Sullivan LM et al: Validation of the Framingham Heart Disease Prediction Score: results of a multiple ethnic groups investigation. *JAMA* 2001; **286**: 180.
27. Brindle P, Beswick A, Fahey T et al: Accuracy and impact of risk assessment in the primary prevention of cardiovascular disease: a systemic review. *Heart* 2006; **92**: 1752.
28. Schouten BWV, Bohnen AM, Bosch JLHR et al: Erectile dysfunction prospectively associated with cardiovascular disease in the Dutch general population: results from the Krimpen Study. *Int J Impot Res* 2008; **20**: 92.
29. Hippisley-Cox J, Coupland C, Vinogradova Y et al: Derivation and validation of QRISK, a new cardiovascular risk score for the United Kingdom: prospective open cohort study. *BMJ* 2007; **335**: 136.
30. Woodward M, Brindle P and Tunstall-Pedoe H: Adding social deprivation and family history to the cardiovascular risk assessment:

Erectile Dysfunction and Cardiometabolic Risk

▼ Continued from page 12

- the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). *Heart* 2007; **2**: 172.
31. Lloyd-Jones DM, Leip EP, Larson MG et al: Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation* 2006; **113**: 791.
 32. Mamma AK, Berry JD, Ning H et al: Distribution of 10-year lifetime predicted risks for cardiovascular disease in US adults: findings from the National Health and Nutrition Examination Survey 2003-2006. *Circ Cardiovasc Qual Outcomes* 2010; **3**: 8.
 33. Araujo AB, Trivison TG, Ganz PA et al: Erectile dysfunction and mortality. *J Sex Med* 2009; **6**: 2445.
 34. Araujo AB, Hall SA, Ganz P et al: Does erectile dysfunction contribute to cardiovascular disease risk prediction beyond the Framingham risk score? *J Am Coll Cardiol* 2010; **55**: 350.
 35. Bohm M, Baumhake M, Koon T et al: Erectile dysfunction predicts cardiovascular events in high risk patients receiving telmisartan, ramipril, or both. *Circulation* 2010; **121**: 1439.

Prostate Cancer Overview 2011

Howard N. Winfield, M.D., West Alabama Urology Associates, Director of Robotic Surgery, Regional Medical Center, Tuscaloosa, Alabama

It is estimated that a male in the United States has a 1 in 6 (17%) lifetime risk of detectable prostate cancer, resulting in the highest incidence of new cancers in the male population. Although there is only a 1 in 34 (3%) lifetime risk of dying from prostate cancer, it accounts for the second most frequent cause of death of the U.S. male population. Thus, the magnitude of this disease entity should play a prominent role in the practice of the primary care physician.

There has been considerable controversy about the role of prostate specific antigen (PSA) screening, and different national health organizations have put forth different opinions and recommendations. Reasons for this controversy are due to 1) the relatively low specificity of PSA testing, 2) the known extended natural history of many prostatic cancers, 3) the concern that “very low risk disease” or “insignificant prostate cancer” may be overdiagnosed and over treated with associated known side effects of such treatment modalities, and 4) lack of clear long-term data that demonstrate a decrease in prostate cancer mortality associated with PSA screening.

Based on the American Urological Association PSA Best Practice Statement 2009 Update, which is an exhaustive review of Level 1 and 2 literature on this subject, it is recommended that 1) screening PSA should begin at age 40 years, 2) men should be well informed of the benefits and risks/pitfalls of PSA screening, and 3) PSA screening benefits appear to decline after age 65 years. The US Preventive Services Task Force has issued guidelines that recommend against screening men older than 75 years.

Based on appropriate referrals from primary care physicians, urologists will further evaluate prostate cancer by digital rectal examination and possible repeat PSA testing (total and percent free component). Pending this initial urological

evaluation, a transrectal ultrasound and prostate biopsy may be recommended. Biopsy is normally performed in the office setting under appropriate antibiotic coverage. If the prostate biopsy demonstrates prostate cancer (vast majority are adenocarcinoma), the grade (Gleason sum) as well as clinical stage will be considered in deciding whether further imaging (bone scan, computerized tomography, endorectal magnetic resonance imaging) is required.

Assuming the cancer is localized, treatment options would include radical prostatectomy (open, laparoscopic or robotic assisted), radiation therapy (external beam-intensity modulated radiation therapy, brachytherapy-seed implantation) or active surveillance (watch closely, with repeat interval PSA tests and biopsy). Other less common treatment options would include cryotherapy, high intensity focused ultrasound (HIFU) or upfront primary androgen suppression (noncurative). Associated with surgery, a pelvic lymph node dissection may be considered.

Following definitive curative therapy, the followup PSA values should decrease and remain at low levels (radiotherapy, cryotherapy, HIFU) or be undetectable (following radical prostatectomy). When posttreatment PSA values do not follow expected patterns, persistent or recurrent prostate cancer is most likely. Advanced or metastatic prostate cancer is usually managed with androgen hormone suppression. A number of newer chemotherapeutic (docetaxel based) and immunological options (Prostvac[®] and Provenge[®]) are used in the case of prostate cancer that is no longer sensitive to androgen suppression (ie hormone resistant). Results, although preliminary, are encouraging but unfortunately not curative.

Are there ways to prevent prostate cancer? A variety of agents such as selenium, vitamin E, Cox-2 inhibitors, estrogen recep-

Prostate Cancer Overview 2011

▼ Continued from page 13

tor modulators etc have been tried and advertised, of which there is little to no level 1 evidence that show a true effect. Although the data are preliminary and “somewhat soft,” there seems to be some advantages of whole tomatoes, pomegranates and statin medications.

Another subject of significant controversy involves the use of 5 α -reductase inhibitors, such as finasteride and dutasteride with respect to decreasing the incidence of prostate cancer. Large, multi-institutional studies, such as the PCPT (Prostate Cancer Prevention Trial) and REDUCE (Reduction by Dutasteride of Prostate Cancer Events) trial, randomizing upwards of 19,000 men followed for upwards of 7 years, demonstrated a 22% to 25% decrease in prostate cancer detection in men on either of these 2 drugs compared to placebo. What

was of concern was that in the finasteride study (PCPT) there appeared to be an increased risk of detecting a higher grade of adenocarcinoma if the patient taking finasteride had prostate cancer but this was not clearly shown in the REDUCE study. At this point, most urologists are not routinely prescribing finasteride or dutasteride solely to prevent prostate cancer. In like fashion, primary care physicians should discuss this issue with their urology colleagues before prescribing these medications other than for bladder outlet obstructive symptoms (benign prostatic hyperplasia).

