Best of the 2008 AUA Annual Meeting

Highlights from the 2008 Annual Meeting of the American Urological Association, May 17-22, 2008, Orlando, FL

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Key words: Tumor markers • Early prostate cancer antigen • Prostate cancer gene 3 • TMPRSS2-ERG • Prostate-specific antigen • Cryotherapy • High-intensity focused ultrasound • Focal therapy • Ultrasound-estimated bladder weight • Intravesical prostatic profusion parameter • Alpha-blocker therapy • Elocalcitol • Lithium triboride laser • Chronic pelvic pain syndromes • Overactive bladder syndrome • Stone formation • Shock wave lithotripsy • Bariatric surgery

Over 2100 posters, abstracts, and videos were presented at the 2008 annual meeting of the American Urological Association (AUA), held this year in Orlando, Florida, from May 17 through 22. The editors of *Reviews in Urology* have culled the enormous volume of information from this premier source and present here the findings most relevant to the practicing urologist.

Reviewed by Michael K. Brawer, MD, URIDEA; Danil V. Makarov, MD, Alan W. Partin, MD, PhD, The Johns Hopkins Medical Institutions and Hospital; Claus G. Roehrborn, MD, FACS, University of Texas Southwestern Medical Center; J. Curtis Nickel, MD, FRCSC, Queen's University; Shing-Hwa Lu, MD, PhD, National Yang-Ming University School of Medicine; Naoki Yoshimura, MD, PhD, University of Pittsburgh; Michael B. Chancellor, MD, William Beaumont Hospital; Dean G. Assimos, MD, Wake Forest University School of Medicine.

Prostate Cancer

Tumor Markers

As in recent years, prostate tumor markers were a major subject at the meeting. Herein are highlighted those abstracts felt most important and based on assays that are either currently available or will likely come online in the near future.

The impact of obesity on serum prostate-specific antigen (PSA) levels continues to be of interest to investigators. Grubb and associates[1] sought to determine if plasma volume was the reason that obesity is associated with lower PSA levels. Utilizing the database of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, they evaluated 28,336 men. Using established formulas to determine body mass index (BMI) and plasma volume, the authors concluded that increased plasma volume in obese men diluted a relatively fixed amount of PSA, resulting in lower serum values. Validation of this investigation using more accurate isotopic determination of plasma volume would certainly be a useful additional investigation.

Chang and colleagues[2] studied the effect of weight gain on PSA and PSA velocity (PSAV) in healthy young men. More than 8100 men younger the 51 years were investigated using 3 PSA determinations. PSA levels negatively correlated with BMI. Older men had a higher PSAV. Intriguingly, men who gained weight during the study had a lower PSAV ($P < .001$). These findings, if confirmed, may mandate stability of weight when utilizing PSAV for clinical decisions.

Banez and colleagues[3] investigated whether PSA predicts adverse pathology in men who are obese, as in weight-appropriate individuals. They examined 2 databases comprised of over 3500 men who underwent radical prostatectomy. They found that there was no statistically significant

difference based on BMI on the ability of PSA to identify Gleason score, positive margins, extracapsular disease, seminal vesicle extension, or positive lymph nodes. Moreover, BMI did not affect the ability of preoperative PSA to predict biochemical recurrence.

The so-called early prostate cancer antigen (EPCA) has been the subject of several studies. Leman and associates[4] identified a new epitope of this protein, EPCA-2.19. They evaluated 328 serum specimens from men with serum PSA levels 2.5 ng/mL and negative biopsies, men with clinical BPH, and men who had organ-confined or extracapsular disease at radical prostatectomy. Amazingly, this assay revealed that a cutoff of 0.5 ng/mL provided specificity of 100% and sensitivity of 91%. Although some suggest these results are too good to be true, if these findings are reproduced in other investigations EPCA-2.19 would be the most accurate assay yet developed for prostate cancer testing.

The prostate cancer gene 3 (PCA3) was the subject of several excellent papers. Wang and coworkers[5] evaluated 173 men prior to a 12-core prostate needle biopsy. PCA3 was obtained by a post–digital rectal examination (DRE) urine specimen before the biopsy. The authors demonstrated significant improvement in overall accuracy for PCA3 compared with PSA. Moreover, they demonstrated significant correlation of positive biopsies with increasing PCA3 level ($P = .0001$).

Chun and associates[6] tested various PCA3 cutoffs in 432 men undergoing repeat prostate biopsy. Cancer was detected in 120 patients (27.8%); both PSA and PCA3 were significantly different in those with cancer. The most informative PCA3 score cutoff was 17, which provided a sensitivity of 80% and a specificity of 45.5%. PSA at a 4.0 ng/mL cutoff afforded higher sensitivity (90%) but significantly lower specificity (9.9%). Although the improved specificity of PCA3 certainly renders it useful in deciding who should undergo repeat biopsy, improvements in test sensitivity would certainly be highly beneficial and would make this assay a major part of evaluating a man with a negative biopsy.

Haese and associates[7] conducted a multi-institutional PCA3 investigation of 432 men undergoing repeat biopsy. Univariate and multivariable analysis was conducted with inputs including age, DRE, PSA, percentage of free PSA, prostate volume, and PCA3. On repeat biopsy, 27.8% of men showed cancer. PCA3 was a statistically significant and independent variable ($P = .006$); PCA3 was the most significant univariable and resulted in significant predictive accuracy ($P = .001$). The authors concluded that PCA3 "meets all criteria of a novel clinically useful marker and should be considered in future clinical practice and applications such as nomograms."

TMPRSS2-ERG gene fusion is a putative novel marker for prostate cancer. Mosquera and colleagues[8] sought to uncover its prevalence in US men. Prior studies showed that discrepancies with gene fusion are found in 36% to 54% of radical prostatectomy single-institution series, but in only 15% of Swedish men in watchful-waiting programs. The authors studied men undergoing needle biopsies at 5 centers. One hundred thirty-four patients had assessable TMPRSS2-ERG gene fusion product on needle biopsy cores as identified by fluorescence in situ hybridization (FISH). Intriguingly, none of the benign cores showed this genetic change, whereas 46/100 cancer cores demonstrated gene fusion ($P < .001$). There was no association with the Gleason score; however, fusion was more commonly found in cribriform growth pattern, cores with blue-tinged mucin, and macronucleoli. The 100% specificity in this study obviously makes this an important marker for further development.

We continue to identify intriguing subforms of PSA. Jansen and associates[9] investigated proPSA and benign prostatic hyperplasia–associated PSA (BPSA) in serum samples from 226 men with and 179 without prostate cancer from the European Randomized Screening for Prostate Cancer study and from 174 men with and 177 without prostate cancer from the University of Innsbruck. In a multivariate analysis, the Innsbruck cohort showed the best predictor of cancer was proPSA density. Cross-validation with the Rotterdam cohort showed significant increase in predictive power. The conclusion of this study is that proPSA in 2 disparate populations provides a significant improvement in cancer detection.

The ability of PSA velocity (PSAV) to predict non–organ-confined disease was studied by Bektic and coworkers.[10] This group examined 366 men in whom at least 3 PSA determinations were made within 4 years of radical prostatectomy. They divided the patients into 4 cohorts based on PSAV. Whereas only 10.6% of men with less than 0.4 ng/mL/year showed non–organ-confined disease, 28.2% of men with PSAV higher than 1.5 ng/mL/year revealed extracapsular tumor. These data support the importance of PSAV before definitive therapy and may allow stratification of men for neoadjuvant trials.

PSA is a member of the Kallikrein class of neutral serine proteases. Vickers and colleagues[11] investigated a panel of associated protein in 753 men undergoing biopsy. In addition to PSA, free PSA and hK2 improved

the predictive accuracy of PSA alone from 0.68 to 0.83. Using a 20% risk of cancer as a threshold, the authors found they could eliminate 60% of biopsies and would miss 17% of cancers, of which only 3% were high grade. Issues with this study include the clinical acceptance (and legal implications) of missing this many cancers and the economic implications of measuring 3 analytes.

Different PSA assay tests give different results on the same blood sample. The magnitude of this potential problem was reexamined by Loeb and associates.[12] The established standard upon which manufacturers base their assay are the Hybritech (now Beckman) assay, which was the first PSA to be approved for testing, and the WHO standard, which is made up of 90% complexed PSA and 10% free PSA. PSA measures with assays based on the WHO standard give a lower result than those standardized by the Hybritech method. This has obvious implications for initial testing and for monitoring patients. The authors examined 1916 specimens from men undergoing screening. All specimens were assayed with the Beckman (Hybritech) and Bayer Centaur (WHO) assays. The median serum PSA level was 0.9 ng/mL by the Bayer method and 1.05 ng/mL using the Beckman assay. The mean serum PSA level was 3.45 and 4.79 ng/mL, respectively. Ninety-four men would have been recommended for biopsy using 1 method but not the other if using a cutoff at 2.5 ng/mL.

A similar investigation of the impact of different manufactured assays was reported by Chun and associates.[13] They compared a nomogram developed based on the Abbott method (WHO) with the Roche approach. The mean (median) PSA and PSA and percentage free PSA for the Abbott method was 7.1 (6.2) and 17% (14.9%) and 7.7 (7.0) and 13.3% (12%), respectively. The accuracy of the nomogram was 78.2% using the Abbott method and 65.4% using the Roche values method.

The implications of these papers are profound. Patients must be tested with the same method on initial evaluation and during management. Not doing so may result in clinical decisions based on spurious results.
[Michael K. Brawer, MD]

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Focal Therapy

There were many exciting discoveries in the field of prostate cancer presented at this year's meeting. Among the most interesting and the most controversial were data presented by various groups on focal therapy for prostate cancer. A sizeable number of abstracts were presented by researchers utilizing cryotherapy for ablation of prostatic tissue; much of these data are becoming more mature with longer term follow-up. New data on high-intensity, focused ultrasound were presented as well, and these data are of great interest to clinicians in the United States, as this technology will soon be investigated by the Food and Drug Administration for potential use in this country. Also discussed were the pitfalls of cryotherapy, both from an oncologic and a reconstructive perspective.

