



THE OFFICIAL NEWSMAGAZINE OF THE AMERICAN UROLOGICAL ASSOCIATION

## The Future of Telehealth Depends on How Congress Will Act

Juan J. Andino, MD, MBA



### Future Investigations to Consider Nocturia a Circadian Rhythm Disorder of the Bladder

Amber S. Herbert, MD  
Ashu Mohammad, PhD  
Claire S. Burton, MD  
Amy D. Dobberfuhr, MD, MS



### Underneath the White Coat: Hypogonadism Among Male Resident Physicians

Gene Austin Krishinger, MD  
Basil F. Mirza, BS  
Kevin J. Campbell, MD, MS



### Lithotripsy for Small, Nonobstructing Renal Calculi

Joseph Borrell, BA  
Kymora B. Scotland, MD, PhD

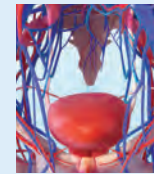


### My Experience as a 2024 AUA/JUA Exchange Program Scholar: An Unforgettable Academic and Cultural Immersion

Nirmish Singla, MD, MSCS, FACS



## INSIDE THIS ISSUE



Developing an Innovative Approach to Neurogenic Bladder Management After Spinal Cord Compromise



A Japanese Urology Resident's Perspective on the AUA Annual Meeting 2024



The Meaning of Mentorship



Understanding the Relationship Between Biofilms and Calcium Stones

## COMING SOON in October

## AUANews<sup>Extra</sup>

- High-Grade Renal Injury Management
- Current Management Strategies for Cystinuria
- What Qualitative Analysis Tells Us About the Experience of Men Undergoing Urethroplasty
- Potential Uses for Acupuncture as a Complementary Therapy in Patients Undergoing Urologic Cancer Surgery
- Mixed Gonadal Dysgenesis: What Exactly Is This Important but Confusing Condition?
- Urine-Based Methylation Markers in the Diagnosis and Surveillance of Upper Tract Urothelial Carcinoma
- Protocols for Immunological Tolerance and Immunosuppression Withdrawal in Bladder Transplantation
- Repurposing Bisphosphonates for the Treatment of Recurrent Calcium-Based Nephrolithiasis
- Utilizing Cell-Free Urine Tumor DNA to Predict Response and Resistance to TAR-210 Erdafitinib

NON-PROFIT ORG.  
U.S. POSTAGE  
PAID  
PERMIT NO. 797  
RICHMOND, VA

American Urological Association  
1000 Corporate Boulevard  
Linthicum, Maryland 21090



American  
Urological  
Association

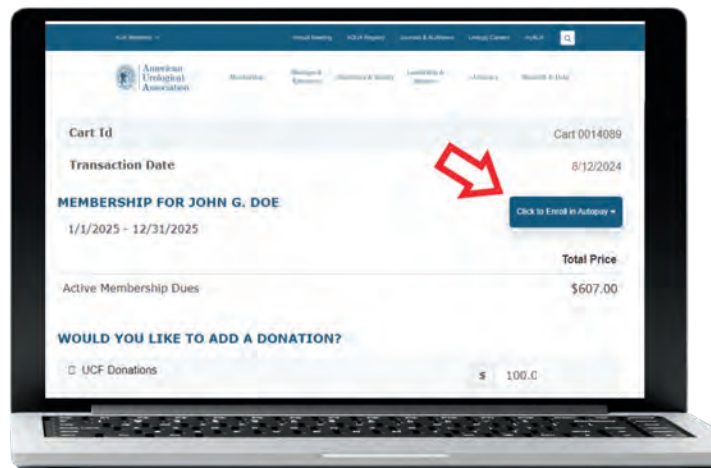
# Renewing Your AUA Membership Just Got Easier!

## Set It and Forget It!

Log into *myAUA* to complete your dues renewal. Select the 'Click to Enroll in Autopay' option on your digital invoice to add your recurring payment.



Log into  
*myAUA*



# AUANews

October 2024, Volume 29 | Issue 10

## EDITOR

Stacy T. Tanaka, MD, MS, FACS  
University of Alabama at Birmingham

## ASSOCIATE EDITORS

**Clinical Trials**  
Raj Pruthi, MD, MHA, FACS, *enGene, Inc*

**DEI and Health Equity**  
Lourdes Guerrios-Rivera, MD, MSc, *University of Puerto Rico*

**Endourology**  
Amy E. Krambeck, MD, *Northwestern University School of Medicine*

**Features**  
Jacob E. Tallman, MD, *Vanderbilt University Medical Center*

**Genitourinary Reconstruction**  
Jeremy B. Myers, MD, *University of Utah*

**Global**  
John D. Denstedt, MD, FRCS, FACS, FCAHS, *Western University*

**Pediatrics**  
Aseem R. Shukla, MD, *Children's Hospital of Philadelphia*

**Oncology**  
Kelly L. Stratton, MD, *University of Oklahoma*

**Outcomes**  
Simon P. Kim, MD, MPH, *University of Colorado*

**Patient Perspectives**  
Tom Hulsey, *UT Southwestern, ZERO Prostate Cancer, Mary Crowley Cancer Research*

## SECTION EDITORS

**Practice Tips & Tricks**  
Neil Baum, MD, *Tulane Medical School*

**Have You Read?**  
Craig Niederberger, MD, FACS, *UIC College of Medicine and UIC College of Engineering*

**From the History Committee: Taking a History**  
Ronald Rabinowitz, MD, *University of Rochester Medical Center*

**Radiology Corner**  
Ardeshir R. Rastinehad, DO, *Smith Institute for Urology at Northwell Health*

**Coding Tips & Tricks**  
Jonathan Rubenstein, MD, *Chair, AUA Coding and Reimbursement Committee*

**Medical Student Column**  
Andrew S. Afyouni, BS, *University of California, Irvine School of Medicine*

Avani P. Desai, BS, *University of North Carolina School of Medicine*

Linda My Huynh, PhD, MSc, *University of Nebraska Medical Center*

Yash B. Shah, BS, *Thomas Jefferson University*

## SPANISH EDITION EDITOR

Alejandro Remigio Rodriguez, MD  
*Wake Forest University School of Medicine*

## PORTUGUESE EDITION EDITOR

Fernando J. Kim, MD, MBA, FACS  
*Denver Health Medical Center*

## AUA STAFF

Patricia Banks  
Heather R. Good  
Heather Holt  
Martha Keyes  
Daniel T. Kulp  
Scott D. Morrow  
Hannah Rinehart  
Kathleen Warshawsky

## AMERICAN UROLOGICAL ASSOCIATION

2024–2025 AUA Officers  
*President*  
Stephen Y. Nakada, MD, FACS, FRCS  
*President-elect*  
Lane S. Palmer, MD, FACS, FSPU  
*Immediate Past President*  
Randall B. Meacham, MD  
*Secretary*  
David F. Penson, MD, MPH  
*Associate Secretaries*  
Jorge Gutierrez-Aceves, MD  
Jose A. Karam, MD, FACS  
Aseem R. Shukla, MD  
*Treasurer*  
Thomas F. Stringer, MD, FACS  
*Treasurer-elect*  
Jennifer Miles-Thomas, MD, URPS, MBA

Renew your AUA Membership and set up Auto Dues Renewal by December 31, 2024 for a chance to win a FREE registration to AUA2025 in Las Vegas.



Renew Today!  
[AUAnet.org/myAUA](http://AUAnet.org/myAUA)

AUA  
2025  
Las Vegas  
APR 26-29

**PUBLICATIONS DEPARTMENT**  
American Urological Association  
publications@AUAnet.org

**PRODUCTION**  
KnowledgeWorks Global Ltd.  
2905 Byrdhill Road, Richmond, VA  
23228

**ADVERTISING SALES**  
The Walchli Tauber Group  
(443) 512-8899  
stephen.tauber@wt-group.com

You are prohibited from using or uploading content you accessed through this print material into external applications, bots, software, or websites, including those using artificial intelligence technologies and infrastructure, including deep learning, machine learning and large language models and generative AI.

*AUANews* is the official newsmagazine of the American Urological Association, located at 1000 Corporate Blvd., Linthicum, MD 21090, and is a function of the AUA Education and Research, Inc. *AUANews* is published 24 times a year by the American Urological Association. Copyright © 2024 by American Urological Association Education and Research, Inc. No part of this publication may be reproduced in any form or language without written permission from the publisher. Published free of charge for AUA membership. Annual non-member subscription rates: individual \$110 (\$155 foreign); institution \$135 (\$180 foreign); industry \$65 (\$135 foreign). U.S. POSTMASTER: Send address changes to *AUANews*, American Urological Association, 1000 Corporate Blvd., Linthicum, MD 21090. Library of Congress ISSN: 1088-7350. All correspondence on editorial matters should be addressed to: Executive Editor, American Urological Association, 1000 Corporate Boulevard, Linthicum, MD 21090.