In summary, the evaluation, detection and treatment of prostate cancer are an enormous undertaking that requires careful collaboration and communication among the patient, primary care physician and urologist.

Urinary Tract Infections and Interstitial Cystitis

C. Lowell Parsons, M.D., Department of Urology, School of Medicine, University of California San Diego, San Diego, California

Traditional concepts of interstitial cystitis (IC), also referred to as bladder pain syndrome (BPS), have evolved into a new understanding of the disease, its origins, diagnosis and treatment. Historically IC was a diagnosis for people with severe disease and intense symptoms of urgency, frequency and pain. Currently, IC is widely recognized to have a beginning stage at which the symptoms are mild, moderate and often intermittent. Only a rare few progress to a point when the bladder is almost destroyed by the disease process. Most who suffer with IC have mild baseline symptoms, usually consisting of an insidiously progressive frequency, punctuated by intense flares of urgency, frequency, pain and perhaps gross hematuria which last for 3 to 21 days and then resolve. It is these flares that are the iatrogenic stimulus and account for millions of outpatient visits per year. New concepts of the disease are reviewed to provide information regarding the development of the disease, its causes and, more importantly how to diagnose and treat it.

Symptoms

The symptoms of IC are frequency, urgency and/or pelvic pain and incontinence, all due to activation of the sensory nerves in the bladder. The 2 types of nerves responsible for triggering the need to void are the stretch or urgency fiber and the pain fiber. In IC these fibers become up-regulated and generate symptoms. These symptoms are affected by the menstrual cycle (they peak the week before menses begin) and are

provoked by sexual intercourse for both sexes. Disease flares associated with sex typically appear a day later but many also experience dyspareunia. The bladder is often not identified as the cause of the pain, although the most common cause of dyspareunia may actually be bladder generated, which is not well known. When this symptom is present, a careful history of voiding frequency should be obtained. If flares occur after sex it is likely that the patient will be treated as if she had a urinary tract infection (UTI). Patients with recurrent episodes of “UTI” should also raise the index of suspicion that they may have IC, especially if cultures show no infection.

The symptoms begin insidiously, with a slowly progressive frequency that goes unnoticed by the patient until it interferes with their lifestyle. Pain cycles may begin with acute onset of urgency, frequency and pain that last for 3 to 21 days and then resolve. These cycles tend to recur with slowly progressive frequency and duration for decades. As the activity of the disease increases the diagnosis of IC becomes more obvious.

Pain of bladder origin is not always obvious and, in fact, most of the time it may be perceived to be a gynecologic problem.¹⁻³ The pain can be anywhere from the navel to the knees, anterior or posterior. It can be episodic, chronic or affected by bladder filling and emptying (easier to identify the bladder origin). The pain can be in the lower abdomen, labial, scrotal, vaginal and/or perirectal but most of the time it is between the pubic arch and the rectum in both sexes, and often not affected by bladder filling. It is the pain that is responsible

▼ Continued on page 15

Urinary Tract Infections and Interstitial Cystitis

▼ Continued from page 14

for the misdiagnoses. For example, if you were a 21-year-old female with low grade frequency (10 to 12 voids a day, which you thought was normal), dyspareunia and pelvic pain that intensified the week before your period you would likely see a gynecologist. The gynecologist would ascribe the problem to a gynecologic source such as endometriosis or vulvodynia,^{1,2} depending on where the patient feels the bladder generated pain. While the disease runs its course, different diagnoses may be ascribed as the cause of the symptoms, such as UTI, overactive bladder (OAB), prostatitis or gynecologic chronic pelvic pain, although the symptoms are likely originating from a primary problem in the bladder.³ That problem is loss of the permeability barrier at the bladder surface resulting in a “leaky epithelium.”

Role of the Bladder Surface Mucus or Glycosaminoglycans Layer in Epithelial Permeability

Transitional epithelium is a protective barrier for the bladder interstitium and functions to prevent urinary metabolites from interacting with the muscle layer and/or being resorbed and recycled back into the bloodstream. Cell membranes and tight junctions are important components of the barrier. The immediate interface between urine and its solutes, and the interstitium of the bladder is the mucous layer on the apical membrane of the umbrella cell at the surface of the transitional epithelium. This mucus is highly anionic. The electro-negativity of these highly charged anions in mucus will by electrostatic force attract water and bind it tightly within the mucous layer. This process results in what has been referred to as an “unstirred water” layer in the gastrointestinal tract,^{4,5} and it provides an excellent barrier to the movements of small solutes.^{6,7}

Rodent experiments provided the initial data that demonstrated the importance of mucus in regulating permeability. Damaging the mucus by exposing it to protamine sulfate caused a marked increase in permeability to urea, water and calcium *in vivo* and *in vitro*.⁷ This damage was reversed by treating the epithelium with a heparinoid, pentosan polysulfate (PPS). Similar experiments in humans had the same results. Injury to the bladder mucus by protamine showed a marked increase in absorption of urea from 5% to 25% which was likewise reversed by a heparinoid (heparin).⁶ Potassium diffusion across human bladder epithelium also increased after mucus injury with protamine which was likewise reversed by

heparin.⁷ Urea absorption from the bladder was 27% in patients with IC/BPS vs 5% in control subjects, demonstrating that there is a “leaky” epithelium in patients with IC.⁸ Since heparinoid could reverse experimentally injured rodent and human bladders, these agents have been used for IC therapy.

Role of Urinary Potassium in the Generation of Bladder Symptoms

Since the bladder epithelium of patients with IC is dysfunctional and “leaky,” it was important to know what urinary solutes were toxic to the bladder interstitium. Potassium has the potential to cause serious reactions. At concentrations greater than 8 mEq/l potassium will depolarize nerves and muscles, and prolonged depolarization will cause the cells to die.⁹ Potassium levels in urine range from 30 to 120 mEq/l (median about 70).¹⁰ At these concentrations potassium would readily diffuse down the gradient into the bladder wall, depolarize bladder nerves and muscles, and cause symptoms and tissue injury. This potassium hypothesis explains all of the clinical observations of IC.