Katz and colleagues[14] described an updated series of men treated with primary prostate cryoablation. These men were tracked using data entered by many different physicians, both academic and community, across the country who participated in the Cryo On-Line Database (COLD) registry; although such voluntary reporting does lead to inconsistencies within the data, the authors felt that any sort of reportable outcomes from this new treatment modality are an important contribution to the literature. Data on 2558 men was available, but only the 415 men with greater than 5 years of follow-up were included in this analysis.

Men treated with cryotherapy are an older and higher risk cohort than most radical prostatectomy series. Mean age was 69.9 ± 7.2 years, mean preoperative PSA level was 10.4 ± 27.7 ng/mL, median Gleason sum was 7 (range, 3-10), and median tumor stage was T2a. Median time to failure was not reached for any group stratified by the D'Amico risk classification system. Complicating the ability to interpret these data are several important factors: (1) 215 patients went on androgen deprivation therapy (ADT) after the procedure. The length of time on ADT is not known. (2) Failure was defined as 3 consecutive PSA rises, a method formerly used, but now abandoned by, the American Society for Therapeutic Radiology and Oncology (ASTRO). (3) Positive biopsy was not counted as a failure, as there was no standardized protocol to perform biopsy in this cohort. Only 1.2% of men were reported to have developed a rectal fistula and only 1.6% of men were incontinent at 12 months. However, only 40.9% of men were able to return to sexual intercourse at 24 months.

Although there is no way to verify whether underreporting or physician-reported outcomes represent a bias in this data set, some tentative conclusions may be drawn. If we can believe the data, then primary cryotherapy is a safe procedure, with the major side

effect being erectile dysfunction; however, longer term outcomes are still necessary to demonstrate its oncologic efficacy.

A number of variations on cryotherapy were also reported. Jones and associates[15] examined the outcomes of 275 men with stage T3 prostate cancer treated with cryotherapy from the COLD registry. In comparison to the overall group in the prior study, men in this cohort had higher PSA (mean, 14.8 ± 16.1 ng/mL) and slightly younger age (mean, 68.3 ± 7.9 years). Median cancer stage was T3b and median Gleason score was 7. Again, because of the logistics of the COLD registry, there is no way to determine whether the seminal vesicles were specifically treated even though median stage described seminal vesicle involvement. Again, length of hormonal therapy in the 59 patients started on ADT was unavailable and the follow-up time (mean, 29.3 ± 24.7) is not long enough to assess true oncologic outcome. However, as 50 of the 138 patients rebiopsied had cancer, it is unlikely that this type of focal therapy is destroying all of the prostate cancer in the patient. The authors, though, conclude that this therapy is a safe alternative for patients with advanced cancer, but this recommendation should properly come with a caveat.[16]

Further work was presented on salvage cryoablation for prostate cancer recurrent after radiotherapy. Pisters and coworkers[17] found 413 men in the COLD registry who had demonstrated local recurrent cancer after definitive radiotherapy. Clinical characteristics were similar to those men treated with primary cryoablation. Mean age was 70.2 ± 6.8 years, mean PSA was 8.5 ± 12.8 ng/mL, median Gleason score was 7 (range, 2-10), and median tumor stage was T2a. Mean follow-up was 24.9 ± 28.3 months, and 53 patients went on hormone therapy after cryoablation; it is not clear how many of these patients were hormone naive nor which patients underwent external beam or brachytherapy nor what dose the patients had received. The rectal fistula rate was low (0.8%), whereas incontinence was 6.3% at 12 months and sexual potency was only 37.8%. This is further follow-up of a somewhat more established practice.[18] As there are few safe options for these men, a safe ablative procedure has more acceptance than the use of cryotherapy in a setting where an effective therapy already exists.

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A more controversial abstract was presented by Ellis and colleagues,[19] who are the first to examine the role of partial prostate cryoablation in a large series (341 patients from the COLD registry). These men, in contrast to the populations in the other abstracts, had a median clinical stage of T1c, mean serum PSA level of 6.8 ± 7.0 ng/mL, and median Gleason score of 6; these patients, at first glance, might be good candidates for any form of therapy. Recurrence-free survival was 82.6% ± 3.2% at 18 months. Rectal fistula rate was 3.3%, incontinence was 1.6% at 3 months, and potency was greater than 74% at 3 years; all of these outcomes are the best of the groups. Adjuvant ADT was not discussed. The authors point out that this modality demonstrates low morbidity, but that its acceptance will be dictated by long-term disease-free rates.

Cryoablation, however, is not the only focally ablative technology available. High-intensity focused ultrasound (HIFU) made a quite a stir at the meeting as well. Conort and a group from Association Française d'Urologie published the results of their first prospective study of patients treated with HIFU who had 5 years of follow-up.[20] The authors used either 1 or 2 sessions of HIFU using the Ablatherm® (EDAP, Lyon, France) machine. In contrast to the COLD registry, data from this cohort had more standardized criteria: hormone naive, treatment naive, serum PSA levels less than 15 ng/mL, Gleason scores lower than 8, less than 50% positive biopsy cores, prostate volumes less than 50 cc, and clinical stage less than T3.

Of the 117 patients included, 49 were stage T2. Mean age was 69 years (range, 47-79), mean serum PSA level was 8.4 ± 3.4 ng/mL (range, 1-15), and median Gleason score was 6 (range, 2-7). Fifty-six (47%) patients required 2 sessions of HIFU, whereas 52% needed some form of re-treatment. There were no cancer-related mortalities and 9 non–cancer-related mortalities; 11 patients were lost to follow-up. Twenty-four patients (22%) experienced HIFU treatment failure; 13 underwent radiation, 10 underwent ADT, and 1 underwent prostatectomy. After over 5 years follow-up, 55 patients (75% of those no undergoing adjuvant therapy) were considered treatment successes. Serum PSA nadir after the first session, according to the authors, seems to be related to success, although no formal analysis is included.

In contrast to the COLD registry, these data are significantly more uniform and perhaps easier to interpret for a patient prior to treatment. However, similar to the COLD registry, the follow-up is not sufficiently long to

determine true oncologic efficacy. A similar abstract comes from a group in the United Kingdom. Zacharakis and coworkers[21] reported their results with the Sonablate® 500 (Focus Surgery, Indianapolis, IN), a visually directed HIFU device, in 172 patients with clinically localized disease. The mean age (64.1 years [SD 8.3]) was younger than in the other series and their follow-up (346 days [SD 237, max 759]) was shorter. Bicalutamide was administered in 50 (29%) of patients in the 3 months prior to treatment to reduce prostate size. Actuarial analysis was not performed; however, patients with serum PSA levels less than 0.2 ng/mL for those who reached 3, 6, 9, 12, 18, and 24 surveillance months were observed in 69.7% (108/155), 65% (78/120), 58% (60/103), 57.8% (48/83), 57% (36/63), and 60.9% (14/23), respectively. Thirteen patients with an elevated or rising PSA had positive biopsies, 4 of whom were treated with repeat HIFU. Although overall 92.4% were deemed disease free, the authors report a 36% stricture rate, worse with patients having a urethral catheter rather than a suprapubic tube. Stress urinary incontinence was seen in 13 patients (7.6%).

Although the authors state that good early biochemical control can be achieved, the urethral stricture rate seems somewhat high. It is also curious that other groups do not report this seemingly startling frequency of urethral stricture. The authors do state that they are working to improve this complication.

Two other abstracts discussed the complications of HIFU. Thueroff and associates[22] analyzed the rate of rectourethral fistula rate with 3MHz HIFU therapy. The authors reported 27 (1.4%) recto-urethral fistula, only 1 of which came in a case of primary HIFU for localized cancer. They observed that fistula formation rates were related more to tissue pretreatment (such as previous transurethral resection of the prostate, radiation, or other surgery), tumor stage, and technology used rather than the application of HIFU transrectally. They conclude that improved software, rectal cooling, and robotic rectal distance control have made recto-urethral fistula formation after HIFU more rare.

Andrich and colleagues[23] report on the treatment of recto-urethral fistula after salvage HIFU for prostate cancer recurring after radiation therapy. The authors describe 8 patients who developed fistulae 3 to 8 months after salvage HIFU. All patients had initial loop colostomy and suprapubic cystostomy. Four patients with fistula after external beam therapy followed by HIFU underwent salvage prostatectomy with omental wrap. Three patients with fistula after external beam and brachytherapy followed by HIFU underwent redo vesico-urethal anastomosis with inferior pubectomy and interposition of either gracilis or omental flaps. One patient elected to forego further repair. After repair, the patients' colostomies were taken down and urethral incontinence was managed with a convene sheath or with artificial urinary sphincter. All patients healed their fistulae with resolution of their perineal pain, but all were incontinent afterward.

A final abstract of interest calls into question the oncological basis of these focal therapies. Wang and coworkers[24] investigated 100 radical prostatectomy specimens that preoperatively satisfied the criteria for low volume disease[25] (< 3 positive cores; $< 50\%$ involvement of any positive core; Gleason score < 7) and that had unilateral positive needle cores. This would presumably qualify a patient for focal therapy. The authors found that the mean number of tumor foci per specimen was 2.9. In 65% of specimens there was tumor on the side of the prostate contralateral to the side of the initial positive biopsy. Thirteen percent of men had tumors greater than 0.5 cm^3 on the side contralateral to the initial positive biopsy. The authors conclude that, even in this highly selected population that would presumably qualify for focal therapy, prostate cancer is multifocal. Focal therapy would inadequately treat prostate cancer in 65% of these men. What is impossible to determine is whether these different foci have different likelihoods of metastasis and whether focal ablation of a dominant focus can affect an oncologic cure.

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[Danil V. Makarov, MD, Alan W. Partin, MD, PhD]

Lower Urinary Tract Symptoms (LUTS) and Benign Prostatic Hyperplasia (BPH)

As in years past, approximately 5% or 96 of over 2100 abstracts at the annual meeting covered the areas of LUTS and BPH: Twenty posters were presented in the Basic Research section, 12 presentations made up the podium session on the Epidemiology and Natural History of LUTS and BPH, and 12 presentations made up the podium session on Evaluation and Markers. Medical and Hormonal Therapy issues were presented in 12 podium sessions and a total of 40 posters were dedicated to Surgery and New Technology, much of it being occupied with a discussion of new and

old lasers used for the treatment of BPH.