**Disclaimer:** The statements and opinions contained in the articles in *AUANews* are solely those of the individual authors and contributors and not of the American Urological Association. The appearance of advertisements in *AUANews* is not a warranty, endorsement or approval of the products or services advertised or of their effectiveness, quality or safety. The content of this publication may contain discussion of off-label uses of some of the agents mentioned. Please consult the prescribing information for full disclosures of approved uses. The American Urological Association disclaims responsibility for any injury to persons or property resulting from any ideas or products referred to in the articles or advertisements.

## AUA ADVOCACY

# The Future of Telehealth Depends on How Congress Will Act

Juan J. Andino, MD, MBA

UCLA Health, Los Angeles, California

AUA Telehealth Task Force

AUA Western Section Health Policy Committee

Why was telehealth one of the AUA Advocacy Summit priorities for the third year in a row? Why does the AUA census include questions about telehealth use? Almost everyone had to use telehealth during the COVID-19 public health emergency. We had to. People were afraid. Clinics were shut down. Social distancing was a necessity, and it was enforced.

Telehealth was the only way to ensure patients had some way to connect with their doctors, surgeons, and other providers. Initially, emergency declarations led to broad flexibility in how telehealth could be used. FaceTime (and other modalities that are not US Health Insurance Portability and Accountability [HIPAA] compliant), care delivery across state lines, and even reimbursing equally for audio-only (phone call) visits were temporarily allowed across the states. As federal and state emergency declarations began to fade, many of these changes were rolled back.

However, certain key flexibilities remain in place until December 31, 2024, thanks to the Consolidated Appropriations Act of 2023.<sup>1</sup> Language included in this appropri-

“Importantly, data support the continued use of telehealth. Even before the pandemic, numerous studies in urology demonstrated high satisfaction and equivalent clinical and safety outcomes.<sup>2,3</sup>”

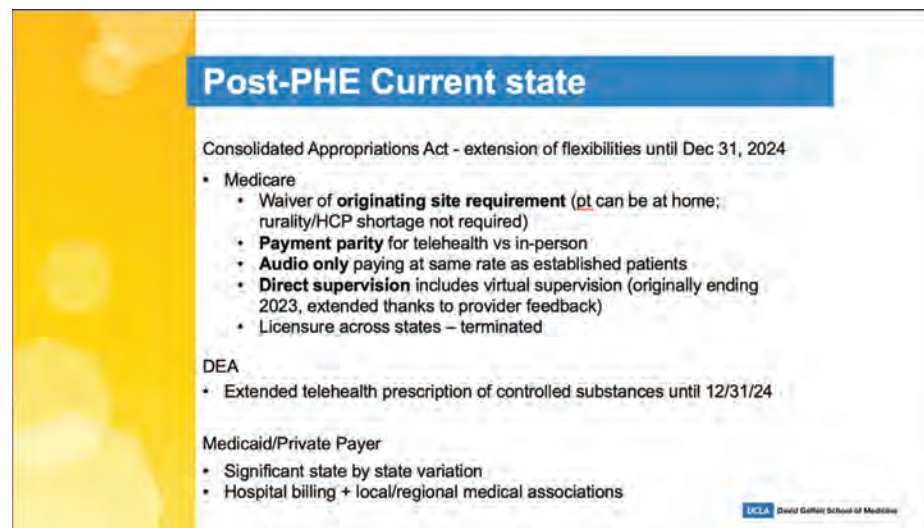


Figure. Post-public health emergency (PHE) current state. DEA indicates Drug Enforcement Administration; HCP, health care provider; pt, patient.

ation bill was supported by AUA members and leadership during the 2022 Advocacy Summit as part of a coalition including the American Medical Association, Alliance of Specialty Medicine, Alliance for Connected Care, and the American College of Surgeons, among many others. At the federal level, key regulatory flexibilities remain in place (Figure):

- Waiving of originating site requirement (patient can engage in telehealth from home; rurality/health care provider shortage not required)
- Payment parity for telehealth and in-person visits by medical decision-making
- Virtual supervision included in direct supervision (residents, advanced practice providers)

Importantly, data support the continued use of telehealth. Even before the pandemic, numerous studies in urology demonstrated high satisfaction and equivalent clinical and safety outcomes.<sup>2,3</sup> Even more recently, a narrative review of telehealth looking at data beyond urology highlighted improved patient-centered outcomes such as cost and time savings, health-system outcomes supporting virtual care used as a substitute for in-person visits, and similar clinical outcomes compared to

clinic encounters.<sup>4</sup> Telehealth should be an option for patients to connect with their urologists; it is not a novel intervention, simply a different way for patients to access specialty care.

Beyond continuing the current public health emergency telehealth flexibilities, there is also ongoing work to prevent the creation of a digital divide—that is, unequal access to telehealth services due to preferential reimbursement for video visits, which require broadband internet and smart devices.<sup>5</sup> For patients who cannot connect with video, phone encounters with evaluation and management of medical conditions should be covered and reimbursed similarly. Otherwise, health systems will be disincentivized to offer anything but in-person

“Telehealth should be an option for patients to connect with their urologists; it is not a novel intervention, simply a different way for patients to access specialty care.”

“As of this writing, 34 federal bills support the expansion of telehealth services, including the AUA-endorsed Connect for Health Act, with bipartisan support from 59 senators.”

or video visits, and the promise of improved access to care will not be realized for rural and marginalized communities.

As of this writing, 34 federal bills support the expansion of telehealth services, including the AUA-endorsed Connect for Health Act, with bipartisan support from 59 senators. If this affects your patients, your loved ones, or your practice, then I encourage you to get involved. Join the AUA Advocacy efforts. Go to the Advocacy Summit, donate to the AUA Political Action Committee, contact your representatives by using our Action Center, join your section health policy committee, and help make the voice of urology heard so we can continue to shape the future of modern medicine. ■

1. HHS.gov. Telehealth policy updates. Accessed May 26, 2024. <https://telehealth.hhs.gov/providers/telehealth-policy/telehealth-policy-updates>

2. Ellimoottil C, Skolarus T, Gettman M, et al. Telemedicine in urology: state of the art. *Urology*. 2016;94:10-16. doi:10.1016/j.urol.2016.02.061

3. Andino JJ, Lingaya MA, Daignault-Newton S, Shah PK, Ellimoottil C. Video visits as a substitute for urological clinic visits. *Urology*. 2020;144:46-51. doi:10.1016/j.urol.2020.05.080

4. Andino JJ, Eyrych NW, Boxer RJ. Overview of telehealth in the United States since the COVID-19 public health emergency: a narrative review. *mHealth*. 2023;9:26. doi:10.21037/mhealth-23-15

5. Eyrych NW, Andino JJ, Fessell DP. Bridging the digital divide to avoid leaving the most vulnerable behind. *JAMA Surg*. 2021;156(8):703-704. doi:10.1001/jamasurg.2021.1143

## AUA2024 RECAPS

# Future Investigations to Consider Nocturia a Circadian Rhythm Disorder of the Bladder

Amber S. Herbert, MD

Stanford University School of Medicine, Palo Alto, California

Ashu Mohammad, PhD

Stanford University School of Medicine, Palo Alto, California

Claire S. Burton, MD

City of Hope, Glendora, California

Amy D. Dobberfuhl, MD, MS

Stanford University School of Medicine, Palo Alto, California

Nocturia is defined by the International Continence Society as “the number of times urine is passed during the main sleep period. Having woken to pass urine for the first time, each urination must be followed by sleep or the intention to sleep.”<sup>1</sup> Two or more nocturnal voids are considered to be an important clinical threshold associated with significant negative outcomes for well-being and health in individuals.<sup>2</sup> Nocturia affects up to 18% of women under the age of 40 years old and up to 61.5% of women above the age of 70 years old.<sup>3</sup> Nocturia can be categorized as (1) nocturnal polyuria, (2) diminished global or low nocturnal bladder capacity, or (3) polyuria.<sup>4</sup> Nocturia is often multifactorial with underlying causative factors, including intake, urological/gynecological, nephrological, hormonal, sleep, and cardiovascular concerns (Table).<sup>5</sup> Frequent night-