The potassium sensitivity test (PST) was developed to test this hypothesis.^{11,12} Asymptomatic human volunteers underwent PST testing and experienced no symptoms after an intravesical challenge of potassium.¹² However, after chemical injury of the mucus layer with protamine, placement of a 0.4 M potassium solution was absorbed into the bladder and the volunteers complained of urgency and pain but did not react to a sodium challenge.¹² To date, the world literature contains more than 35 published reports on potassium testing in more than 3,000 patients with IC/BPS. The data are robust, with 80% of patients testing positive for potassium sensitivity. Furthermore, several reports include data on about 200 normal subjects, and the test result was negative in 98.3%.^{1, 12-14} Other symptomatic patient populations were tested for potassium sensitivity, including gynecologic patients with chronic pelvic pain (80% positive),¹ OAB (71% positive)¹⁵ and prostatitis (84% positive),¹⁴ suggesting for most that epithelial dysfunction is the generator of the symptoms and that all of them, including IC, are basically the same disease.

Diagnosis and Therapy

Diagnosis of IC is relatively straightforward. If the patient has symptoms and there is no obvious cause then therapy can be initiated. The most practical test is urinalysis and, if it shows

▼ Continued on page 16

Urinary Tract Infections and Interstitial Cystitis

▼ Continued from page 15

no infection in an acutely symptomatic patient, then treat for IC. If the diagnosis is OAB that has not responded to therapy, then treat for IC. Similarly in a male with recurrent symptoms of “prostatitis” despite antibiotics, treat for IC. Women with what appears to be a gynecologic problem, eg vulvodynia and urinary frequency or dyspareunia, premenstrual abdominal pain and frequency (endometriosis), which has not responded to treatment, consider the bladder the source of the problem and treat for IC.

The principles of therapy are 1) correct the epithelial dysfunction, 2) inhibit neural hyperactivity and 3) control allergies (histamine flares, IC symptoms). Treating the symptoms alone does not correct the problem. The underlying disease will remain active and usually will progress. Hence the cornerstone of therapy is to correct the epithelial dysfunction. Heparin and heparinoid can restore the bladder epithelial mucous barrier successfully.¹⁶ The drugs used clinically are oral PPS and heparin placed intravesically. PPS does not relieve symptoms but helps restore the barrier function of the epithelium.¹⁶ It works best over time. In a large clinical trial PPS during an 8-month period had up to 70% efficacy.¹⁷ Patients taking PPS are encouraged to stay on it to get the maximum benefit for well past 6 months. The approved dosage is 100 mg 3 times daily but many physicians treating IC prefer to use 200 mg twice daily since it is easier for patients to adhere to that regimen. Consider using PPS for persistent or repeated symptom flares and refer the patient to a urologist when there is no response to the medication after 4 or 5 months.

Amitriptyline, at a dose of 25 to 50 mg at bedtime, is perhaps one of the most effective medications for treating symptoms. Anticholinergics and antimuscarinics are less effective but can be tried. Allergies and mast cells play a substantial role in IC symptom flares, and the best medication to suppress histamine production by mast cells is hydroxyzine. Used at bedtime it is even more effective after 2 or 3 months at inhibiting mast cell release of histamine. Start the patient on 25 mg 1 hour before bedtime to minimize the sedating effects. The dose can be increased to 50 or 75 mg at bedtime after several weeks of therapy if necessary.

Acute flares of IC can be treated with bladder instillations consisting of alkalized lidocaine and heparin.¹⁸ Two or three treatments in 1 week relieve the symptoms in most patients with acute flares. The instillation procedure can be billed under the CPT code 51700. The mixture consists of 40,000 units of heparin plus 200 mg lidocaine (10 ml of 2% solution) and 2 ml of 8.4% sodium bicarbonate. It is instilled and left

indwelling for 30 minutes. Therapy can be extended for weeks if necessary.

In summary, if IC is diagnosed begin treatment with PPS to restore the epithelial permeability barrier, add drugs to aid in symptom control, use hydroxyzine to control mast cell secretion of histamine and refer the patient who is not responding to treatment to a urologist.

1. Parsons CL, Dell J, Stanford EJ et al: The prevalence of interstitial cystitis in gynecologic patients with pelvic pain, as detected by intravesical potassium sensitivity. *Am J Obstet Gynecol* 2002; **187**: 1395.
2. Kahn BS, Tatro C, Parsons CL et al: Prevalence of interstitial cystitis in vulvodynia patients detected by bladder potassium sensitivity. *J Sex Med* 2010; **7**: 996.
3. Parsons CL: The role of a leaky epithelium and potassium in the generation of bladder symptoms in interstitial cystitis/overactive bladder, urethral syndrome, prostatitis and gynaecological chronic pelvic pain. *BJU Int* 2011; **107**: 370.
4. Dietschy JM, Sallee VL and Wilson FA: Unstirred water layers and absorption across the intestinal mucosa. *Gastroenterology* 1971; **61**: 932.
5. Wilson FA, Sallee VL and Dietschy JM: Unstirred water layers in intestine: rate determinant of fatty acid absorption from micellar solutions. *Science* 1971; **174**: 1031.
6. Lilly JD and Parsons CL: Bladder surface glycosaminoglycans is a human epithelial permeability barrier. *Surg Gynecol Obstet* 1990; **171**: 493.
7. Parsons CL, Boychuk D, Jones S et al: Bladder surface glycosaminoglycans: an epithelial permeability barrier. *J Urol* 1990; **143**: 139.
8. Parsons CL, Lilly JD and Stein P: Epithelial dysfunction in nonbacterial cystitis (interstitial cystitis). *J Urol* 1991; **145**: 732.
9. Krishnan AV and Kiernan MC: Uremic neuropathy: clinical features and new pathophysiological insights. *Muscle Nerve* 2007; **35**: 273.
10. Parsons CL, Greene RA, Chung M et al: Abnormal urinary potassium metabolism in patients with interstitial cystitis. *J Urol* 2005; **173**: 1182.
11. Parsons CL, Stein PC, Bidair M et al: Abnormal sensitivity to intravesical potassium in interstitial cystitis and radiation cystitis. *Neurourol Urodyn* 1994; **13**: 515.
12. Parsons CL, Greenberger M, Gabal L et al: The role of urinary potassium in the pathogenesis and diagnosis of interstitial cystitis. *J Urol* 1998; **159**: 1862.
13. Parsons CL, Dell J, Stanford EJ et al: Increased prevalence of interstitial cystitis: previously unrecognized urologic and gynecologic cases identified using a new symptom questionnaire and intravesical potassium sensitivity. *Urology* 2002; **60**: 573.
14. Parsons CL and Albo M: Intravesical potassium sensitivity in patients with prostatitis. *J Urol* 2002; **168**: 1054.
15. Minaglia S, Ozel B, Bizhang R et al: Increased prevalence of interstitial cystitis in women with detrusor overactivity refractory to anticholinergic therapy. *Urology* 2005; **66**: 702.
16. Parsons CL, Forrest J, Nickel JC et al: Effect of pentosan polysulfate therapy on intravesical potassium sensitivity. *Urology* 2002; **59**: 329.
17. Barkin J, Forrest J, Mosbaugh PG et al: Randomized, double-blind, dose-ranging study of pentosan polysulfate sodium for interstitial cystitis. *Urology* 2005; **65**: 654.
18. Parsons CL: Successful downregulation of bladder sensory nerves with combination of heparin and alkalized lidocaine in patients with interstitial cystitis. *Urology* 2005; **65**: 45.