Basic Research

Much effort has been expended on the issue of alpha receptors in tissues of the lower urinary tract. Researchers such as Dr. Debra Schwinn from Seattle, Washington, have speculated based on their own research that, although the $alpha_{1A}$ receptor in the prostate may be most important in terms of the relief of the typical voiding or obstructive symptoms, the $alpha_{1D}$ receptor, which she found to be present in the detrusor muscle, might be responsible for irritative or storage symptoms. Thus, selective blockage of the $alpha_{1D}$ receptor might in turn be an effective therapeutic target for the treatment of overactive bladder (OAB) or storage symptoms.[26] It is in this context that the contribution by Hampel and colleagues[27] is of some interest. The authors examined 73 detrusor specimens of patients with prostate cancer who had undergone preoperative pressure-flow studies. They divided the population into 23 normal men, 25 men with mostly voiding symptoms, 10 men with mostly storage symptoms, and 15 men with both voiding and storage symptoms. Tissue RNA was extracted and revertly transcribed into cDNA, and the expression of $alpha_{1A, B}$, and $_{D}$ receptors was analyzed. The authors found that bladder dysfunction was neither associated with a significant alteration of absolute $alpha_{1}$ adrenoceptor gene expression, nor did the relative subtype shares change considerably between the groups of normal, mostly voiding, mostly storage, or mixed symptomatology. In all groups, the $alpha_{1A}$ subtype receptor was most prevalent and $alpha_{1B}$ and $alpha_{1D}$ contributed roughly equal to the remainder of the total receptor expression. Although this is certainly not an unequivocal proof that the $alpha_{1D}$ receptor does not play a role, it does partially clarify the question of whether different symptomatologies are associated with different expression levels of receptor subtypes. (See Table 1.)

Recently, several phase II studies have reported on the clinical efficacy of luteinizing hormone releasing hormone (LHRH) antagonists that, in contrast with the LHRH agonists used in the treatment of prostate cancer, induce a nearly immediate reduction in serum testosterone that is dose dependent. Even without achieving a reduction of serum testosterone to castrate level, and only achieving such partial reduction for a period of 4 weeks, these injectable agents have shown efficacy in the treatment of LUTS and BPH lasting approximately 6 months. Engel and coworkers[28] presented evidence of the expression of messenger mRNA for LHRH receptors in 33 of 35 BPH specimens, and 18 of 20 (90%) of the samples showed a single class of specific, high-affinity binding sites. One of the LHRH antagonists, Cetrorelix, showed high-affinity binding to the LHRH receptors expressed in BPH tissue. The authors speculate that the expression of the specific receptor proteins for LHRH in human BPH provides a rationale for the effect that LHRH antagonists have on improving LUTS and BPH symptomatology in men.

The Astellas Best Basic Science Poster Award was given to the work presented by Irina Grishina,[29] who examined the role of the Notch-1 pathway and its interference by bone morphogenic protein 7 (BMP-7) in the developing prostate gland. The authors have already reported in 2005[30] on the inhibition of branching morphogenesis in the prostate gland by BMP-7 and its interference with Notch signaling. The authors demonstrated that Notch-1 activity is associated with formation of a prostate bud and that Notch-1 signaling is derepressed in BMP-Null urogenital epithelium. The authors propose a model that BMP-7 inhibits branching morphogenesis in the prostate and

Table 1
Quantitative RT-PCR Results (Mean ± SD)

Urodynamic Pattern	Alpha 1a/GAPDH Amplification Ratio	Alpha 1b/GAPDH Amplification Ratio	Alpha 1d/GAPDH Amplification Ratio	Total Alpha 1/GAPDH Amplification Ratio
Normal	3.6 ± 5.3	1.2 ± 0.9	1.4 ± 0.5	6.2 ± 6.9
Obstructive-non irritative	2.1 ± 3.8	0.7 ± 0.3	0.8 ± 0.8	3.5 ± 4.6
Obstructive-irritative	4.2 ± 8.1	1.0 ± 0.5	1.1 ± 1.1	6.4 ± 9.4
Non obstructive-irritative	2.2 ± 2.8	0.8 ± 0.5	1.3 ± 0.9	4.3 ± 3.6

Reprinted from Hampel et al,[27] with permission from the American Urological Association.
GAPDH, glyceraldehyde-3-phosphate dehydrogenase; RT-PCR, reverse transcription-polymerase chain reaction.

limits the number of domains with high Notch-1 activity. It should be noted that BMP-7 has been shown to regulate branching morphogenesis of the lacrimal duct by promoting mesenchymal proliferation and condensation by a different group of investigators from the Children's Hospital Research Foundation in Cincinnati.[31]

Several studies have demonstrated the clinical effectiveness of phosphodiesterase type 5 (PDE-5) inhibitors upon lower urinary tract symptoms in men. Substances such as sildenafil, taldafil, and vardenafil have been shown to have efficacy in the improvement of symptoms, bother, and quality of life associated with BPH. None, however, have shown an effect on maximum urinary flow rate. This paradox has caused some degree of consternation on the part of investigators and the pharmaceutical industry. Based on the presence of phosphodiesterase isoenzymes in the lower urinary tract tissues, it had been assumed that these compounds may affect LUTS by inducing a relaxation of the smooth muscle and, thus, acting in a way similar to the presumed mechanism of action of alpha-receptor blockers, which exert their action through the adrenergic nervous system.

Two groups studied this topic and specifically asked whether phosphodiesterase inhibitors add to the relaxation effect of alpha-blockers in isolated human prostate tissue strips. The research group from UroSphere[32] presented a poster in which they showed that the combination of the alpha-blocker alfuzosin and the PDE-5 inhibitor tadalafil showed a greater relaxant effect than alfuzosin alone. In a very similar setup, a group from Paris[33] demonstrated using the same compounds (alfuzosin and tadalafil) that the combination achieved a statistically significant improvement in the relaxing effect. The group observed that this potentiation is similar to the value observed in human isolated corpus cavernosum tissue when alfuzosin and tadalafil are combined and suggests that this might be the reason for the clinical efficacy of phosphodiesterase inhibitors in LUTS and BPH. We await research in this area as a urodynamic study is currently underway that examines the effect of tadalafil upon pressure-flow parameters in men with LUTS and BPH. (See Figure 1.)

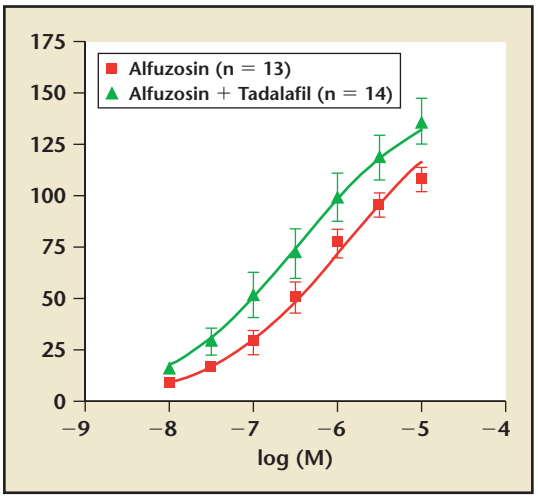


Figure 1. *Alfuzosin and tadalafil show a greater relaxant effect than alfuzosin alone. Reprinted from Palea S et al.*[32]

Epidemiology and Natural History

The Boston Area Community Health Study (BACH) is a tremendous resource regarding the epidemiology and natural history of LUTS in men and women. It is a survey of urologic symptoms in a racially and ethnically diverse population and uses a multistage cluster design to sample 5503 adults, aged 30 to 79, of which 2301 are men and 3202 are women, 767 are black, 1877 are Hispanic, and 1859 are white. Interviews are conducted in the respondent's home and analyzed at the New England Research Institute (NERI). No fewer than 8 abstracts were presented from the BACH survey at this year's meeting. The effect of urologic symptoms upon peoples' quality of life was presented by Link and associates.[34] For this particular analysis, information regarding urologic symptoms and comorbidities, such as self-reported cardiac disease, hypertension, diabetes, stroke, chronic lung disease, arthritis, cancer, and dyslipidemia, were collected. The effect of urological symptoms and comorbidities on quality of life for men and women are depicted in a graph (Figure 2), where the physical health and mental health components of the SF-12 are plotted on the *x*- and *y*-axis, respectively. The significant impact that urologic symptoms have on the quality of life for both men and women with overactive bladder associated with incontinence is clearly the most important issue, not only in terms of physical health, but also in terms of mental health.

Carol Link presented another interesting abstract on the question of whether American's expanding waistline increases the likelihood of urological symptoms.[35] This analysis between adiposity and LUTS suggests that for men the association of urological symptoms and adiposities are often U-shaped, whereas in women the prevalence of urological symptoms