“Frequent nighttime urination can have a profound impact on the overall quality of life in many patients, with reports of sleeplessness, decreased slow-wave sleep, and daytime somnolence.”<sup>3</sup>

time urination can have a profound impact on the overall quality of life in many patients, with reports of sleeplessness, decreased slow-wave sleep, and daytime somnolence.<sup>3</sup> Individuals with nocturia who wake up 3 or more times at night have a significantly higher rate of mortality than the general public.<sup>3,6</sup> Nocturia not only impacts one’s ability to rest, but it also impacts day-to-day activities such as work, household chores, exercise, and intimacy.<sup>7</sup> Despite its prevalence, only 1.5 million individuals out of the 50 million individuals affected by nocturia receive treatment.<sup>6</sup> The pathophysiology of nocturia is often complex, which makes it difficult to treat patients with current therapies.<sup>7</sup>

Light is the primary zeitgeber for the circadian rhythm system as it acts through the retina to regulate the suprachiasmatic nucleus or the master circadian oscillator.<sup>8</sup> The circadian rhythm modulates many visceral organs, including the bladder, through peripheral clocks.<sup>9</sup> This is ultimately facilitated by the detection of light changes throughout the day via photoreceptors in the retina. In response, there is an increase or decrease in the expression of certain genes, such as *CLOCK* and *Bmal1*. Typically, during the awake phase, there is increased arousal, increased urine output, and decreased functional bladder capacity.<sup>9,10</sup> The opposite is seen during the nocturnal sleeping phase. There is an intricate balance that determines functional capacity and the bladder’s ability to store urine. Capacity may be determined by the 24-hour circadian cycle, and it is postulated that capacity is regulated at the ion channel level by *CLOCK*-related genetic machinery.<sup>10</sup> Further research needs to be conducted on patients experiencing nocturia to understand how *CLOCK* gene transcription regulates urothelial signaling in the bladder. In the long term, we hope that the molecular information will guide the creation of novel therapeutic agents to improve the symp-

**Table.** Summary of Nocturia Causative Factors, Underlying Pathophysiology, and Lifestyle Interventions

Causative factors	Underlying pathophysiology	Lifestyle interventions
Intake	Water, proteins, sodium, obesity	Limit drinking, calories, salt, protein restriction
Urological/gynecological	Overactive bladder, bladder outlet obstruction, neurogenic bladder	Bladder and pelvic floor training, weight loss
Nephrological	Water diuresis, salt diuresis, hypercalciuria, nephrogenic diabetes insipidus	Salt and protein restriction, weight loss, prevention of diabetes and obesity
Hormonal	Sex hormones, diabetes insipidus, diabetes mellitus	Sleep hygiene, limit drinking, bladder and pelvic floor training, weight loss in diabetes mellitus
Sleep	Obstructive sleep apnea, sleep disruption and shortage, low dopamine diseases	Sleep hygiene, losing weight, physical activity
Cardiovascular	Blood pressure, metabolic syndrome, physical activity	Physical activity, salt restriction, weight loss, postural drainage, stockings

Data from Everaert et al.<sup>5</sup>

“Light is the primary zeitgeber for the circadian rhythm system as it acts through the retina to regulate the suprachiasmatic nucleus or the master circadian oscillator.<sup>8</sup> The circadian rhythm modulates many visceral organs, including the bladder, through peripheral clocks.”<sup>9</sup>

toms and, even more importantly, the quality of life of the millions of patients suffering from nocturia.

The extensive impact that nocturia has on the lives of patients has prompted it to be studied in animal models. Early studies assessing mic-

ture and the circadian rhythm in the bladder used rodents as animal models.<sup>10</sup> Rodents are nocturnal animals in that their sleep-wake cycle is opposite of humans. Initial studies have shown that the bladder capacity of rats is elevated during the lights-on sleep phase cycle and decreased during the lights-off wake phase cycle. Oscillations in the circadian clock influence the transcription of certain genes, including *Per*, *Cry*, and *Bmal1*.<sup>10</sup>

Additional studies have been conducted using mouse models. Ihara et al evaluated restraint stress on mice to investigate the circadian bladder function and rhythmicity of gene expression.<sup>9,11</sup> Investigators found that intermittent stress results in a loss of *Per2* rhythm. Ultimately, restraining resulted in the loss of animals’ innate rhythm of void volume and frequency.<sup>9,11</sup> Control mice showed typical circadian expression of bladder genes *Per2*, *Bmal1*, and *Rev-erba*. Similarly, when assessing the knockout of mammalian cryptochrome proteins, *Cry1* and *Cry2*, in mice, it was found that those with a genetic knockout of

## FUTURE INVESTIGATIONS TO CONSIDER NOCTURIA

→ Continued from page 4

“In the long term, we hope that the molecular information will guide the creation of novel therapeutic agents to improve the symptoms and, even more importantly, the quality of life of the millions of patients suffering from nocturia.”

both proteins resulted in free-running circadian rhythms.<sup>9</sup> The study ultimately demonstrated that both proteins are essential for maintaining intrinsic circadian rhythm.

Bladder circadian rhythm genes in rodents can be altered based on induced stress. The bladders of rodents, including mice and rats, are sufficiently similar to the human urinary tract to warrant investigation. In humans, despite specific lifestyle interventions directed at the underlying pathophysiology of each of the 6 main causative factors resulting in nocturia (Table),<sup>5</sup> nocturia may be refractory, leading us to pursue further investigations into the study of nocturia as a circadian bladder dysfunction.

We hope to fill this knowledge gap by determining the impact of sleep interruption on circadian bladder gene expression. Using such an approach, it should be possible to extrapolate information from animal models to the human urinary tract and better understand the pathophysiology of gene regulation for patients with nocturia. ■

- Weiss JP, Ruud Bosch JLH, Drake M, et al. Nocturia Think Tank: focus on nocturnal polyuria: ICI-RS 2011. *Neurourol Urodyn.* 2012;31(3):330-339. doi:10.1002/nau.22219
- Everaert K, Hervé F, Bosch R, et al. International Continence Society consensus on the diagnosis and treatment of nocturia. *Neurourol Urodyn.* 2019;38(2):478-498. doi:10.1002/nau.23939
- Leslie SW, Sajjad H, Singh S. Nocturia. StatPearls; 2023. Accessed December 6, 2023. <http://www.ncbi.nlm.nih.gov/books/NBK518987/>
- Kurtzman JT, Bergman AM, Weiss JP. Nocturia in women. *Curr Opin Urol.* 2016;26(4):315-320. doi:10.1097/MOU.0000000000000287
- Mure LS, Le HD, Benegiamo G, et al. Diurnal transcriptome atlas of a primate across major neural and peripheral tissues. *Science.* 2018;359(6381):eaao0318. doi:10.1126/science.aao0318
- Ramsay S, Zagorodnyuk V. Role of circadian rhythms and melatonin in bladder function in health and diseases. *Auton Neurosci.* 2023;246:103083. doi:10.1016/j.autneu.2023.103083
- Negoro H, Kanematsu A, Yoshimura K, Ogawa O. Chronobiology of micturition: putative role of the circadian clock. *J Urol.* 2013;190(3):843-849. doi:10.1016/j.juro.2013.02.024
- Ihara T, Nakamura Y, Mitsui T, et al. Intermittent restraint stress induces circadian misalignment in the mouse bladder, leading to nocturia. *Sci Rep.* 2019;9(1):10069. doi:10.1038/s41598-019-46517-w

## ASSI®'s Lipshultz Urology Microsurgical Set

For Vasovasostomy and Vasoepididymostomy

Recommended by Larry I. Lipshultz, M.D.,  
Professor of Urology,  
Baylor College of Medicine

### ASSI.LVAS1 SET Lipshultz Urology Microsurgical Set

Set features Lipshultz Epididymovasostomy Dissecting Scissors, including instruments tailored specifically for Vasovasostomy and Vasoepididymostomy surgery.