Urinary Tract Infections and Hematuria

Diane K. Newman, DNP, FAAN, Penn Center for Continence and Pelvic Health, Division of Urology, University of Pennsylvania Medical Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Providers in primary care settings often encounter men and women who present with urinary tract infections (UTIs) and/or have asymptomatic hematuria. Urinary tract infections account for 3.5 to 7 million office visits a year and are the most common bacterial infection seen in women. The antimicrobial drugs used to treat UTI account for 15% of all prescriptions. Hematuria is a frequently encountered symptom that has a broad differential diagnosis, ranging from insignificant etiology to potentially life threatening neoplastic lesions. These 2 common urological conditions are reviewed briefly.

Urinary Tract Infections

UTI is seen in 11% of women in any given year and in more than 50% in their lifetime. The definition of genitourinary infections is presented in the Appendix. UTI will develop in 1 in 3 women before age 24 years, most commonly occurring with the onset of sexual activity.¹ Asymptomatic bacteriuria (ASB) is seen in 3% of female teenagers, increasing 1% per decade, and in 25% of community dwelling women 65 years old or older. ASB occurrence increases by 20% to 50% at long-term facilities. It is rarely seen in young and middle-aged men, but its prevalence increases in aging men because of prostatic enlargement.

UTI has minimal morbidity in healthy individuals, and is a benign illness in nonpregnant, nonobstructed females. Risk factors include contraceptive diaphragm, spermicides and intercourse frequency in sexually active women, and estrogen deficiency in postmenopausal women. In healthy individuals UTI is basically a nuisance, usually resolves spontaneously if untreated and rarely leads to renal scarring, hypertension or renal failure.

However, UTI screening and treatment should be performed in pregnant and older women. Although ASB is common in pregnancy, most women do not have symptoms. Pregnancy induced physiological changes in the urinary tract increase the likelihood of upper UTI. If a pregnant woman is not appropriately treated for UTI the incidence of pyelonephritis is 30% to 40%. Untreated UTI in these women has been associated with obstetric complications such as preterm labor and low birth weight. UTI in postmenopausal women is common as approximately 10% to 15% of women 60 years old or older experience frequent and recurrent UTI. Risk factors

in this age group include increased post-void residual volume (150 to 200 ml), urinary incontinence, pelvic organ prolapse, estrogen depletion and loss of normal “flora” in the vagina, specifically lactobacillus.

The usual signs and symptoms of UTI include urinary frequency, urgency, dysuria and suprapubic discomfort. Women are usually systemically well but symptoms such as fever, malaise, nausea and vomiting can occur if the infection ascends. Renal angle flank pain and tenderness, chills and fever are often predominant symptoms of pyelonephritis. In the elderly patient mental changes, malaise and confusion may be the only presenting symptoms of UTI.

For suspected UTI, a urinalysis (dipstick) to check for leukocytes and bacterial nitrite production is quick and easy. A positive dipstick test result has sensitivity in the region of 70% and specificity of 80% for finding significant pathogens in urine. Urine microscopy to determine the diagnosis of UTI is not always necessary for patients with uncomplicated infection.² If performed, urine must be cultured in the presence of antimicrobials to determine sensitivities. Most UTIs in women result from bacterial ascent from the bowel or vagina mucosae. The most common organism is *Escherichia coli* (80%), followed by *Klebsiella* (5%), *Enterobacter* (2%) and *Proteus* (2%). *Staphylococcus saprophyticus* causes 10% of cases of acute cystitis in young women. Anaerobic infections of the urinary tract are rare. If the UTI becomes complicated, ultrasound imaging may be indicated.

Primary care providers should assess patients who have recurrent UTI following adequate treatment as complicated infection is seen in those with an abnormal urinary tract, in men secondary to bladder outlet obstruction, in elderly patients, in diabetics if immunosuppressed and in those who have undergone recent instrumentation or have an indwelling catheter.

Pathological conditions that can lead to recurrent UTI include bladder or urethral diverticulum, urinary tract calculi, bowel fistula (normally secondary to Crohn’s disease, diverticulitis or radiation treatment), urethral strictures/any cause of obstruction, carcinoma and incomplete bladder emptying.

Hematuria

Hematuria, blood in the urine, is a common clinical problem with an overall prevalence of 1% to 16%. It is often found in-

Urinary Tract Infections and Hematuria

▼ Continued from page 17

identally as a result of a routine examination and patients do not usually have urinary tract symptoms. Early and appropriate diagnosis of this common symptom results in improved clinical outcomes.³

Blood in the urine can originate from anywhere in the urinary tract and may be an indicator of an underlying pathological condition. Microscopic hematuria is defined as no visible color change in the urine, and 3 or more red blood cells (RBCs) per high power field from 2 of 3 freshly voided clean-catch midstream urine samples. Macroscopic hematuria presents with a visible urine color change and is also known as “gross hematuria.” Reported prevalence is 2% to 16.1%, and varies widely with age and gender.