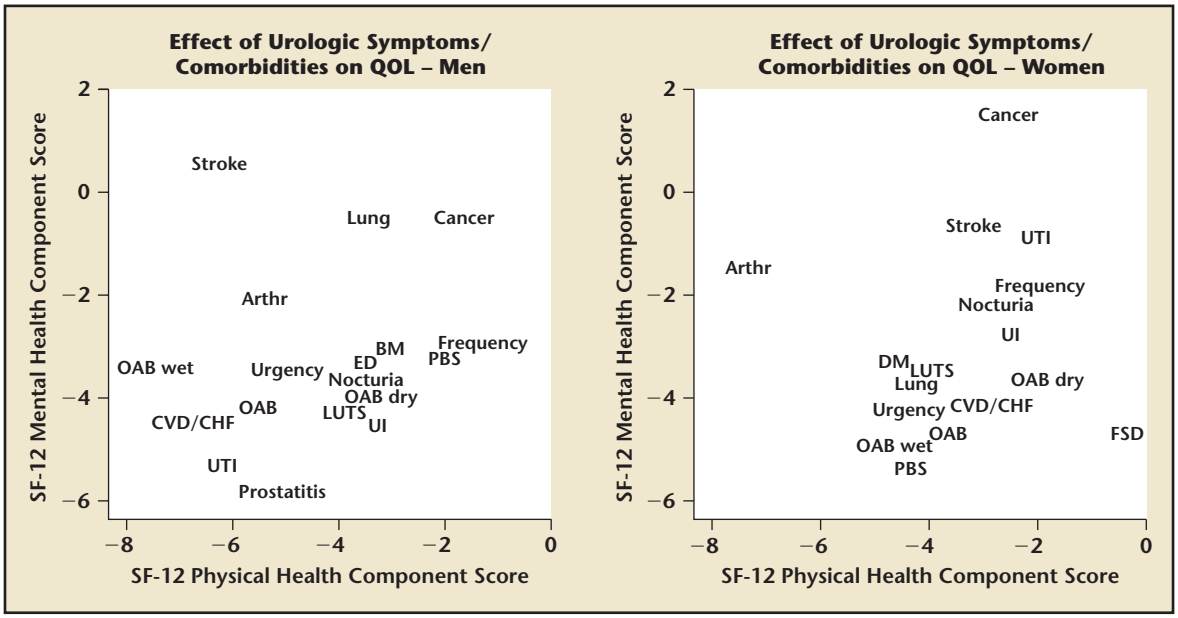


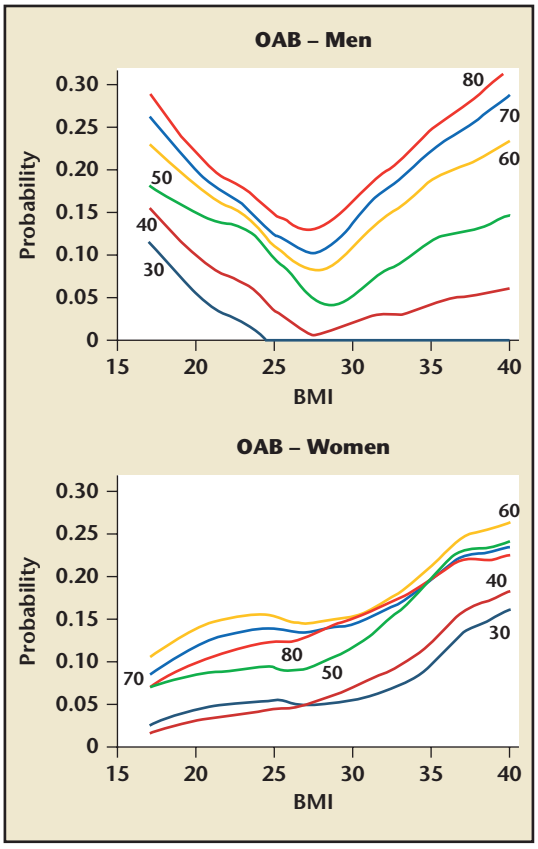
Figure 2. *Effect of urologic symptoms and comorbidities on quality of life (QOL). Reprinted from Link and McKinlay,[34] with permission from the American Urological Association.*

seem to increase with increasing adiposity. This suggests different pathophysiological pathways for treating men and women and that some urological symptoms may be eliminated through weight reduction. (See Figure 3.)

In a separate abstract from the BACH study, Travison and colleagues[36] reported that the U-shaped association between body mass index and LUTS appears to be accounted for by U-shaped association with fat mass in men, whereas lean mass exhibited little association with LUTS, also suggesting that control of fatness may be effective for controlling LUTS.

Another excellent natural history study is the Krimpen study, a longitudinal study on the natural history of LUTS among men aged 50 to 78 years living in Krimpen aan den Ijssel in the Netherlands.[37] In this study, with over 4300 person-years of follow-up, 180 events were recorded in which men moved from an International Prostate Symptom Score (IPSS) below 7 to an

Figure 3. *For men, the association of urological symptoms and adiposities are often U-shaped, whereas in women the prevalence of urological symptoms seem to increase with increasing adiposity. OAB, overactive bladder symptoms. Reprinted from Link and McKinlay.[35]*



IPSS over 7, defined as development of moderate-to-severe LUTS symptomatology. The authors performed multivariate age-adjusted analysis to identify determinants for reaching a moderate-to-severe symptom severity level and identified as significant functional bladder capacity, postvoid residual, treatment for cardiac disease, history of a first- or second-degree relative with prostate cancer, use of antidepressants, erectile dysfunction, and increase in PSA levels. Specifically, the use of antidepressants was associated with a hazard ratio of 2.74, treatment for cardiac disease with a hazard ratio of 2.48, and a PSA from 1 to 3 versus less than 1 associated with a hazard rate of 1.7, whereas a PSA of greater than 3 had the highest hazard ratio of 2.86. The authors, however, are quick to add that more than 50% of men not having any of these risk factors will still get the clinical diagnosis of BPH between the ages of 50 and 80.

Evaluation and Markers

Several ultrasound-derived markers were studied by different groups of investigators and provided important information about these markers and their usefulness in the initial evaluation and follow-up of men with LUTS and BPH. The BVN 6500 is a handheld, 3-dimensional ultrasound device that allows the user to measure residual urine volume, bladder surface area, bladder wall thickness, and a parameter called ultrasound-estimated bladder weight (UEBW), which is based upon the calculation of surface area wall thickness and wall thickness. It had been speculated in the literature that UEBW would be a useful parameter in assessing the level of obstruction and in following patients during conservative or medical therapy for BPH.[38]

Housami[39] examined 34 patients who underwent urodynamic testing with the device. UEBW was found to be only weakly correlated with bladder outlet obstruction, although it did differentiate it between men with detrusor overactivity (mean UEBW, 53.1) and those who did not have detrusor overactivity (mean UEBW, 48.9).

Sauver and coworkers[40] also used the BVN 6500 in the clinic cohort of the Olmsted County Study of Urinary Symptoms in Men. They found that bladder wall thickness and bladder surface area were more strongly related to symptom severity, peak flow rate, prostate volume, and postvoid residual volume compared with the UEBW; these findings are similar to those from the group from Bristol, reported by Housami.[39]

Intravesical prostatic protrusion parameter and bladder wall thickness have a role in the assessment and evaluation of men with lower urinary tract symptoms and benign prostatic hyperplasia, particularly when considering that they are essentially noninvasive and can be used as a proxy parameter for the absence or presence of obstruction and possibly for the prediction of response to various therapeutic interventions.

Another parameter derived from ultrasound is the intravesical prostatic protrusion parameter (IPP). It is assessed by performing either abdominal or transrectal ultrasound of the partially filled bladder and prostate, measuring the protrusion of the prostate gland on the sagittal view relative to the bladder base. The parameter is classified as grade I if it is 5 mm or less, grade II if it is 5 mm to 10 mm, and grade III if it is greater than 10 mm. This measure has thus far only been popularized by Dr. Foo (Singapore) in a series of publications.[41]

The IPP parameter was tested by Lieber and associates,[42] again using the Olmsted County Community Study for Men and, specifically, 318 patients in the clinic cohort. In this study, 44 or 13.8% had an IPP higher than 10 mm, whereas 60.7% of men had no detectable protrusion. The authors found that age was not correlated with IPP, but there was an inverse correlation with maximum urinary flow rate and a positive correlation with total prostate volume, serum PSA levels, and obstructive symptoms, but no such correlation with the irritative symptoms. Dr. Foo and coworkers[43] presented data on a cohort of men treated nonsurgically, that is, with medical therapy. Clinical progression was defined as an increase in the symptom score by more than 4 points, acute urinary retention, or a persistently elevated postvoid residual volume of greater than 100 mL or requiring surgery, such as transurethral resection of the prostate (TURP). By univariate analysis using men with a grade I IPP as a reference group, the unadjusted odds ratio for clinical progression was 5.1 and 16.4 for men with grade II and III, respectively. In a multivariate analysis, the odds ratio was 6.8 and 19.2 when comparing men with grade II and grade III with those with grade I, respectively. Lastly, Tandogdu and associates[44] examined 45 men with a mean age of 66 and also found that IPP and bladder wall thickness, assessed ultrasonographically, were of greatest significance in predicting the presence or absence of bladder outlet obstruction by invasive urodynamic measures compared with the symptom severity level, prostate volume, or postvoid residual volume.

It appears that measures such as IPP and bladder wall thickness have a role in the assessment and evaluation

of men with LUTS and BPH, particularly when considering that they are essentially noninvasive and can be used as proxy parameter for the absence or presence of obstruction and possibly for the prediction of response to various therapeutic interventions. Whether UEBW as calculated by the BVN 6500 software is equally useful remains to be determined.

Medical and Hormonal Therapy

The BPH Registry is a multicenter observational disease registry that prospectively collects demographic, clinical, and quality-of-life data and tracks BPH management by both urologists and primary care physicians. Three abstracts were presented from the registry at this year's meeting.

Wei and coworkers[45] observed in 3649 men with 5235 follow-up visits that watchful-waiting strategies were associated with only a minimal change in total IPSS, BPH Impact Index, and Quality of Life measures. All medical therapy—most significantly, however, the selective alpha-adrenergic receptor blockers—were associated with a significant improvement in the Quality of Life and BPH Impact indices as well as IPSS score.

Miner and coworkers[46] examined factors associated with changes in management of patients enrolled in the registry. Only 10%, or 379 patients, had a change in BPH management in a multivariate adjusted model, greater LUTS, severity and bother, International Index of Erectile Function (IIEF) Sexual Health Inventory for men, and management by urologists. These factors were associated with a change from watchful waiting to medical therapy, where there was a higher BPH Impact Index and higher symptom score associated with a change from medical therapy to another medical therapy that could be triggered by avoidance of sexually related side effects.

Finally, Rosen and colleagues[47] examined the effect of concomitant PDE-5 inhibitor medications in the registry. Of 5178 men, 2688, or 52%, were on BPH medical therapy and 27% were using the PDE-5 inhibitors. Patients on watchful waiting tend to use more PDE-5 inhibitors than those on medical therapy, and in those patients, the PDE-5 inhibitor appeared to be associated with a significant decrease in IPSS, whereas in those men on medical therapy there were no notable changes between those with or without PDE-5 inhibitors. This could be interpreted in several different ways, and 1 interpretation would allow for the possibility that PDE-5 inhibitors do not have an additive effect to existing medical regimens for BPH, although they impart a beneficial effect on patients on watchful waiting.