Set consists of the following: (no substitutions)

QUANTITY	CATALOG NUMBER	PRODUCT DESCRIPTION
Four	ASSI.4318	Castroviejo Forceps, 12mm
One	ASSI.B158	Round Handle Needle Holder
One	ASSI.SDC15RVL	“Lipshultz” Epididymovasostomy Dissecting Scissors
One	103000BP	Microtip Bipolar Forceps
Two	ASIM5511	Jewelers Forceps, 0.3mm Tip
Two	ASSI.JF4	Jewelers Forceps, 0.4mm Blunt Tip
One	ASSI.NHF2	Vas Holding Forceps, 2mm
One	ASSI.NHF2.5	Vas Holding Forceps, 2.5mm
One	ASSI.NHF3	Vas Holding Forceps, 3mm
One	ASSI.NHF3.5	Vas Holding Forceps, 3.5mm
One	ASSI.BHS11	Blade Holder, 11cm
One Box	ASSI.CBS35	Straight Blades, Sterile (10 blades/box)
One	AS1174C	Instrument Case with Silicone Mat

**assi**®  
ACCURATE SURGICAL & SCIENTIFIC INSTRUMENTS®  
For diamond perfect performance®

accurate surgical & scientific instruments corporation  
516.333.2570 fax: 516.997.4948 west coast: 800.255.9378  
800.645.3569 • Info: [assi@accuratesurgical.com](mailto:assi@accuratesurgical.com)  
Orders: [orders@accuratesurgical.com](mailto:orders@accuratesurgical.com) • [accuratesurgical.com](http://accuratesurgical.com)

Not all ASSI products shown in our literature or on our website are available for sale in Canada

©2024 ASSI

- Hashim H, Blanker MH, Drake MJ, et al. International Continence Society (ICS) report on the terminology for nocturia and nocturnal lower urinary tract function. *Neurourol Urodyn.* 2019;38(2):499-508. doi:10.1002/nau.23917
- Van Kerrebroeck P, Andersson KE. Terminology, epidemiology, etiology, and pathophysiology of nocturia. *Neurourol Urodyn.* 2014;33(Suppl 1):S2-S5. doi:10.1002/nau.22595
- Bosch JLHR, Weiss JP. The prevalence and causes of nocturia. *J Urol.* 2013;189(1Suppl):S86-S92. doi:10.1016/j.juro.2012.11.033

# Underneath the White Coat: Hypogonadism Among Male Resident Physicians

Gene Austin Krishingner, MD

University of Florida College of Medicine, Gainesville

Basil F. Mirza, BS

University of Florida College of Medicine, Gainesville

Kevin J. Campbell, MD, MS

University of Florida College of Medicine, Gainesville

Hypogonadism is a significant medical condition that has been gaining increased attention in recent years. The prevalence of hypogonadism varies, with estimates ranging from 2.1% to 30% in men ages 40 to 79, depending on the definition and population studied.<sup>1</sup> The severity of hypogonadism can range from mild to severe, with symptoms including reduced libido, erectile dysfunction, decreased energy, depression, and anemia, among others.<sup>2</sup> The economic burden of hypogonadism is substantial, with one study estimating the 20-year cost of testosterone deficiency in US men ages 45 to 74 at \$190 billion to \$525 billion.<sup>3</sup> The importance of addressing hypogonadism is underscored by its potential long-term health impacts, including increased risk of cardiovascular disease and osteoporosis.<sup>4</sup> Understanding and addressing hypogonadism are crucial for improving patient quality of life and reducing health care costs.

Despite the growing recognition of hypogonadism as a significant health issue, its prevalence and impact on resident physicians remain largely unexplored. In contrast to the aging male population, little information exists regarding the epidemiology of hypogonadism in young adult males. However, one estimate indicates that testosterone deficiency may be present in up to 20% of adolescent and young adult males ages 15 to 39.<sup>5</sup> Clinical diagnosis in young adults may be more challenging than in males over 45, as they may present with nonspecific symptoms, such as fatigue, rather than sexual dysfunction more commonly seen in older men. Recent evidence also shows that the cutoff of 300 ng/dL used to determine testosterone deficiency in adult men at any age may be inappropriately low to accurately

diagnose hypogonadism in young adults, with a cutoff of 400 ng/dL likely being more appropriate for men ages 20 to 44.<sup>6</sup>

Resident physicians, the majority of whom are under the age of 45, are a group known to experience high levels of stress, irregular sleep patterns, and long working hours. These factors have been associated with hypogonadism in other populations. Nonstandard shift work and insufficient sleep have also been positively associated with urologic complications in males.<sup>7,8</sup> Furthermore, the symptoms of hypogonadism, such as fatigue, depression, and decreased libido, overlap significantly with symptoms of burnout and depression, conditions known to be prevalent among resident physicians.<sup>9</sup> This overlap may lead to misdiagnosis or underdiagnosis of hypogonadism in this population, potentially exacerbating the health and wellness challenges they face. Therefore, our objective was to evaluate the prevalence and impact of hypogonadism among male resident physicians at our institution.

We conducted a prospective study involving male physicians in medical training at our institution. The data for the study were obtained through a combination of survey questionnaires and laboratory tests. The survey data were collected using the Research Electronic Data Capture (RedCAP) system. After obtaining approval by the Institutional Review Board, potential participants were identified through study protocol distribution to Accreditation Council for Graduate Medical Education resident and fellow program physicians at our institution. The participants were not restricted by age, specialty, or postgraduation year (PGY). Of the 651 eligible male residents and fellows, 27 residents expressed interest in participation. The exposure variables of interest in this study were the working conditions of the resident physicians, assessed through the participants' specialty and PGY level, as well as overnight call schedule and night

shift work within the preceding months.

The primary outcome of interest was the prevalence of hypogonadism among the participants, as measured by testosterone levels in the blood. Participants were asked to complete lab work, including a basic metabolic panel, complete blood count, lipid panel, thyroid panel, and measurements of testosterone, follicle-stimulating hormone, luteinizing hormone, and estradiol. Secondary outcomes included the severity of hypogonadism symptoms, as measured by the Androgen Deficiency in the Aging Male (ADAM) questionnaire, and overall health status, as measured by the 36-Item Short Form Health Survey. The ADAM questionnaire is a sensitive screening tool for hypogonadism in males ages 40 and above.<sup>10</sup> Although this sensitivity has not been demonstrated to the same extent in young adults, we felt the ADAM questionnaire was a reasonable tool for detecting hypogonadism symptoms in our participants. The prevalence of hypogonadism was calculated as the proportion of participants with total testosterone levels below 400 ng/dL.

The characteristics of the study subjects are presented in Table 1. Out of the 651 male residents and fellows contacted, 27 expressed interest in participation, yielding a response rate of 4.1%. Of these, 88.9% (24/27) provided demographic data and 66.7% (18/27) completed the surveys. Among those who filled out the survey, 33.3% (6/18) completed the lab work. The participants were diverse in terms of age, specialty, and PGY. These values are reported independently in Table 1 to maintain anonymity. The results of the laboratory tests are presented in Table 2. Two-thirds (4/6) of the participants who completed the lab work had total testosterone levels below 400 ng/dL. Two participants met the serum criteria (<300 ng/dL) for hypogonadism. The results of the ADAM questionnaire and 36-Item Short Form Health Survey are presented in Table 3. Half (9/18) of the par-

Table 1. Participant Characteristics (n = 24)

	No.	%
<b>Specialty</b>		
Critical care	3	12.5
Dermatology	4	16.7
Radiology	1	4.2
Orthopedics	1	4.2
Neurology	1	4.2
Anesthesia	9	37.5
Emergency	1	4.2
Surgery	2	8.3
Urology	1	4.2
Oral surgery	1	4.2
<b>PGY</b>		
1	5	20.8
2	3	12.5
3	5	20.8
4	5	20.8
5	2	8.3
6	3	12.5
9	1	4.2

Abbreviations: PGY, postgraduate year.

ticipants scored positively on the ADAM questionnaire, indicating the presence of hypogonadal symptoms. Furthermore, 44.4% (8/18) of the participants reported that their health was worse compared to a year prior. Among the participants who reported not taking any overnight calls, 20% (1/5) scored positively on the ADAM questionnaire. For those who reported regularly taking overnight calls (ie, every third day, every fourth day, etc) or working night float in the past 6 months, 61.5% (8/13) scored positively.

The key finding of this study is the presence of hypogonadal symptoms in male resident physicians at our institution. Two-thirds of the participants who completed the lab work had total testosterone levels below 400 ng/dL, and half of the participants scored positively

→ Continued on page 7

## UNDERNEATH THE WHITE COAT: HYPOGONADISM AMONG MALE RESIDENT PHYSICIANS

→ Continued from page 6

**Table 2.** Results of Serum Testosterone Testing

Subject	Serum testosterone (ng/dL)	Positive ADAM? (Y/N)
1	398	N
2	612	Y
3	298	Y
4	305	Y
5	339	N
6	849	N

Abbreviations: ADAM, Androgen Deficiency in the Aging Male questionnaire.

on the ADAM questionnaire. Additionally, residents who reported taking overnight calls or night floats were more likely to score positively. This cohort is too small to provide an accurate estimate of the prevalence of hypogonadism in the male resident population, although our findings suggest that the lifestyle and working conditions of residents may contribute to hypogonadal symptoms or the development of hypogonadism. Our findings also highlight the potential overlap between hypogonadism and other health issues common among resident physicians, such as burnout and depression.