Many patients with blood in the urine have asymptomatic hematuria. When there is no detectable pathological condition in the urinary tract, small amounts of blood are released into urine so that 1 or 2 RBCs per high power field may normally be visible on microscopic examination of the spun sediment. Prevalence of clinically detectable disease in patients with asymptomatic microscopic hematuria is low. Minimal microhematuria in an asymptomatic young adult needs no evaluation. A higher prevalence of microscopic hematuria is seen in women than men. Hematuria in women tends to be transient, caused by exercise, sexual intercourse or mild trauma, and has been reported in 13% of postmenopausal women.

Prevalence of hematuria on urine dipstick in adults is estimated at 2% to 16%. Urinary tract pathology is found in 2% to 10% of patients younger than 50 years with microscopic hematuria. It is rarely seen in individuals younger than 40 years but 10% to 20% of those older than 50 years have microscopic hematuria. Malignancy is more common in this age group when gross hematuria is present.

Common causes of hematuria in adults include calculi, urinary tract stones, UTI, nephritis and benign prostatic hyperplasia with obstruction. Less common causes include cancer (bladder, kidney, prostate, urothelial), bleeding diathesis, over anticoagulation, medications (eg nonsteroidal anti-inflammatory drugs, cyclophosphamide), diabetes, hypertension, sickle cell anemia, congenital causes, and vascular malformations and aneurysms. Patients with microscopic hematuria and a high risk of bladder cancer (smoking history, previous urological disease, analgesia abuse, pelvic irradiation) should be referred for urological evaluation.⁴ Further studies are needed

to evaluate the usefulness and effectiveness of guidelines for hematuria.

A urine dipstick is the most common and easiest test to evaluate urine, and provides an analysis of the number of RBCs.⁵ Dipstick urinalysis detects 1 to 2 RBCs per high power field and, therefore, is at least as sensitive as microscopic examination of the urine sediment.⁶ Cytology of exfoliated cells in the urine has excellent sensitivity and specificity for high grade urothelial carcinoma but less so for low grade disease.

Carefully selected patients may require no further evaluation if the clinical history can reasonably determine the cause of hematuria. Indications for prompt evaluation include hematuria with hypertension, edema, oliguria, proteinuria or RBC casts. Hematuria, symptomatic and incidental, that involves more than 3 RBCs per high power field on 2 of 3 properly collected urinalysis specimens warrants some type of imaging to evaluate the upper tracts.⁷ Excretory urography and computerized tomogram urography represent the leading techniques, with an increasing trend for use of the latter because of its significant advantages.⁸ Ultrasonography and magnetic resonance imaging have secondary roles in selected populations. Cystoscopy is recommended, as many bleeding urinary tract lesions occur in the bladder and lower urinary tract, and no imaging technique is completely satisfactory for ruling out disease at these sites.

1. Dielubanza EJ and Schaeffer AJ: Urinary tract infections in women. *Med Clin N Am* 2011; **95**: 27.
2. Lane DR and Takhar SS: Diagnosis and management of urinary tract infection and pyelonephritis. *Emerg Med Clin North Am* 2011; **29**: 539.
3. Loo R, Whittaker J and Rabrenivich V: National practice recommendations for hematuria: how to evaluate in the absence of strong evidence? *Perm J* 2009; **13**: 37.
4. Elias K, Svatek RS, Gupta S et al: High-risk patients with hematuria are not evaluated according to guideline recommendations. *Cancer* 2010; **116**: 2954.
5. Shen X: Diagnostic algorithm for the evaluation of hematuria. *J Am Acad Nurse Pract* 2010; **22**: 186.
6. Margulis V and Sagalowsky AI: Assessment of hematuria. *Med Clin North Am* 2011; **95**: 153.
7. Grossfeld GD, Wolf JS Jr, Litwin MS et al: Asymptomatic microscopic hematuria in adults: summary of the AUA best practice policy recommendations. *Am Fam Physician* 2001; **63**: 1145.
8. Choyke PL: Radiologic evaluation of hematuria: guidelines from the American College of Radiology's appropriateness criteria. *Am Fam Physician* 2008; **78**: 347.

Urinary Tract Infections and Hematuria

▼ Continued from page 18

Appendix: Genitourinary infections and definitions

Terms	Definition
Bacteriuria	Bacteria in the urine, can be symptomatic or asymptomatic
Pyuria	White blood cells in the urine; pyuria without bacteriuria rule out tuberculosis, calculi, cancer
Colonization	ASB in the absence of symptoms or pyuria
Bacterial cystitis	Culture positive results
Acute pyelonephritis	Infection that involves the parenchyma and renal pelvis caused by gram negative bacteria (<i>Proteus</i> producing urease) and is ascending; sometimes confused with pancreatitis and appendicitis; in addition to positive leukocytosis and nitrites on urinalysis, sedimentation rate may be increased; urinalysis may indicate pyuria, bacteriuria, proteinuria, hematuria.
Chronic pyelonephritis	Usually originates in childhood as a result of vesicoureteral reflux; if left untreated, can progress to end stage renal disease, renal atrophy, scarring of calyces, calyceal distortion, tubular degeneration.
Uncomplicated UTI	UTI occurring in a normal urinary tract of a healthy individual; most common organism is <i>E. coli</i>
Complicated UTI	UTI occurring in a functionally or structurally abnormal urinary tract; most common organism is <i>Enterococcus</i>

Geriatric Urology: Demographics, Theories and Physiology of Aging, and Common Clinical Conditions in Older Adults

Tomas L. Griebeling, M.D., MPH, The Landon Center on Aging and University of Kansas, Kansas City, Kansas

Ted M. Johnson, II, M.D., MPH, Birmingham/Atlanta GRECC, Department of Medicine and Epidemiology, Emory University, Atlanta VA Medical Center, Decatur, Georgia

Definitions

The term “geriatrics” refers to the study and clinical care of older adults, which in the United States has traditionally included people older than 65 years. However, this definition is partially a social construct because that is the age when Medicare and Social Security benefits usually begin. As more people live to a longer and healthier older age, many clinicians would argue that geriatrics may be more descriptive of care for those older than 70 or 75 years. Geriatrics forms a large part of urological health care because of the diseases that affect older adults.