As in past years, the concept of adding an antimuscarinic agent to an already existing alpha-blocker regimen in patients particularly bothered by storage or OAB symptoms generated significant interest. Herschorn and colleagues[48] reported on the ADAM study, in which tolterodine extended release was added to an already existing regimen with an alpha-blocker in a placebo-controlled study involving nearly 660 patients. The addition of tolterodine to the existing alpha-blocker regimen improved micturition, urgency episodes, and severe urgency episodes per 24-hour period significantly, as well as improving the storage domain of the IPSS, whereas the voiding domain improved in a nonsignificant manner. (See Table 2.)

Kaplan and colleagues[49] performed a single-institutional study in which 45 men with refractory OAB on alpha-blocker therapy were randomized to tolterodine, solifenacin, or darifenacin in addition to their existing alpha-blocker regimen. As it turned out, under all 3 regimens patients experienced an improvement in 20-hour frequency, urgency, and the total in-storage component of the IPSS. The authors concluded that add-on antimuscarinic agents were a reasonable strategy, but also suggested that the darifenacin was less well suited due to increased rate of constipation and other side effects, as well as significant increase in postvoid residual

Table 2
Changes in Bladder Diary Variables and IPSS Scores at Week 12

Assessment	TER + Alpha-Blocker (n = 329)	PBO + Alpha-Blocker (n = 323)	Treatment Difference
Diary variables, LS mean change ± SD			
Micturitions per 24 h	−1.8 ± 0.1	−1.2 ± 0.1	$P = .0079$
Urgency episodes per 24 h	−2.9 ± 0.2	−1.8 ± 0.2	$P = .0010$
Severe urgency episodes per 24 h	−1.1 ± 0.1	−0.7 ± 0.1	$P = .0495$
Frequency-urgency sum	−7.8 ± 0.6	−5.4 ± 0.6	$P = .0065$
IPSS, mean change ± SD			
Total	−4.5 ± 5.9	−3.8 ± 6.7	$P = .4223$
Storage domain	−2.6 ± 2.9	−1.9 ± 3.2	$P = .0370$
Voiding domain	−1.8 ± 4.0	−1.9 ± 4.3	$P = .7655$

IPSS, International Prostate Symptom Score; LS, least squares; SD, standard deviation.
Reprinted from Herschorn et al,[48] with permission from the American Urological Association.

urine volume not seen with the other antimuscarinic drugs used.

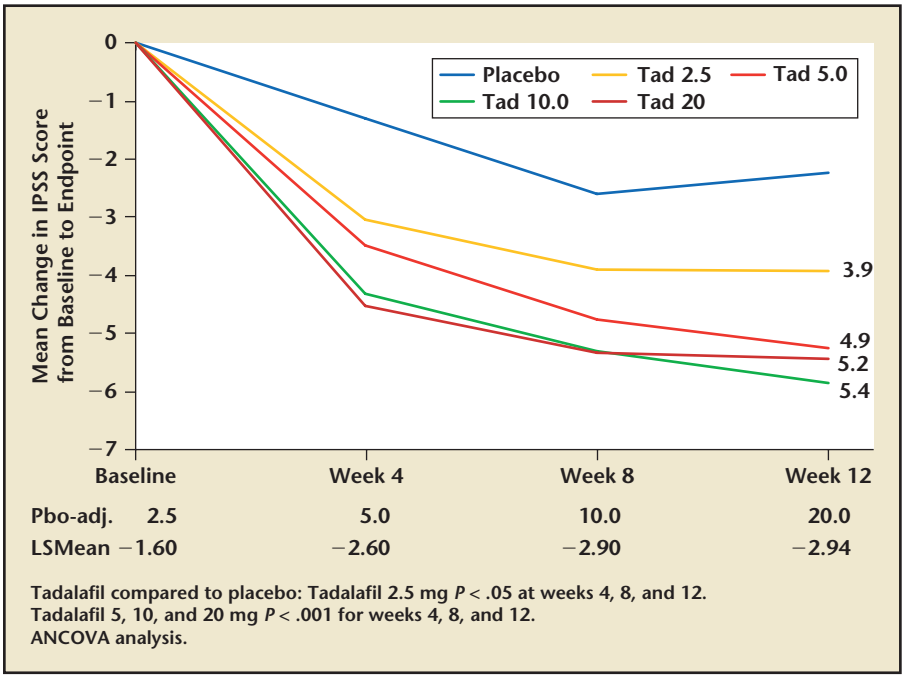
The Combination of Avodart® and Tamsulosin (CombAT) study is a 4-year trial enrolling more than 4800 patients into 1 of 3 arms with either Avodart® (GlaxoSmithKline, Philadelphia, PA) 0.5 mg daily, tamsulosin 0.4 mg daily, or a combination of both medications. Patients had to be 50 years or older with an IPSS of 12 points and, more importantly, had to have an enlarged prostate with a volume of 30 cc or greater and a PSA level of 1.5 or greater. The overall study results have been reported in the *Journal of Urology*.[50] Two separate analyses were presented at this year's meeting. Barkin and colleagues[51] reported on improvements in quality of life in different treatment arms. The main findings were an overall benefit of combination therapy over both monotherapies in improving Quality of Life and BPH Impact indices throughout the 24 months prior to interim analysis. The test drug proved to be numerically superior to tamsulosin in terms of improvement on quality-of-life questions and the BPH Impact Index in prostate volumes 42 and greater, which encompasses the upper 2 tertiles of the CombAT study, whereas in the lower most tertile, which includes prostate volumes from 30 to 42 g, tamsulosin was numerically superior to dutasteride, although both were inferior to the combination therapy.

Becher and associates[52] analyzed the impact of dutasteride and tamsulosin and combination therapy on storage and voiding symptoms, also stratified by prostate volume. The conclusion of this analysis was that there was a differential effect between dutasteride and tamsulosin on voiding scores, but not on storage symptoms. Dutasteride provides greater relief than tamsulosin in voiding symptoms at 24 months, whereas the effect on storage symptoms is comparable to tamsulosin. Regardless of stratification and symptoms, combination therapy was superior to both individual therapies.

As was already mentioned, the use of PDE-5 inhibitors in the treatment of men with LUTS and BPH was of significant interest at this year's meeting. To this end, Eli Lilly conducted a dose-ranging study administering tadalafil 2.5, 5.0, 10.0, and 20 mg daily compared with placebo over a period of 12 weeks in a 5-group multinational study of efficacy, dose response, and safety in men with LUTS and BPH. This particular abstract[53] was presented in the late-breaking science forum on Tuesday, May 20, a new and apparently quite successful feature of the AUA program. The results of the study were that tadalafil at 5, 10, and 20 mg daily improved IPSS by 4.9, 5.2, and 5.4 points, respectively, at 12 weeks, whereas the improvement against placebo was 2.6, 2.9, and 2.94 points, respectively. With nearly a 3-point improvement against placebo and an excellent safety profile, it appeared that the daily 5-mg tadalafil dose was suitable for the long-term treatment of men with LUTS and BPH. Although no effect was seen regarding flow rate and postvoid residual urine volume, the improvement was independent of the presence or absence of erectile dysfunction at baseline, and thus, it was not an indirect effect induced by improvement of erectile function. These findings will likely be explored further in phase II and III studies and perhaps lead to an additional indication for the PDE-5 inhibitors in our aging male population.

Fitzpatrick and colleagues[54] reported on a worldwide survey of 3785 men who suffered from acute urinary retention secondary to BPH. A multivariate analysis was presented that emphasized factors favoring or not favoring the success of trial without

Figure 4. *Tadalafil at 5, 10, and 20 mg daily improved the International Prostate Symptom Score (IPSS) by 4.9, 5.2, and 5.4 points, respectively, at 12 weeks, whereas the improvement against placebo (pbo) was 2.6, 2.9, and 2.94 points. Reprinted from Roehrborn,[53] with permission from the American Urological Association.*



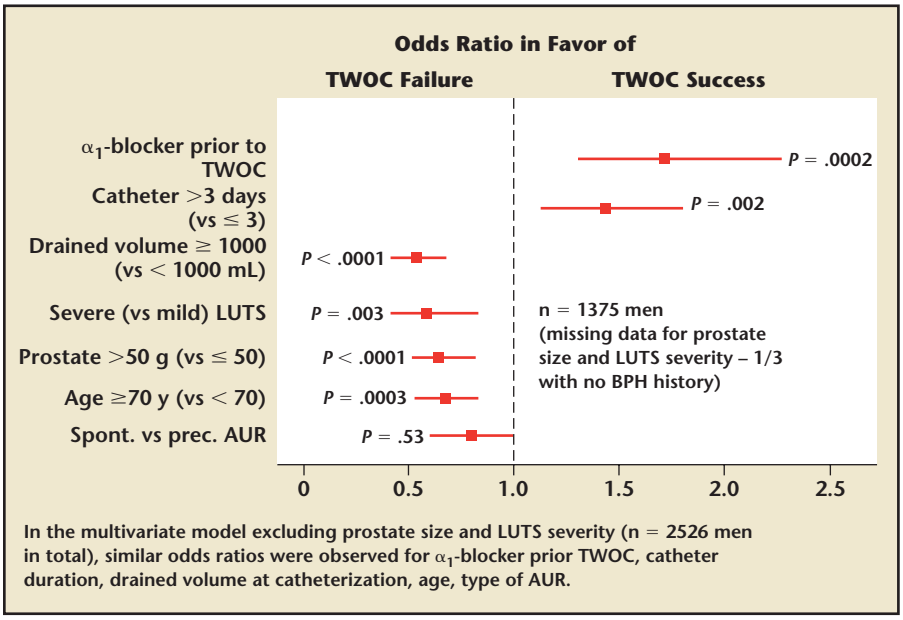


Figure 5. *A 3-day catheterization with immediate initiation of alpha-blocker therapy is the standard of care in the management of patients with acute urinary retention (AUR), hopefully leading to a 60% or greater success in the initial trial without catheter (TWOC). LUTS, lower urinary tract symptoms. Reprinted from Fitzpatrick et al.*[54]

catheter (TWOC). As Figure 5 demonstrates, alpha-blocker therapy with catheterization for 3 days or greater is associated with a successful TWOC, whereas retained volumes of over 1 L, severe LUTS, prostates over 50 g, and age over 70 years and a history of spontaneous acute urinary retention (AUR) are negative predictive factors. This multivariate analysis is very useful for any physician who manages AUR in everyday practice or emergency department settings. It is quite clear from this and other relevant literature that a 3-day catheterization with immediate initiation of alpha-blocker therapy is the standard of care in the management of patients with acute urinary retention, hopefully leading to a 60% or greater success in the initial trial without catheter.