These findings are consistent with previous research showing a link between stressful working conditions and hypogonadism. However, they extend the existing literature by demonstrating this link in a population of resident phy-

**Table 3.** Androgen Deficiency in the Aging Male Questionnaire Positivity Rates and 36-Item Short Form Health Survey<sup>a</sup>

	Hypogonadal, % (n = 2)	Eugonadal, % (n = 4)	All participants, % (n = 18)
<b>Positive ADAM</b>	100	25	50
<b>SF-36<sup>b</sup></b>			
Physical functioning	82.5	95.0	94.4
Role limitations due to physical health	62.5	75.0	73.6
Role limitations due to emotional problems	33.3	75.0	59.3
Energy/fatigue	32.5	51.3	43.1
Emotional well-being	60.0	66.0	64.7
Social functioning	62.5	68.8	70.1
Pain	68.8	87.5	81.0
General health	35.0	61.3	59.4
Health change	37.5	43.8	42.6

Abbreviations: ADAM, Androgen Deficiency in the Aging Male questionnaire; SF-36, 36-Item Short Form Health Survey.

<sup>a</sup>Questionnaire averages for all study participants and those who obtained lab work with hypogonadal vs eugonadal results.

<sup>b</sup>For the SF-36, 100% represents the highest level of function.

sicians, a group that has not been extensively studied in this context. This pilot's data demonstrate a need for further investigation to properly assess the prevalence of hypogonadism in male residents. A repeat of this study in a larger cohort, while controlling for potential confounding factors such as age, lifestyle factors, and comorbidities, can give stronger insight into the effects of residency on young

adult males. Despite its limitations, the findings of our study have important implications for the health and wellness of resident physicians, suggesting that male residents may benefit from early screening and education on recognizing symptoms of hypogonadism. ■

*Funding Statement: The authors have indicated that they have no funding or support relevant to this article to disclose.*

*Disclosure Statement: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.*

*Ethics Review: This study was conducted in accordance with the ethical standards of the Institutional Review Board at our institution. All participants provided informed consent prior to their inclusion in the study.*

1. Traish AM, Miner MM, Morgentaler A, Zitzmann M. Testosterone deficiency. *Am J Med.* 2011;124(7):578-587. doi:10.1016/j.amjmed.2010.12.027
2. Cohen J, Nassau DE, Patel P, Ramasamy R. Low testosterone in adolescents & young adults. *Front Endocrinol (Lausanne).* 2020;10:916. doi:10.3389/fendo.2019.00916
3. Moskovic DJ, Araujo AB, Lipshultz LI, Khera M. The 20-year public health impact and direct cost of testosterone deficiency in U.S. men. *J Sex Med.* 2013;10(2):562-569. doi:10.1111/j.1743-6109.2012.02944.x
4. Khera M, Broderick GA, Carson CC III, et al. Adult-onset hypogonadism. *Mayo Clin Proc.* 2016;91(7):908-926. doi:10.1016/j.mayocp.2016.04.022
5. Lokeshwar SD, Patel P, Fantus RJ, et al. Decline in serum testosterone levels among adolescent and young adult men in the USA. *Eur Urol Focus.* 2021;7(4):886-889. doi:10.1016/j.euf.2020.02.006
6. Zhu A, Andino J, Daignault-Newton S, Chopra Z, Sarma A, Dupree JM. What is a normal testosterone level for young men? Rethinking the 300 ng/dL cutoff for testosterone deficiency in men 20-44 years old. *J Urol.* 2022;208(6):1295-1302. doi:10.1097/JU.0000000000002928
7. Deng N, Haney NM, Kohn TP, Pastuszak AW, Lipshultz LI. The effect of shift work on urogenital disease: a systematic review. *Curr Urol Rep.* 2018;19(8):57. doi:10.1007/s11934-018-0815-y
8. O'Byrne NA, Yuen F, Niaz W, Liu PY. Sleep and the testis. *Curr Opin Endocr Metab Res.* 2021;18:83-93. doi:10.1016/j.coemr.2021.03.002
9. Dyrbye LN, West CP, Satele D, et al. Burnout among U.S. medical students, residents, and early career physicians relative to the general U.S. population. *Acad Med.* 2014;89(3):443-451. doi:10.1097/ACM.0000000000000134
10. Morley JE, Charlton E, Patrick P, et al. Validation of a screening questionnaire for androgen deficiency in aging males. *Metabolism.* 2000;49(9):1239-1242. doi:10.1053/meta.2000.8625

## Lithotripsy for Small, Nonobstructing Renal Calculi

Joseph Borrell, BA

David Geffen School of Medicine at University of California, Los Angeles

Kymora B. Scotland, MD, PhD

University of California, Los Angeles

### Approach to Small, Nonobstructing Renal Calculi

Small renal calculi are often asymptomatic and incidentally detected on imaging modalities

during the workup of other medical conditions. While the treatment approach is clearer for symptomatic and larger renal calculi, managing smaller and lower-burden stones depends on patient history, imaging, and laboratory studies. Although most nonobstructing small renal stones are asymptomatic, they may still progress to become symptomatic either due to infection or obstruction in up to one-third of cases.<sup>1</sup> While small nonobstructing stones have commonly been active-

ly surveilled, recent literature shows that their removal results in a lower incidence of future complications of up to 82% compared to stones that are not removed.<sup>2</sup> Therefore, patients with small renal stones should be aware of all management options when presenting to the clinic.

### Common Treatment Options

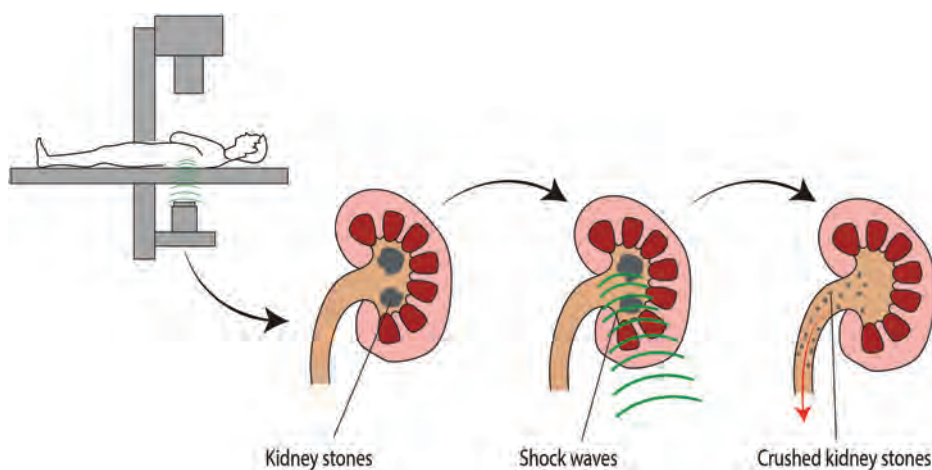
For patients who seek treatment for their small, nonobstructive re-

nal stones, the 2 contemporary treatment options are ureteroscopy (URS) and extracorporeal shock wave lithotripsy (ESWL). While studies have shown that URS may be more effective than ESWL as an initial approach to achieving a stone-free outcome, URS commonly includes ureteral stent placement. Stents have several well-known complications, including increased rates of hematuria, irritative urinary

→ Continued on page 8

## LITHOTRIPSY FOR SMALL, NONOBSTRUCTING RENAL CALCULI

→ Continued from page 7



**Figure 1.** Mechanism of extracorporeal shock wave lithotripsy. A lithotripter machine generates shock waves that create ultrasonic vibrations that fragment the kidney stones.

symptoms, infection, and dysuria. In contrast, studies have shown that stents have no benefit and are therefore not needed for patients undergoing ESWL, especially if the stone is small (<15 mm).<sup>3</sup>

Lastly, URS involves general or spinal anesthesia, unlike ESWL, which can be done with intravenous sedation or even local anesthesia.<sup>4</sup> Thus, while both are reasonable treatment options for small, non-obstructive stone removal, ESWL may be a better option for patients who prefer a less invasive outpatient procedure without stent placement (Figure 1).