Population Demographics

Ongoing changes in the population will have continued influence on the urological needs of the elderly. Currently, adults older than 65 years comprise about 13% of the total U. S. population but this is expected to increase to approximately 20% of our population by 2030.¹ Approximately 10,000 people turn 65 years old each day in the U. S. and those older than 85 years represent the fastest growing segment of our population.

This worldwide phenomenon occurs in essentially all areas except for portions of Africa where longevity is lower due to infectious diseases and other endemic health conditions. This sharp increase in the elderly population will translate into increased needs for quality primary and urological care.

Theories of Aging

Several general theories have been proposed to explain the natural but inevitable process of aging of humans and other living organisms,² all of which have scientific plausibility and are not necessarily mutually exclusive. An evolutionary approach would suggest that multiple mutations occur within an organism over time, leading to a state of antagonistic pleiotropism and subsequent decline in organ system function. More physiological theories attribute the aging process to genetic errors in DNA sequencing or alterations in mitochondrial function. Free radicals and other forms of oxidative stress may influence aging at a cellular level associated with shortening of telomeres and development of apoptosis or programmed cell death. Another theory suggests immune modulation as

▼ Continued on page 20

Geriatric Urology: Demographics, Theories and Physiology of Aging, and Common Clinical Conditions in Older Adults

▼ Continued from page 19

a primary contributor. It is most likely that a combination of these factors leads to the overall changes observed with human aging.

Physiology of Aging

All organ systems in the human undergo definable changes that occur naturally with aging, and influence structure and function. There are important changes to the genitourinary system which may cause functional alterations. In the kidney atherosclerosis and other vascular issues lead to a decrease in renal blood flow and size of the renovascular bed.³ These changes in cortical vasculature eventually lead to an approximately 25% reduction in renal mass, which leads to a decrease in glomerular filtration and creatinine clearance of about 10 ml per minute per decade. Urine concentrating capacity, and renin and aldosterone production decrease, causing impaired ability to excrete drugs and other toxins, and greater challenges with fluid and electrolyte balance. It is important to remember that because of changes in muscle mass and multiple other factors, serum creatinine level may not be an accurate predictor of actual renal function, particularly in frail elderly patients.

Changes in the bladder include a relative decrease in detrusor smooth muscle and an increase in collagen deposition, which lead to decreased bladder wall compliance and contractility, and a reduction in overall bladder volume.⁴ Alterations in neurotransmitter production and function in the urothelium may cause alterations in the sensory perception of bladder filling, which can lead to changes in behavior associated with the frequency and efficacy of voiding. Changes in prostatic architecture include hyperplasia of the stroma, and hyperplasia and involution of the glandular elements, which can lead to obstructive voiding symptoms in many elderly men. Other disorders, including prostatitis and prostate cancer, are associated with aging.

Alterations in penile physiology may be associated with erectile and sexual dysfunction, which is related to changes in the microvascular and larger blood vessels, and in the tissues of the corpus cavernosum. Emerging data have shown that erectile dysfunction may be a marker condition for other underlying pathological conditions such as diabetes, metabolic syndrome, heart disease and hypertension. Testicular function changes with aging as characterized by a reduction in number and function of seminiferous tubules, which tends to cause decreased testicular size and softer consistency on palpation. Leydig cell response to gonadotropins is decreased, leading to

a reduction in serum testosterone levels. The most common testicular malignancy seen in elderly men is lymphoma.

From a more general perspective, overall functional reserve capacity decreases, which in turn leads to a diminished ability to respond to internal and external stressors. The interaction among altered physiology, impaired functional reserve and stress response, and chronic comorbidity makes clinical decision making in this population much more challenging. Recently there has been keen interest in frailty as a clinical entity that can influence many other conditions. Key physical changes as components of the frailty phenotype are loss of muscle strength, easy fatigability, difficulty rising from a chair or walking independently, reduced grip strength and unintentional weight loss.⁵ The relationships between frailty and other health outcomes including urinary incontinence, falls and fractures, and mortality are the subject of ongoing research.

Common Clinical Conditions

Urological malignancies, benign prostatic hyperplasia (BPH), urinary incontinence, pelvic organ prolapse, urinary tract infections (UTIs), and erectile and sexual dysfunction comprise the various urological conditions that have a high incidence and prevalence in older adults. UTI, hematuria and nocturia will be used as examples of the unique aspects of clinical evaluation and treatment for urinary conditions in elderly patients.

Urinary Tract Infections

UTI is a combination of bacteriuria and pyuria usually associated with inflammation in the urothelium of the bladder (cystitis) or kidneys (pyelonephritis). UTI needs to be differentiated from asymptomatic bacteriuria (ASB) which occurs frequently in older adults.⁶ Common symptoms of UTI include irritative voiding symptoms (urgency, frequency and dysuria), fever and chills. However, due to alterations in the immune system, many older adults may instead present with symptoms such as lethargy, anorexia or confusion. UTI needs to be treated with antibiotics, and urine cultures with drug susceptibilities are important in guiding appropriate therapy. In contrast, ASB occurs in approximately 20% of postmenopausal women and 5% to 10% of elderly men, and it does not generally require antibiotic treatment. Elderly men may have symptomatic epididymitis or prostatitis which should be treated with antibiotics.

The most common organisms causing UTI in elderly patients are gram negative coliform bacteria, particularly *Esch-*

Geriatric Urology

▼ Continued from page 20

erichia coli, and Enterococcus and Enterobacter species. Recurrent infections with multiple different organisms should prompt evaluation for possible genitourinary fistula. Topical estrogen therapy in postmenopausal women can help prevent UTI by re-acidifying the vaginal fluid, allowing Lactobacillus, a natural host defense, to grow in the vagina.⁷ Another potential benefit of this therapy is a reduction in vaginal irritation and improvement in dyspareunia in older sexually active women. Although controversial, some data suggest that cranberry supplements may reduce the risk of UTI in older adults.⁸ Chemicals in cranberry appear to prevent the adherence of the bacteria to the urothelium.