Finally, a new compound was introduced to the attendees of the meeting. Elocalcitol, a vitamin D_3 analogue, was tested against placebo either alone or in combination with an alpha-blocker in men with LUTS and BPH.[55] There is evidence that elocalcitol plays a role in prostate physiology and acts upon several different mechanisms. It interferes with the vitamin D_3 receptor, but it also appears to have anti-inflammatory and antiproliferative activities.[56,57] In animal experimentation, it has been shown to suppress bladder overactivity and prevent prostate growth in dog models. An initial clinical study was reported in 2006. At this year's meeting, data were presented in which patients underwent transrectal magnetic resonance imaging to determine accurate prostate volumes. In the elocalcitol 75-mg group, the prostate volume increase was 1.52%, whereas it was 0.54% in the 150-mg group. In the placebo group, however, the total prostate increase was as expected by natural history predictions of 3.52% with significant difference to the 150-mg dose. At the same time, the compound had a positive and significant effect mostly on urgency and frequency–storage symptoms. The compound is remarkably free of side effects and is very well tolerated. It is likely that the company will pursue further trials and perhaps embark upon a protocol focusing on patients most likely to be susceptible to the combined mechanisms of action involving antiproliferative, anti-inflammatory, and overactive bladder types of activity.

There is evidence that elocalcitol plays a role in prostate physiology and acts upon several different mechanisms.

Minimally Invasive Treatments

In contrast to previous meetings, only 1 abstract was presented strictly falling into the category of minimally invasive surgical treatment. Mynderse and colleagues[58] presented 5-year follow-up data on a multicenter trial of a cooled ThermoCath manufactured by Urologix (Minneapolis, MN) for the TARGIS microwave device. Of 65 patients, 42 reached the 4-year follow-up mark and 28 patients reached the 5-year follow-up. Fundamentally, a 50% improvement in symptom score was observed as well as a roughly 50% improvement in BPH Impact and Quality of Life score and approximately a 3-to-4–mL/second improvement in peak urinary flow rate. One interesting aspect of the presentation was the Kaplan-Meier analysis of freedom from re-treatment. After 5 years, approximately 10% of patients had undergone salvage re-treatment, and an additional 22% of patients had been treated with medications for a total failure rate of roughly 32% at 5 years.

Surgical Treatments

A new laser, a lithium triboride (LBO) laser for photoselective vaporization of the prostate, was presented in 5

abstracts by Dr. Carson Wong from Oklahoma City, Oklahoma.[59-63] The LBO is a 532-nm laser with a variable power setting, from 20 to 120 W, employing a noncontact site firing fiber that allows rapid vaporization of tissue in a hemostatic fashion with minimal loss of vaporization efficiency within fibrous tissue. Initial efficacy data appear quite promising. One-year data suggested an improvement in IPSS from 22 to 4 points and an improvement in the peak flow rate from 10 to 22 mL/second in a cohort that started out with 119 patients, of which 39 were available for 1-year follow-up. Prostate volume was measured preoperatively and at 12 weeks and apparently dropped from 74 to 38 g. Somewhat surprisingly, however, serum PSA level was 2.6 at baseline, 2.4 at 12 weeks, and 3.1 or mostly unchanged at 52 weeks. This would suggest a less-than-optimal removal of tissue and further evaluation of this particular device is awaited.

Elhilali and colleagues[64] compared holmium laser ablation (HoLEP) with photoselective vaporization (PEP) of the prostate in a randomized, perspective trial and found similar efficacy in terms of IPSS improvement, flow rate improvement, and any other outcome parameters in a study of 109 patients over 1 year. A reduction in serum PSA level from 2.8 to 1.6 with the HoLEP and 2.1 to 1.4 in the potassium titanyl phosphate (KTP) procedure was reported with a concomitant decrease in prostate volume at 40% and 34.4%, respectively.

The group from Indianapolis led by Dusing[65] suggested improvement in the HoLEP technique by using a single posterior groove, starting the enucleation at the apex posteriorly, moving the anterior apical advancement past the midline, and employing a mucosal strip and circling technique. Using such techniques, they reported a great improvement in the efficiency of the technique demonstrated by a significant reduction in operating room time in over 250 cases, particularly in prostates with a gland size of over 100 g.

Peter Gilling, who contributed much to the popularity of the holmium laser for BPH treatment, reported on a 7-year follow-up of a randomized trial comparing HoLEP with TURP in urodynamically obstructed patients.[66] Of the original 61 patients, 31 patients were available for follow-up and fundamentally similar outcomes in terms of symptom severity, quality of life, peak flow rate, and other parameters were reported The only distinction was an 18% re-treatment rate in the TURP group compared with a 0% re-treatment rate in the HoLEP group.

[Claus G. Roehrborn, MD, FACS]

Urological Chronic Pelvic Pain Syndromes

The 2008 annual AUA meeting provided a forum for new and exciting developments in the understanding, diagnosis, and treatment of the urologic chronic pelvic pain syndromes, chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and interstitial cystitis/painful bladder syndrome (IC/PBS). This review will focus only on the clinically relevant treatment-based developments presented at this year's meeting.

Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS)

Presentations of treatment trials, attesting to maturation of the research endeavors in this field, dominated the sessions.

Dr. J. Curtis Nickel (for the National Institutes of Health [NIH] Chronic Prostatitis Collaborative Research Network)[67] presented a late-breaking abstract that reported for the first time the results of a randomized, multicentered, double-blind clinical trial evaluating the efficacy and safety of alfuzosin in the treatment of CP/CPPS in recently diagnosed and/or newly symptomatic alpha-blocker–naive patients. Previous studies suggested that prolonged treatment with alpha-adrenergic blocking agents in CP/CPPS patients early in the course of the disorder provides beneficial effect. The investigators compared 12 weeks of treatment with alfuzosin versus placebo in newly diagnosed, alpha-blocker–naive CP/CPPS patients. The primary outcome defined responders as a subject who achieved at least a 4-point decrease in the NIH-Chronic Prostatitis Symptom Index (CPSI). The major secondary outcome was a comparison of subjective global assessment responders, defined as subjects who reported a moderate-to-marked improvement in overall symptoms at the end of the study. The overall withdrawal rate in the 272 CP/CPPS patients was 14.3%, balanced between the alfuzosin and placebo arms. The investigators identified no safety issues. Alfuzosin and placebo decreased the symptoms of CP/CPPS at an identical rate in men diagnosed with this condition within the past 2 years and not previously treated with this drug. The results of this trial do not support the use of alfuzosin as an initial therapy in newly diagnosed alpha-blocker–naive men. The results are a major disappointment

The results of this trial do not support the use of alfuzosin as an initial therapy in newly diagnosed alpha-blocker–naive men. The results are a major disappointment for prostatitis patients and the physicians who treat them.

for prostatitis patients and physicians who treat them, but does not necessarily mean that other, less selective alpha-blockers such as terazosin would not be effective in selected patients (eg, those with associated voiding dysfunction).

Dr. S. W. Lee[68] reported the results of a randomized, double-blind comparison of acupuncture versus sham acupuncture for CP/CPPS. Anecdotal evidence suggests that acupuncture may ameliorate CP/CPPS symptoms but to date, no investigators report results from a randomized, comparative study. In this particular study, investigators randomized 44 subjects to acupuncture and 45 to sham acupuncture. Median NIH-CPSI increased from 25.0 to 14.5 in the acupuncture group and from 25.0 to 19.0 in the sham group ($P = .03$). This study shows that acupuncture is more effective than sham in treating CP/CPPS and suggests that a further study in this area be considered.

Acupuncture is more effective than sham in treating chronic prostatis/chronic pelvic pain syndrome and suggests that a further study in this area be considered.

Dr. G. Morgia and colleagues[69] reported a randomized, multicenter, placebo-controlled study evaluating the treatment of CP/CPPS with *Serenoa repens* plus selenium and lycopene (Profluss®). Investigators randomized a total of 102 category IIIB (noninflammatory) CP/CPPS patients into 2 groups of 52 subjects each to receive the combination herbal therapy (Profluss 320 mg) or placebo once daily for 8 weeks. There was what appeared to be a clinically significant decrease in the total NIH-CPSI score from 27.5 to 13.3 in the treated group, but also a reasonable decrease in CPSI in the placebo group (27.8 to 20.6). Unfortunately, the authors did not compare the between-group changes in CPSI (the relevant treatment effect). It looks like Profluss ameliorates symptoms associated with category IIIb CP/CPPS, but conclusions will have to wait appropriate peer review that will likely insist upon appropriate statistical comparisons of the 2 groups over time.

Dr. H. J. Park[70] reported the efficacy of tadalafil for CP/CPPS by randomizing 78 CP/CPPS men, in a single-blind fashion, to receive either levofloxacin or levofloxacin and tadalafil for 4 weeks. The NIH-CPSI score changed from baseline at 4 weeks to −2.7 in the tadalafil and levofloxacin group compared with −1.2 in the levofloxacin-alone group ($P < .05$). This suggested that tadalafil once daily showed significant symptomatic improvement in CP/CPPS men, however, the magnitude of difference between the 2 groups, although statistically significant, was perhaps clinically insignificant.

Dr. J. D. Dimitrakov and coworkers[71] reported a randomized, sham-controlled trial evaluating pelvic floor electrical stimulation in the treatment of CP/CPPS. The group randomly assigned 77 CP/CPPS patients to receive transrectal electrostimulation protocol or transrectal sham treatment. Procedures were performed twice daily for 1 month and then twice weekly for an additional 5 months. The NIH-CPSI pain score and total score decreased by −2.9 and −4.6, respectively, in the electrostimulation group compared with −1.1 and −1.7, respectively, in the sham group ($P = .001$). The authors concluded that transrectal electrostimulation appears effective in the alleviation of CPPS symptoms. The reviewer notes that this is a very time-intensive therapy and the subjects were able to correctly guess what treatment arm they were in (significant bias), however, if effective (and the authors noted a difference at 1 month), it may be a treatment that can be added to the urologist's armamentarium for the treatment of this condition.