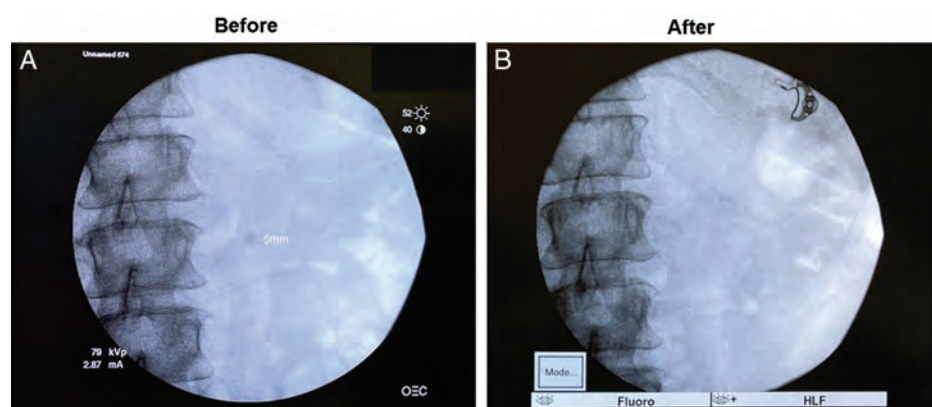
### Outcomes of ESWL

ESWL can break up stones anywhere in the urinary tract but is guideline recommended as first-line treatment for stones in the kidney or upper ureter.<sup>3</sup> Contemporary lithotripters can fragment most stone types with low-risk, short recovery periods, and low analgesic use. Postoperative flank pain typically presents as soreness lasting 1 to 2 days. Patients may also experience

self-limited hematuria. More rarely, there is a risk of hematoma.<sup>3,5</sup> Other documented complications, including infection, obstruction, altered kidney function, and hypertension, are even more rare, and much of the literature is outdated.<sup>6</sup>

Recent studies estimate the initial success rate of ESWL after one visit to be 69%, with a success rate of up to 93% after repeated treatment.<sup>7</sup> However, the success of ESWL may be higher depending on the stone composition, size, and the urologist's experience with the procedure (Figure 2). For patients with smaller stone sizes < 10 mm, studies have shown success rates up to 99% after initial treatment.<sup>8</sup> Thus, while URS may result in higher single-session stone-free rates, ESWL remains an effective option for patients with small asymptomatic stones who wish to minimize surgical side effects.

It should be noted that ESWL is generally contraindicated in pregnancy, active anticoagulation, untreated coagulopathies, and aneurysms due to risks of bleeding, although the current literature has mixed opinions on the latter.<sup>9</sup>



**Figure 2.** Extracorporeal shock wave lithotripsy outcomes. Renal calculus present before extracorporeal shock wave lithotripsy session (A) with resolution after a single session (B).

“Therefore, patients with small renal stones should be aware of all management options when presenting to the clinic.”

### Tips for Improving ESWL Outcomes

ESWL is most successful in patients with small, less dense stones (<10 mm and <1500 Hounsfield units) and skin-to-stone distances < 15 cm. While there is increased clearance of upper and interpolar stones, lower pole stones < 15 mm diameter show clearance after one procedure. Urologists should consider anatomical location and renal abnormalities, such as large renal cysts near the stone or kidney malrotations, as in the case of horseshoe kidney, which may impact stone clearance. Additionally, stone composition should be considered, as cystine and denser calcium oxalate monohydrate stones may be less favorable. Finally, uric acid stones are often not visible on fluoroscopy; patients with these stones should be counseled on adjustments that may be necessary to the procedure or urged to consider URS.<sup>10</sup>

### Conclusion

Current literature has shown that the removal of small, asymptomatic renal calculi may decrease rates of future complications such as renal colic and growth of secondary stones. Patients seeking treatment for small, nonobstructing kidney stones should be properly educated on the outcomes and complications of both URS and ESWL. ESWL continues to be an attractive treatment option. It is the only truly noninvasive kidney stone treatment and presents a safe and effective option for patients seeking an outpatient procedure without stent placement. ■

*Conflict of Interest Disclosures:* Dr Scotland reported being a consultant for Storz

Medical and an advisor for Advanced MedTech.

1. Dropkin BM, Moses RA, Sharma D, Pais VM. The natural history of nonobstructing asymptomatic renal stones managed with active surveillance. *J Urol.* 2015;193(4):1265-1269. doi:10.1016/j.juro.2014.11.056
2. Sorensen MD, Harper JD, Borofsky MS, et al. Removal of small, asymptomatic kidney stones and incidence of relapse. *N Engl J Med.* 2022;387(6):506-513. doi:10.1056/NEJMoa2204253
3. Manzoor H, Leslie SW, Saikali SW. *Extracorporeal Shockwave Lithotripsy.* StatPearls; 2024.
4. Loening S, Kramolowsky EV, Willoughby B. Use of local anesthesia for extracorporeal shock wave lithotripsy. *J Urol.* 1987;137(4):626-628. doi:10.1016/S0022-5347(17)44158-9
5. Tzelvels L, Geraghty R, Mourmouris P, et al. Shockwave lithotripsy complications according to modified Clavien-Dindo grading system: a systematic review and meta-regression analysis in a sample of 115 randomized controlled trials. *Eur Urol Focus.* 2022;8(5):1452-1460. doi:10.1016/j.euf.2021.11.002
6. D'Addessi A, Vittori M, Racioppi M, Pinto F, Sacco E, Bassi P. Complications of extracorporeal shock wave lithotripsy for urinary stones: to know and to manage them—a review. *ScientificWorldJournal.* 2012;2012:619820. doi:10.1100/2012/619820
7. Nielsen TK, Jensen JB. Efficacy of commercialised extracorporeal shock wave lithotripsy service: a review of 589 renal stones. *BMC Urol.* 2017;17(1):59. doi:10.1186/s12894-017-0249-8
8. Alić J, Heljić J, Hadžiosmanović O, et al. The efficiency of extracorporeal shock wave lithotripsy (ESWL) in the treatment of distal ureteral stones: an unjustly forgotten option?. *Cureus.* 2022;14(9):e28671. doi:10.7759/cureus.28671
9. Reynolds LF, Krocak T, Pace KT. Indications and contraindications for shock wave lithotripsy and how to improve outcomes. *Asian J Urol.* 2018;5(4):256-263. doi:10.1016/j.ajur.2018.08.006
10. Krocak T, Scotland KB, Chew B, Pace KT. Shockwave lithotripsy: techniques for improving outcomes. *World J Urol.* 2017;35(9):1341-1346. doi:10.1007/s00345-017-2056-y

### ERRATUM

AUA2024 Plenary Recap:  
Avulsed Ureter, a Urologist's  
Nightmare, and How to Avoid  
and Repair: Erratum

AUANews, August 2024,  
Volume 29, Issue 8, Page 4.

The last 2 sentences of the “How to Avoid” section have been changed to “If the rigid scope is stuck from advancing too far, use a small endoscope to incise the ureteral orifice medially to release the scope. If the scope is stuck in the deflected position, straighten manually with a coaxial dilator alongside the scope or cut the handle of the URS and cut distal end with percutaneous access.” This change has been made online: <https://auanews.net/issues/articles/2024/august-2024/aua2024-recap-avulsed-ureter-a-urologists-nightmare-and-how-to-avoid-and-repair>



# My Experience as a 2024 AUA/JUA Exchange Program Scholar: An Unforgettable Academic and Cultural Immersion

**Nirmish Singla, MD, MSCS, FACS**  
*The Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland*

I had the honor and privilege to participate as an exchange scholar in the 2024 AUA Exchange Pro-

gram with the Japanese Urological Association (JUA). During my exchange, which took place in April 2024, I spent considerable time with the faculty and residents in the Department of Urology at Dokkyo Medical University in Japan, led by

Professor Takao Kamai (Figures 1 and 2). The experience culminated with the 111th Annual Meeting of the JUA in Yokohama on April 25 to 27, 2024 (Figures 3-5).

This was a truly unique opportunity to learn how urology is practiced in Japan and to gain exposure to the Japanese health care system. Dokkyo Medical University Hospital



Figure 1. Dokkyo Medical University in Mibu, Tochigi Prefecture, Japan.



Figure 2. Faculty and residents in the Department of Urology at Dokkyo Medical University gather for a welcoming party at a traditional Japanese restaurant.



Figure 3. Scholarship Forum at the 111th Annual Meeting of the Japanese Urological Association in Yokohama, featuring the exchange scholars from the AUA and the European Association of Urology.



Figure 4. Faculty, residents, and students representing the Department of Urology at Dokkyo Medical University at the 111th Annual Meeting of the Japanese Urological Association.