Urinary retention is common in older adults but no absolute volume of residual urine has been established to increase the risk of UTI.⁹ Retention may be caused by obstruction due to BPH or poor detrusor contractility. Intermittent catheterization is preferable to indwelling catheters to minimize infection risk, and helps reduce the risk of falls, urethral and bladder neck erosion, and other injuries associated with indwelling catheters.

The choice of antibiotic therapy to treat symptomatic UTIs should ideally be based on culture and susceptibility results, and drug interactions with other medications must be considered. Additionally, changes in renal and hepatic metabolism with aging may preclude use or require alterations in dosing for some antibiotics.

Hematuria

Hematuria is a common condition in older adults. The American Urological Association has published guidelines regarding the definitions, evaluation and management of hematuria in adults.¹⁰ Gross hematuria may be associated with voiding difficulty, particularly if the patient has clot retention. Microscopic hematuria is defined as the presence of greater than 3 red blood cells per high power field on at least 2 separate specimens. Because hematuria may be associated with significant genitourinary pathology, such as bladder or kidney cancer, stones, trauma, or infection, additional evaluation is indicated.¹¹

History and examination are important to determine the characteristics of hematuria including duration, frequency and associated pain. Exposure history such as tobacco use, environmental chemicals or analgesic abuse is important. Additional evaluation typically involves a contrast based upper tract imaging study such as abdominal and pelvic

computerized tomography, and cystourethroscopy. In elderly patients with impaired renal function kidney ultrasound and retrograde pyelography can be used to avoid intravenous contrast administration. Urine cytology specimens and examination of biomarkers also help evaluate for potential malignancy in these patients.

Many older adults are receiving anticoagulant medications to prevent cardiovascular problems such as myocardial infarction or stroke, which may increase the risk of hematuria. However, hematuria cannot be attributed solely to anticoagulation because 15% to 20% of patients will be found to have underlying genitourinary pathology that may require treatment.¹² If the initial evaluation is negative and hematuria persists, repeat examination may be warranted. Referral for nephrology consultation should also be considered, particularly if the patient has evidence of possible renal pathology, which includes hypertension and proteinuria.¹³

Nocturia

Nocturia, defined as waking from sleep at night to void,¹⁴ is a common and bothersome condition¹⁵⁻¹⁷ associated with poor sleep,¹⁶ higher rates of absenteeism from work,¹⁸ increased risk of accidental falls^{19,20} and a higher rate of mortality.²¹ It is much more common in older than younger adults.² It is important to understand the etiology and treatment of nocturia in older adults. First, the usual simplified framework of disease is that exposure or a single cause results in the incidence of a disease condition (for example, exposure to influenza virus leads to clinical influenza and repeated tobacco exposure may lead to lung cancer). While nocturia might be considered a problem of low volume urinary void or overproduction of urine, it not only affects the bladder but the kidney as well. Interestingly, nocturia has been associated in several studies with increased mortality.^{21,22} Epidemiological studies linking nocturia with increased mortality are relatively new and these data are sparking debate. That nocturia might be related to increased mortality suggests that it can be considered more broadly to be an indicator or marker of underlying health, and not simply a bladder symptom.

Because nocturia is a symptom known to be related to many other diseases and conditions (overactive bladder syndrome, benign prostatic enlargement, obstructive sleep apnea, congestive heart failure),²³ management involves identifying the relevant conditions and deciding on therapy.^{24,25} There is a growing appreciation that not all of

▼ Continued on page 22

Geriatric Urology

▼ Continued from page 21

the reasons that people are waking up at night is to urinate, and that sleep disorders may cause people to awaken and then falsely attribute the sleep disruption to the need to void. Most treatment guidelines focus on an initial attempt to identify and treat the “primary cause.” However, there are often multiple risk factors of nocturia²⁵ and no single factor is present in more than 50% of patients.¹⁵ Indeed, a patient might have multiple likely causes for nocturia, making many single intervention strategies only modestly effective.^{26,27} Multicomponent therapy may include behavioral modification designed to change fluid intake patterns and improve sleep hygiene, treatment for peripheral edema, a bladder relaxant and an alpha-blocker.²⁸ This framework of multicomponent therapy was developed for the treatment of accidental falls and delirium, and is probably a more familiar concept in geriatric medicine.²⁵ There may even be a role for nondrug therapy, such as pelvic floor muscle exercises, for nocturia in men and women.^{28,29}

Conclusions

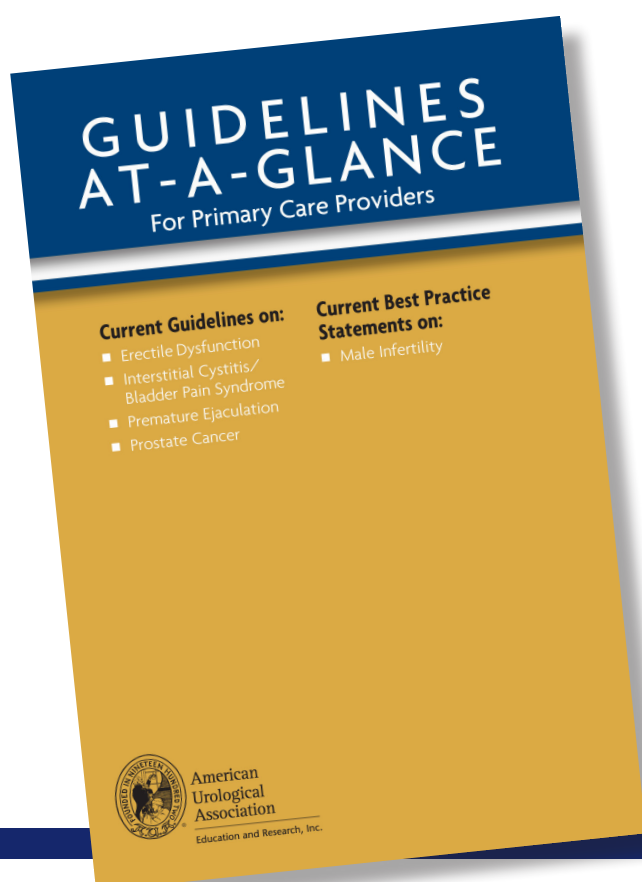
Urological conditions are common in older adults, and elderly patients comprise a significant part of the urological health care population. Primary care providers are well suited to provide initial evaluation and management for many urological conditions in older adults. Close collaboration between primary care providers and urologists may help optimize this care.