Dr. S. J. Antolak and Dr. C. M. Antolak[72] reported on 31 out of 94 men who originally presented with chronic pelvic pain secondary to pudendal neuralgia who were not improved by monthly perineural injections of bupivacaine and triamcinolone and underwent bilateral decompression surgery of the pudendal nerve via a transgluteal approach. The authors reported that 12 of the 31 men were cured or significantly improved, 7 had no change in symptoms, and 3 were worse. Compression of the pudendal nerve does appear to be a real phenomenon that causes a defined chronic pelvic pain syndrome in men presenting with CP/CPPS, and directed therapy in may benefit some patients.

Interstitial Cystitis/Painful Bladder Syndrome (IC/PBS)

As in other years, the interstitial cystitis session focused on research that attempts to understand further the etiology and pathogenesis of this enigmatic condition. Unfortunately, as is usual in the annual AUA meeting, only a few treatment studies were presented. As our understanding of this condition improves with basic science studies, investigators will evaluate and report new and novel treatment approaches at this meeting. However, with this being said, some studies evaluating exciting and novel treatment approaches were presented this year.

Dr. K. Peters presented a late-breaking abstract describing the results of the NIH Urologic Chronic Pelvic Pain Network (made up of members of the

Chronic Prostatitis Collaborative Research Network and the Interstitial Cystitis Collaborative Research Network)[73] evaluating directed pelvic physiotherapy in a pilot feasibility study. The group randomized 47 patients (male and female) diagnosed with CP/CPPS or IC/PBS to 8 sessions of a standardized, directed physiotherapy focused on the pelvis and pelvic floor or to an unfocused, relaxation massage physiotherapy over the same period of time. Dr. Peters reported that in this small pilot study, IC/PBS patients receiving focused pelvic floor therapy had a statistically and clinically significant improvement in objective global assessment (responders were defined as those that reported moderate or marked improvement) compared with IC/PBS patients who received a relaxation massage therapy. These results were not confirmed in men with CP/CPPS receiving directed pelvic floor therapy. These results are exciting and for the first time (based on the knowledge of this reviewer), specific physiotherapy has been shown to be possibly effective in IC/PBS in a prospective, randomized, sham-controlled clinical trial. This feasibility study (investigators randomized very few patients to each group in this particular study in the IC/PBS arms) indicates that further research is indicated and, in fact, the NIH sponsors an ongoing, definitive clinical trial, properly designed and powered, to determine the efficacy of directed and focused pelvic floor therapy compared with relaxation massage therapy in women diagnosed with IC/PBS.

Interstitial cystitis/painful bladder syndrome (IC/PBS) patients receiving focused pelvic floor therapy had a statistically and clinically significant improvement in objective global assessment compared with IC/PBS patients who received a relaxation massage therapy.

Dr. J. Curtis Nickel and colleagues[74] evaluated the safety and efficacy of intravesical alkalized lidocaine in patients with IC/PBS in a phase II multicenter, placebo-controlled trial. Conversion of local anaesthetics instilled into the bladder to the lipid-soluble base form may not occur because urine is usually acidic, leaving most local anaesthetics essentially ion trapped within the bladder. Previous studies have determined that instilling alkalizing solution after instillation of the lidocaine increases the lidocaine absorption. In this short-term pilot study, 102 patients with IC/PBS were randomized to receive daily instillations of intravesical alkalized lidocaine or placebo (double blind) for 5 consecutive days. At day 15, investigators offered all patients voluntary open-label treatment for 5 more days. Significantly more patients treated with the alkalized lidocaine solution rated their overall bladder symptoms as moderately or markedly improved on the Global Response Assessment (GRA; responders were defined as those with moderate or marked improvement) 8 days following the start of treatment (30.0% and 9.6%, respectively; $P = .012$). Improvement continued at day 15. Eighty-six percent of the patients elected to receive a second course of treatment. Sixty-three percent and 56% reported moderate or marked improvement in GRA on days 22 and 29, respectively. The authors concluded that alkalized lidocaine is effective and safe for the short-term treatment of symptoms of IC/PBS and that maintenance of treatment effect extends beyond the end of treatment. Home use of this approach may be very practical. This approach also allows phenotypic differentiation of bladder pain syndrome patients (allows determination of the bladder contribution to the symptom/pain complex). A longer phase III, randomized, placebo-controlled trial is required and, in fact, planned. [J. Curtis Nickel, MD, FRCSC]

Neurourology

More comments were heard about a presentation by a group from the William Beaumont Hospital (Royal Oak, MI) during and after the 2008 AUA meeting than about any other talk. In 2003, Xiao introduced the idea of restoring bladder function in patients with spina bifida via the creation of a skin-central nervous system-bladder reflex arc.[75] Despite a high reported success rate of 87%, the procedure has not gained widespread acceptance outside of China. Girdler[76] reported the first US results from a study conducted by Ken Peters and associates at the William Beaumont Hospital.

Nine patients with median age of 8 years (range, 6-37 years) were included in the study. The Xiao procedure was performed with intraoperative neurophysiologic monitoring. Of the 9 patients, 5 had a prior defect closure, 3 had intrauterine closure, and 1 patient did not have prior surgery. Postoperative evaluation included neurological examination at 1 month, follow-up questionnaires and urodynamic testing (including attempted stimulation of the reflex arc), and repeat imaging and laboratory test results at 6 months.

Mean operative time was 183 minutes (range, 127-278 minutes). Donor motor roots were L2 in 1 patient, L3 in 3 patients, L5 in 3 patients, and S1 in 2 patients. Mean estimated blood loss during surgery was 57 mL (range, 10-100 mL); no transfusions were

required and no intraoperative complications occurred. The patient length of stay averaged 3.4 days (range, 2-7 days). Perioperative complications included foot-drop in 1 patient, wound drainage in 3 patients, and prolonged inability to bear weight in 1 patient. Initially, neurological examination revealed major changes in gait in a minority of patients and most patients displayed variable weakness of more than 1 lower extremity muscle group. Physical therapy and time returned most patients to baseline. After several months, 3 patients reported a sudden worsening of urinary and/or fecal incontinence and/or increased sensation, followed by improved continence and the ability to initiate voiding. At 6 months, 3 patients were able to voluntarily void with an intermittent flow pattern. Also at 6 months, patient satisfaction was high, with 78% of patients reporting that they would undergo the procedure again.

The bladder nerve rerouting (Xiao) procedure enables patients with spina bifida to voluntarily void as early as 6 months postoperatively.

The bladder nerve rerouting (Xiao) procedure enables patients with spina bifida to voluntarily void as early as 6 months postoperatively. We are looking forward to a larger series with longer follow-up, as this is a truly exciting development in neurourology.

A presentation by Smith and associates,[77] which won the Best Poster ribbon and the Lapides Essay contest in neurourology, examined changes in urothelial adenosine triphosphate (ATP) and nitric oxide (NO) release in normal and spinal cord injured (SCI) animals, as well as in SCI animals treated with botulinum toxin type A (BoNT-A). The study also correlated changes in transmitter release with functional changes in bladder contraction frequency and with efferent nerve function.

Normal and SCI rat bladders were injected with either vehicle (saline with bovine serum albumin) or BoNT-A. In vitro neurotransmitter release, bladder strip contractility studies, and in vivo cystometrographic studies were conducted 2 days after bladder injections. Smith and associates found that resting ATP release was significantly enhanced following spinal cord injury and was unaffected by BoNT-A treatment. SCI greatly increased hypo-osmotic evoked urothelial ATP release, whereas BoNT-A treatment reduced evoked ATP release in bladders. Notably, stimulated hypo-osmotic NO release was somewhat inhibited following SCI, but recovered in BoNT-A–treated rats.

The investigators hypothesize that alterations in the ratio of excitatory (ie, ATP) and inhibitory (ie, NO) urothelial transmitters promote bladder hyperactivity following SCI that can be reversed, to a large extent, by treatment with BoNT-A. It is novel that NO release can be altered by BoNT-A, and this opens new avenues of research.

The investigators hypothesize that alterations in the ratio of excitatory (ie, ATP) and inhibitory (ie, NO) urothelial transmitters promote bladder hyperactivity following spinal cord injury that can be reversed, to a large extent, by treatment with botulinum toxin type A.

Interstitial cystitis/painful bladder syndrome (IC/PBS) is a chronic, inflammatory bladder disease with unknown etiology. Diagnosing the disease is often difficult for general clinicians. Ueda and his team[78] reported a novel new aid to help the cystoscopic diagnosis of IC/PBS: a cystoscope with a narrow band imaging (NBI) system that can detect mucosal angiogenic lesions.

Fifty-two subjects suspected of having IC/PBS were evaluated (49 females, 3 males; mean age, 59 years [range, 19-85 years]). Conventional cystoscopy to examine ulcerative lesions was performed with spinal anesthesia by a urologic specialist. Other health care professionals then made a separate observation of the superficial layer of the bladder mucosa by cystoscopy using the NBI system. Biopsies of the NBI lesions were performed, followed by hydrodistention to examine petechial hemorrhages, and the diagnoses were compared with those obtained using conventional cystoscopy.

Among 52 patients, 37 cases were found to have ulcers by conventional cystoscopy, which were also recognized as capillary-rich brownish areas using the NBI system (100% accuracy); 13 cases were found to have NBI-positive areas without ulcer, which coincided with those with petechial hemorrhages and glomerulations following subsequent hydrodistention; and 2 cases of normal mucosa were detected. Furthermore, 6 cases of bladder cancer (carcinoma in situ) were detected by biopsies that were obtained from the ulcerative lesions positively identified by NBI cystoscopy.

Ueda and associates report an important new development, as examining the bladder mucosa with a cystoscope

with the NBI system makes it possible to detect ulcers of bladder mucosa and areas with angiogenesis. They conclude that because this procedure does not require hydrodistention, IC/PBS diagnosis can be made simply, less invasively, and at lower cost. NBI cystoscopy can clearly indicate the area for biopsy in the case of bladder ulcerative lesions (often difficult to differentiate from bladder carcinoma in situ), thereby enhancing the diagnostic accuracy of IC/PBS.