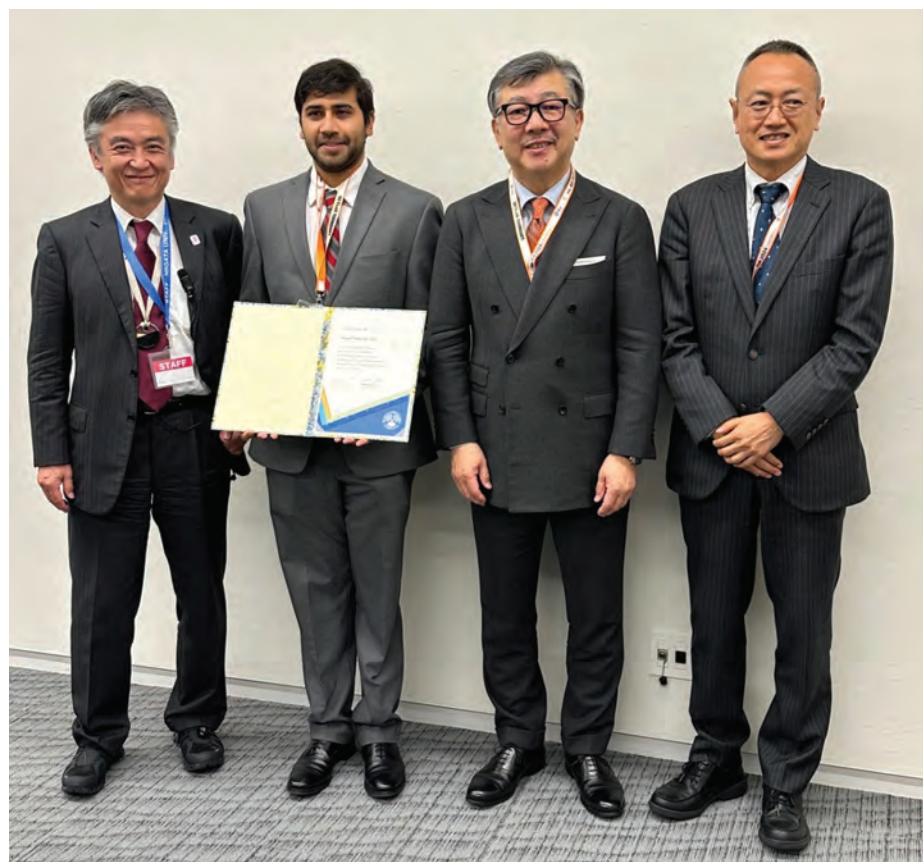


Figure 5. Presentation of awards to the AUA scholars by Professor Yoshihiko Tomita (chairperson of the 111th Annual Meeting of the Japanese Urological Association), Professor Masatoshi Eto (president of the Japanese Urological Association), and Professor Takahiko Mitsui.

## MY EXPERIENCE AS A 2024 AUA/JUA EXCHANGE PROGRAM SCHOLAR

→ Continued from page 9



**Figure 6.** Open right adrenalectomy for a large pheochromocytoma, performed by Professor Takao Kamai.

is among the busiest hospitals in Japan, with 1195 beds at the main university hospital alone and 2 Intuitive da Vinci Xi robotic consoles. The experience provided firsthand clinical and surgical exposure, with a broad swath of open, robotic, laparoscopic, and endoscopic cases across the spectrum of urologic oncology (Figure 6).

The experience also entailed a reciprocal academic exchange of ideas with an invitation to present several lectures to the urology department on each day of my stay. My talks spanned various topics in kidney cancer, testicular cancer, upper tract urothelial cancer, and career development, followed by engaging discussions with the residents and faculty. The program helped me broaden my global professional network in urology and even helped bridge a new research collaboration between our institutions. To solidify these collaborations, we are currently building a new program at my home institution to host a postdoctoral fellow from Dokkyo Medical University in my research lab each year.

Aside from the unique clinical experiences, the social and cultural experiences were truly unforgettable. Some of the highlights of my trip outside of the hospital setting included

- Visiting Mount Fuji using the Shinkansen (bullet train) with

breathtaking views of the mountain from Lake Kawaguchiko (Figure 7). Not only was I fortunate to be able to see the mountain, but I also caught the cherry blossoms (*sakura*) in full bloom.

- Touring an underground Oya stone mine near Utsunomiya with Professor Kamai.
- Visiting Nikko, a World Heritage site in Tochigi Prefecture, with Professor Toshiki Kijima and a few residents on April 23, which happened to be the anniversary of Dokkyo Medical University's founding. We changed into traditional kimonos and visited Nikko Toshogu Shrine, followed by Nikko Edo Village, where we witnessed a procession of courtesans, a ninja show, and a water performance (Figure 8).
- Visiting the historic Odawara Castle with Professors Kamai and Kijima.
- Joining the excursion to Kamakura organized by the JUA to visit numerous temples, shrines, and other historical monuments, including the famous Koutoku-in (Great Buddha) statue.

Despite being vegetarian and not knowing how to speak Japanese, I did not feel these posed challenges during my stay, as the faculty and residents at Dokkyo Medical University were extremely welcoming and hospitable.



**Figure 7.** View of Mt Fuji and Lake Kawaguchiko with pink cherry blossoms (*sakura*) in the foreground.



**Figure 8.** Wearing traditional kimonos with Professor Toshiki Kijima and accompanying urology residents in Nikko Edo Village.

Furthermore, the AUA ensured a smooth itinerary by coordinating my travel and accommodations. I want to extend a special thanks to Professors Kamai and Kijima for going above and beyond to make sure I was always taken care of and for detailing my trip on their department website (<https://dept.dokkyomed.ac.jp/dep-m/uro/category5/>). Aside from the in-

valuable professional enrichment and expanded academic network, I gained a deep and immense appreciation for Japanese history and culture by being completely immersed in it throughout my stay. I am extremely grateful to the AUA, JUA, and the Department of Urology at Dokkyo Medical University for this unique and fruitful opportunity. *Domo arigato gozaimasu!* ■

## AUA AWARD WINNERS

# Developing an Innovative Approach to Neurogenic Bladder Management After Spinal Cord Compromise

Venkat M. Ramakrishnan, MD, PhD

Boston Children's Hospital, Massachusetts  
Harvard Medical School, Boston, Massachusetts  
The Koch Institute, Massachusetts Institute of  
Technology, Cambridge

Gabriel-Luis Ocampo, MS

Boston Children's Hospital, Massachusetts

Kyle Costa, BS

Boston Children's Hospital, Massachusetts

Hatim Thaker, MD

Boston Children's Hospital, Massachusetts  
Harvard Medical School, Boston, Massachusetts

Michael J. Cima, PhD

The Koch Institute, Massachusetts Institute of  
Technology, Cambridge

Rosalyn M. Adam, PhD

Boston Children's Hospital, Massachusetts  
Harvard Medical School, Boston, Massachusetts

Neurogenic bladder (NGB) following spinal cord compromise presents a significant clinical challenge. Characterized by disrupted neural control of bladder and sphincter functions, NGB evolves from initial detrusor hyperreflexia and sphincter dyssynergia to chronic atrophy and fibrosis.<sup>1</sup>

NGB management is critically predicated on maintaining low bladder-storage pressures to preserve upper urinary tract function and prevent complications such as neurogenic detrusor overactivity, urinary incontinence (UI), urinary tract infections and urosepsis, and renal failure. Comprehensive assessments using urodynamic studies, postvoid residual measurements, and imaging are essential in guiding medical and surgical therapies. Current hallmarks of NGB management include intermittent catheterization and systemic pharmacologic agents, such as anticholinergics and/or  $\beta_3$  adrenergic agonists, which are hampered by inconsistent therapeutic adherence and potentially a partial modulation of underlying targets. Globally, these early management strategies can result in infection, local and upper tract tissue damage, and the exacerbation of neurogenic bowel and cardiovascular symptoms.

Yet, efforts to circumvent these barriers are often more invasive and adverse. For example, intravesical botulinum toxin injections carry a transient therapeutic benefit necessitating recurrent anesthesia exposure in children.<sup>2</sup> Augmentation cystoplasty is also associated with significant surgical, metabolic, and oncologic risks.<sup>3</sup> Therefore, there is a critical need for a minimally invasive, effective, and targeted solution that enhances therapeutic adherence, improves symptom control, localizes treatment to the bladder, and reduces systemic side effects and morbidity. We seek to develop an intravesical long-term drug-delivery platform that addresses these needs.