1. United States Census Bureau. www.census.gov.
2. Kelly DP: Cell biology: ageing theories unified. *Nature* 2011; **470**: 342.
3. Perico N, Remuzzi G and Benigni A: Aging and the kidney. *Curr Opin Nephrol Hypertens* 2011; **20**: 312.
4. DuBeau CE: The aging lower urinary tract. *J Urol* 2006; **175**: S11.
5. Fried LP, Ferrucci L, Darer J et al: Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci* 2004; **59**: 255.
6. Chenoweth CE and Saint S: Urinary tract infections. *Infect Dis Clin North Am* 2011; **25**: 103.
7. Ewies AAA and Alfhaily F: Topical vaginal estrogen therapy in managing postmenopausal urinary symptoms: a reality or a gimmick? *Climacteric* 2010; **13**: 405.
8. Howell AB, Botto H, Combescure C et al: Dosage effect on uropathogenic *Escherichia coli* anti-adhesion activity in urine following consumption of cranberry powder standardized for proanthocyanidin content: a multicentric randomized double blind study. *BMC Infect Dis* 2010; **10**: 94.
9. Palese A, Buchini S, Deoma L et al: The effectiveness of the ultrasound bladder scanner in reducing urinary tract infections: a meta-analysis. *J Clin Nurs* 2010; **19**: 2970.
10. Jung H, Gleason JM, Loo RK et al: Association of hematuria on microscopic urinalysis and risk of urinary tract cancer. *J Urol* 2011; **185**: 1698.
11. Grossfeld GD, Wolf JS Jr., Litwin MS et al: Asymptomatic microscopic hematuria in adults: summary of the AUA best practice policy recommendations. *Am Fam Phys* 2001; **63**: 1145.
12. Descazard A, Robert G, Lebdaï S et al: Impact of oral anticoagulation on morbidity of transurethral resection of the prostate. *World J Urol* 2011; **29**: 211.
13. DeCoster C, McLaughlin K and Noseworthy TW: Criteria for referring patients with renal disease for nephrology consultation: a review of the literature. *J Nephrol* 2010; **23**: 399.
14. van Kerrebroeck P, Abrams P, Chaikin D et al: The standardisation of terminology in nocturia: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodynam* 2002; **21**: 179.
15. Tikkinen KA, Auvinen A, Johnson TM 2nd et al: A systematic evaluation of factors associated with nocturia: the population-based FINNO study. *Am J Epidemiol* 2009; **170**: 361.
16. Endeshaw Y: Correlates of self-reported nocturia among community-dwelling older adults. *J Gerontol A Biol Sci Med Sci* 2009; **64**: 142.
17. van der Vaart CH, Roovers JP, de Leeuw JR et al: Association between urogenital symptoms and depression in community-dwelling women aged 20 to 70 years. *Urology* 2007; **69**: 691.
18. Kobelt G, Borgstrom F and Mattiasson A: Productivity, vitality and utility in a group of healthy professionally active individuals with nocturia. *BJU Int* 2003; **91**: 190.
19. Stewart RB, Moore MT, May FE et al: Nocturia: a risk factor for falls in the elderly. *J Am Geriatr Soc* 1992; **40**: 1217.
20. Vaughan CP, Brown CJ, Goode PS et al: The association of nocturia with incident falls in an elderly community-dwelling cohort. *Int J Clin Prac* 2010; **64**: 577.
21. Nakagawa H, Niu K, Hozawa A et al: Impact of nocturia on bone fracture and mortality in older individuals: a Japanese longitudinal cohort study. *J Urol* 2010; **184**: 1413.
22. Kupelian V, Fitzgerald MP, Kaplan SA et al: Association of nocturia and mortality: results from the Third National Health and Nutrition Examination Survey. *J Urol* 2011; **185**: 571.
23. Weiss JP and Blaivas JG: Nocturia. *Adv Exp Med Biol* 2003; **539**: 751.
24. Weiss JP, Blaivas JG, Bliwise DL et al: The evaluation and treatment of nocturia: a consensus statement. *BJU Int* 2011; **108**: 6.
25. Vaughan CP, Endeshaw Y, Nagamia Z et al: A multicomponent behavioural and drug intervention for nocturia in elderly men: rationale and pilot results. *BJU Int* 2009; **104**: 69.
26. Johnson TM 2nd, Burrows PK, Kusek JW et al: The effect of doxazosin, finasteride and combination therapy on nocturia in men with benign prostatic hyperplasia. *J Urol* 2007; **178**: 2045.
27. Johnson TM 2nd, Jones K, Williford WO et al: Changes in nocturia from medical treatment of benign prostatic hyperplasia: secondary analysis of the Department of Veterans Affairs Cooperative Study Trial. *J Urol* 2003; **170**: 145.
28. Burgio K, Goode P, Johnson TM 2nd et al: Behavioral versus drug treatment for overactive bladder in men: the male overactive bladder treatment in veterans (MOTIVE) trial. Unpublished data.
29. Johnson TM 2nd, Burgio KL, Redden DT et al: Effects of behavioral and drug therapy on nocturia in older incontinent women. *J Am Geriatr Soc* 2005; **53**: 846.

UROLOGIC EDUCATION FOR PRIMARY CARE PROVIDERS

Throughout our 100-year history, the American Urological Association (AUA) has dedicated itself to promoting the highest standards of urological clinical care through physician education, research and health policy.

The AUA is pleased to offer educational opportunities for primary care physicians looking to enhance their knowledge in treating common urologic conditions and to help improve patient care.



NEW CLINICAL GUIDELINES-AT-A-GLANCE FOR PRIMARY CARE PROVIDERS

Visit www.AUAnet.org/PrimaryCareGuidelines
for current guidelines on

- Erectile Dysfunction
- Interstitial Cystitis/Bladder Pain Syndrome
- Premature Ejaculation
- Prostate Cancer

PLUS
Current Best Practice Statements on
Male Infertility



American
Urological
Association

Education and Research, Inc.



**American
Urological
Association**

Education and Research, Inc.
1000 Corporate Boulevard
Linthicum, MD 21090