OAB clinical diagnosis has great variation and is based on subjective symptoms. This study by Chen and colleagues[79] was designed to measure the urinary nerve growth factor (NGF) levels in OAB patients to evaluate whether urinary NGF can be a biomarker for diagnosis. Dr. Kuo is the leader in this new and exciting research area of OAB urine biomarkers. The investigators reported that urinary NGF levels were measured in patients with increased bladder sensation, OAB dry and OAB wet, and in a group of control subjects. They defined the presence of increased bladder sensation as patient reports of symptoms of frequency and nocturia but no urgency or urge incontinence. They defined *OAB dry* and *OAB wet* as patient reports of urgency without and with urge incontinence, respectively. Measurement of urinary NGF levels was performed by enzyme-linked immunosorbent assay (ELISA). The investigators normalized the total urinary NGF levels to the concentration of urinary creatinine (NGF/Cr level).

A total of 197 urine samples were collected. The study subjects included normal controls, patients with increased bladder sensation, and patients experiencing OAB dry and OAB wet. Urinary NGF/Cr levels were very low in normal control and patients with increased bladder sensation. Patients with OAB dry and OAB wet had significantly higher urinary NGF levels compared with the control and patients with increased bladder sensation. Thus, the study suggests that an elevated urinary NGF level is important for mediating the sensation of OAB urgency and could be an important biomarker for OAB diagnosis.

Norepinephrine and serotonin (5-HT) reuptake inhibitors have demonstrated clinical efficacy in the treatment of stress urinary incontinence (SUI). However, the role of serotonergic mechanisms in sneeze-induced urethral continence reflex is not fully understood. In a poster presentation that was selected as the best poster in the session, Miyazato and associates[80] investigated the effect of fluoxetine (a serotonin reuptake inhibitor), 8-OH-DPAT (a 5-HT_{1A} agonist), and mCPP (a 5-$HT_{2B/2C}$ agonist) using a rat model that can examine the neurally evoked continence reflex during sneezing.

Normal female rats and rats with SUI induced by vaginal distension (VD) were used. Sneezes were induced by a rat's whisker, cut and inserted into the nostril. In normal rats, urethral responses were measured using a microtip transducer catheter inserted to the middle urethra from the urethral orifice. The effect of intrathecal (i.t.) fluoxetine, 8-OH-DPAT, or mCPP at the level of L6-S1 spinal cord on the amplitude of urethral responses during sneezing (A-URS) as well as urethral baseline pressure (UBP) was evaluated. In VD rats, sneeze-induced leak point pressure (S-LPP) measurements were performed before and after i.t. injection of fluoxetine, 8-OH-DPAT, or mCPP. In normal rats, A-URS was not changed after fluoxetine (i.t.). However, 8-OH-DPAT (i.t.) decreased A-URS by 49.0%, whereas mCPP (i.t.) increased A-URS by 38.8%. Fluoxetine, 8-OH-DPAT, or mCPP (i.t.) did not change UBP. In VD rats, S-LPP was not changed after fluoxetine (i.t.). However, S-LPP was decreased by 10.4 cm H_2O after 8-OH-DPAT (i.t.), whereas S-LPP was increased by 8.5 cm H_2O after mCPP (i.t.).

These results indicate that urethral sphincter reflexes are regulated by complex balance among facilitatory adrenergic (alpha$_1$) and 5-HT_2 receptors and inhibitory 5HT_{1A} receptors. These mechanisms could contribute to the clinical efficacy of norepinephrine/5-HT reuptake inhibitors in the treatment of SUI in humans.

Many patients report a benefit of cannabinoids for bladder symptoms, but the pharmacology of cannabinoids, especially the peripheral influence of cannabinoids in the bladder, is unknown.[81] In addition, the functional features of CB_1 receptors in the lower urinary tract have not been characterized. Arachidonyl-2-chloroethylamide hydrate (ACEA) is a potent CB_1 agonist with over 1400-fold selectivity for CB_1 receptors over CB_2 receptors.

Tyagi and colleagues[81] performed transurethral open cystometrograms on female rats under urethane anesthesia by continuously filling the bladder with saline. Rats were treated 1 hour prior to induction of bladder irritation by adding 0.125% acetic acid to the infused saline. Treated rats were either instilled with ACEA alone or with a co-administration of ACEA with selective CB_1 antagonist AM251. Dwell time for instillations was 30 minutes. ACEA and AM251 were coformulated into phospholipid liposomes.

Vehicle-treated rats showed a relative intercontraction interval (ICI) decrease after acetic acid infusion relative to ICI in saline infusion. Rats pretreated with GP1a provided a significant protection against bladder irritation as revealed by a marginal ICI reduction. The protective effect of CB_1 agonist ACEA was reversed by co-administering it with excess of CB_1 antagonist AM251. This podium presentation nicely support that locally

administered CB_1 agonists can buffer the pain signals emerging from bladder following acetic acid infusion. Locally administered cannabinoids likely involves action on CB_1 receptors existing in suburothelial nerve plexus for reducing afferent excitability.
[Shing-Hwa Lu MD, PhD, Naoki Yoshimura, MD, PhD, Michael B. Chancellor, MD]

Stone Disease and Endourology

There were a number of excellent papers on stone disease and endourology delivered at the 2008 annual AUA meeting. The highlights of selected papers are reviewed.

Stone Formation

In the majority of cases, stone formation is due to an interaction between genetic and environmental factors. There is a positive correlation between mean annual temperature in a region and stone formation. Theoretically, global warming could influence stone formation. Pearle and colleagues[82] utilized published data on the temperature dependence of stone disease and then applied predictions of temperature increases to estimate the impact of global warming on the incidence and economics of stone disease in the United States. Investigators applied linear and nonlinear temperature-dependence models of stone risk to the predicted mean annual temperature in a geographic region in 2050 to generate an estimate of stone prevalence in that year. The group also predicted cost changes for patient management. The investigators predicted the fraction of inhabitants of the United States living in areas at high risk for stones would increase from 40% in 2000 to 50% in 2050, with a rise in the cost of managing stone patients by $1 billion per year. The group predicted that the impact of climate-influenced changes would not be distributed uniformly; the southern and midwestern regions of the United States are predicted as the hotbeds of stone activity.

Shock Wave Lithotripsy

Urologists commonly utilize shock wave lithotripsy (SWL) to treat patients harboring ureteral or renal calculi requiring stone removal. Animal experimentation demonstrates that shock waves delivered to the kidney cause traumatic lesions, mainly hemorrhagic due to injury of small and medium-sized blood vessels. This may ultimately result in scar formation within the targeted renal unit. Connors and coworkers showed that a positive correlation between the area of hemorrhage and the number and power of shock waves exists.[83] Administering 100 shock waves at 12 kV to the targeted or ipsilateral kidney before the standard amount of energy has been shown to attenuate significantly the hemorrhagic lesion in a porcine model. The investigators conducted a similar experiment in which a priming dose of 100 shock waves delivered at either 12 kV or 24 kV was followed by a 3-minute pause and subsequent delivery of 2000 shock waves at 24 kV. In addition, 2000 shock waves at 24 kV were given without the priming dose. The hemorrhagic lesions involved a mean of 0.39% and 0.5% of the functional renal volumes with the 12 kV and 24 kV priming doses, respectively, as compared with 6% without priming. This indicates that the protective effects are not voltage dependent but are most influenced by the delay between the priming and clinical doses of shock wave energy. Investigators should define the mechanisms behind these responses and conduct clinical trials to assess the efficacy of this renal protective strategy.

It can be difficult to determine when SWL adequately fragments a stone. Consequently, some patients are treated with more shock waves than necessary. Owen and colleagues developed a technique that assesses acoustic scatter from stones to determine stone fragmentation.[84] The group based this technique on the idea that the frequency at which stones vibrate will rise when stones become smaller. The investigators used an ultrasound monitor to determine frequency bands between 0 and 3 MHz. In vitro studies demonstrated that energy shifted to higher frequencies as stones fragmented into smaller pieces. In a clinical setting, urologists could utilize such technology to determine the endpoint in the delivery of shock wave energy.

The investigators predicted the fraction of inhabitants of the United States living in areas at high risk for stones would increase from 40% in 2000 to 50% in 2050, with a rise in the cost of managing stone patients by $1 billion per year.

Residual Stone Fragments

An important goal of any stone-removing procedure is rendering the patient stone free. However, this may not always be possible. Raman and colleagues[85] assessed the natural history of residual fragments in patients subjected to percutaneous nephrostolithotomy. The group followed 42 patients with such fragments for a median of 41 months. Eighteen patients (42.9%) experienced a stone-related event at a median time of 32 months. A multivariate analysis demonstrated that stone fragments greater than 2 mm and fragments

located in the renal pelvis or ureter were predictive of a subsequent stone event. In addition, fragment size greater than 2 mm was associated with the need for a subsequent stone-removing procedure. Urologists can use the information generated from this study to discuss management of residual fragments with patients. A stone-free status remains an important goal, especially in those with larger residual fragments or those located in the renal pelvis or ureter.

Effects of Bariatric Surgery

There is an obesity epidemic in the United States that has prompted performance of more than 150,000 bariatric operations per year. There have been reports of patients developing kidney stones associated with hyperoxaluria after this procedure. In addition, some patients develop oxalate nephropathy. In a study by Patel and coworkers,[86] non–stone-forming adult patients collected 2 24-hour urine specimens 6 months or longer after bariatric surgery via either Roux-en-Y gastric bypass (RY) or biliopancreatic diversion/duodenal switch (DS). Investigators made comparisons between a group of healthy non–stone-forming adults and stone formers from a commercial database. The mean oxalate excretion of the bariatric cohort was 67 mg per day, significantly higher than both other cohorts. The mean oxalate excretion of those subjected to DS was significantly higher than those undergoing RY; 90 mg versus 62 mg. Seventy-four percent of those subjected to bariatric surgery were hyperoxaluric and 26% had profound hyperoxaluria (> 100 mg/day). Therefore, it might be appropriate to evaluate patients who have undergone bariatric procedures with postoperative 24-hour urine testing (> 6 months after surgery) to assess for hyperoxaluria because this metabolic abnormality may place them at risk for stone formation and oxalate nephropathy. ■

[Dean G. Assimos, MD]

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