Trospium chloride (TrCl) is a competitive muscarinic receptor antagonist with minimal central nervous system penetration due to its large molecular size and polarity. Such attributes reduce the risk of cognitive side effects, which are otherwise common with other anticholinergics like oxybutynin. In clinical trials, a 20 mg oral dose of TrCl taken twice daily significantly improved NGB management, increasing bladder capacity, reducing detrusor pressure, and enhancing compliance.<sup>4</sup>

While it has relative benefits compared to other anticholinergics, TrCl still exerts significant systemic side effects. Yet, it also presents a unique pharmacokinetic profile that makes it preferable to other anticholinergics in the context of intravesical administration. For instance, TrCl is known for its poor oral bioavailability, which is less than 10%, and its absorption is further reduced by food intake.<sup>5</sup> Furthermore, TrCl is predominantly eliminated from the body in its unchanged form through renal excretion. As such, intravesical delivery of TrCl offers the advantage of high local bladder concentrations with minimal systemic absorption.<sup>6</sup>

Studies on single intravesical TrCl instillations in NGB patients indeed demonstrated minimal systemic absorption and substantial local efficacy.<sup>7</sup> Controlled-release drug delivery systems using TrCl-loaded polymer carriers have demonstrated significant reductions in spontaneous bladder contractions in porcine models.<sup>8</sup> Perhaps the most convincing evidence regarding long-term intravesical TrCl delivery came from a recent clinical trial in which a novel intravesical silicone device was preloaded with 800 mg of TrCl for managing nonneurogenic overactive bladder.<sup>9</sup> Congruent with preclinical findings indicating that the device could generate high local TrCl concentrations with minimal systemic absorption, trial results showed that the device produced local urine TrCl levels significantly higher than oral dosing with negligible systemic exposure. Subjects reported a 75% reduction in UI episodes as well as significant improvements in quality of life. While some adverse effects, such as hematuria and bladder discomfort, were noted, the study concluded that continuous exposure to suprathreshold levels of TrCl for 6 weeks was safe, well-tolerated, and effective in reducing UI episodes and enhancing patient quality of life.

From all of this, we plan to use a rodent spinal cord injury model of NGB and TrCl as a test pharmacologic agent to assess 3 key aspects vital to the creation of any drug-delivery system (timing, dosing, and frequency) and their effects on bladder compliance, neurogenic detrusor overactivity, and UI. Building on prior experience evaluating rodent bladders via cystometry,<sup>10</sup> we hypothesize that (1) early TrCl therapy, (2) suprathreshold intravesical TrCl dosing, and (3) continuous intravesical TrCl delivery will improve NGB functional outcomes.

The AUA/Urology Care Foundation™ Research Scholars Award af-

fords us the meaningful opportunity to work with motivated colleagues to investigate ways to improve upon the current standards of care. By developing a novel intravesical drug-delivery platform, we hope to enhance therapeutic adherence, improve bladder compliance, and reduce the need for invasive procedures. We also hope to better understand the pathogenesis of NGB and how intravesical treatments can alter the disease course. Most importantly, the successful implementation of this platform in NGB patients could result in significantly improved outcomes, diminished complications, and an enhanced quality of life. ■

1. Foditsch EE, Roeder K, Patras I, et al. Structural changes of the urinary bladder after chronic complete spinal cord injury in minipigs. *Int Neurourol J*. 2017;21(1):12-19. doi:10.5213/inj.1732666.333
2. Kuo HC. Comparison of effectiveness of detrusor, suburothelial and bladder base injections of botulinum toxin a for idiopathic detrusor overactivity. *J Urol*. 2007;178(4 Pt 1):1359-1363. doi:10.1016/j.juro.2007.05.136
3. Chang J-W, Kuo F-C, Lin T-C, et al. Long-term complications and outcomes of augmentation cystoplasty in children with neurogenic bladder. *Sci Rep*. 2024;14(1):4214. doi:10.1038/s41598-024-54431-z
4. Stohrer M, Bauer P, Giannetti BM, et al. Effect of trospium chloride on urodynamic parameters in patients with detrusor hyperreflexia due to spinal cord injuries: a multicentre placebo-controlled double-blind trial. *Urol Int*. 1991;47(3):138-143. doi:10.1159/000282207
5. Doroshenko O, Jetter A, Odenthal KP, Fuhr U. Clinical pharmacokinetics of trospium chloride. *Clin Pharmacokinet*. 2005;44(7):701-720. doi:10.2165/00003088-200544070-00003
6. Giannantoni A, Di Stasi SM, Chancellor MB, Costantini E, Porena M. New frontiers in intravesical therapies and drug delivery. *Eur Urol*. 2006;50(6):1183-1193. doi:10.1016/j.eururo.2006.08.025
7. Walter P, Grosse J, Bihl AM, et al. Bioavailability of trospium chloride after intravesical instillation in patients with neurogenic lower urinary tract dysfunction: a pilot study. *Neurourol Urodyn*. 1999;18(5):447-453. doi:10.1002/(SICI)1520-6777(1999)18:5<447::AID-NAU6>3.0.CO;2-Q
8. Von Walter M, Michaelis I, Jakse G, Grosse JO. Trospium chloride released from intravesically applied PLGA-based carriers decreases bladder contractility in an isolated whole pig bladder model. *Eur Urol Suppl*. 2009;8(4):178. doi:10.1016/S1569-9056(09)60235-9
9. Cutie C, Efros M, Sobol J, et al. Continuous intravesical delivery of trospium chloride significantly improves OAB symptoms: results of a phase 1b study. Presented at: the International Continence Society Annual Meeting; September 3-6, 2019; Gothenburg, Sweden.
10. Tu DD, Seth A, Gil ES, et al. Evaluation of biomaterials for bladder augmentation using cystometric analyses in various rodent models. *J Vis Exp*. 2012;66:3981. doi:10.3791/3981

## AUA2024: REFLECTIONS

# A Japanese Urology Resident's Perspective on the AUA Annual Meeting 2024

Hiroki Nishiyama, MD

Uonuma Institute of Community Medicine,  
Niigata University Medical and Dental Hospital,  
Minamiuonuma, Niigata, Japan

## Introduction

I am a second-year urology resident at Niigata University in Japan. I was selected for the AUA/Japanese Urological Association Resident Program and attended the AUA Annual Meeting 2024 in San Antonio, Texas, from May 3 to 6. This was my first trip to the United States and my first attendance at the AUA, which provided an invaluable opportunity to observe and interact with the international urology community.

## Meeting Experience

The meeting sessions started as early as 7:00 AM, and each room was filled with lively discussions. In the largest meeting room, plenary sessions were held throughout the day. Discussions on new treatment methods and lectures on new guidelines were held at intervals of 10 to 30 minutes. The educational content provided valuable insight into new treatments and surgical techniques.

The Resident Pavilion was one of the most crowded in the Science & Technology Hall from the first day of the conference, largely due to the Resident Bowl. The competition featured a wide range of questions, covering topics from the selection of antibiotics and the mechanisms of new drugs to more specialized subjects like the wavelength of thulium lasers and the history of San Antonio. The teams were all highly skilled, and some matches were so competitive that they required overtime to determine a winner. It was felt that holding a similar competition in Japan would be a valuable and stimulating experience.

In the Japanese Urological Association international session, the differences in clinical approaches between the United States and

Japan were highlighted. In the United States, innovative diagnostics and therapies, such as prostate-specific membrane antigen positron emission tomography/CT for

castration-resistant prostate cancer, are widely available and utilized. In contrast, these technologies are not yet covered by insurance in Japan, limiting their accessibility. The broad-

er availability of such advanced diagnostics and therapies in Japan is highly anticipated.

→ Continued on page 13



FOR YOUR PATIENTS WITH **mHSPC** OR **nmCRPC**

## HELP HIM LIVE FOR WHAT HE LOVES




**NUBEQA REDUCED THE RISK OF DEATH BY >30% ACROSS **mHSPC** and **nmCRPC**<sup>1-3</sup>**

In **mHSPC**, NUBEQA is the only ARI approved in combination with docetaxel in mHSPC. NUBEQA in combination with docetaxel and ADT significantly extended OS beyond docetaxel + ADT; HR: 0.68; 95% CI: 0.57-0.80;  $P < 0.0001$ .<sup>1,2</sup>

**ARASENS Study Design:** 1305 mHSPC patients on ADT\* with docetaxel who received ADT within 12 weeks before study entry were randomized 1:1 and treated with concurrent 600 mg NUBEQA twice daily (n=651) or placebo (n=654) in a multicenter, double-blind, phase III trial. Treatment with NUBEQA or placebo continued until symptomatic progressive disease, change of antineoplastic therapy, or unacceptable toxicity. Concomitant docetaxel was administered at 75 mg/m<sup>2</sup> every 21 days for 6 cycles within 6 weeks of starting NUBEQA or placebo. OS was statistically significant for the NUBEQA arm vs placebo arm; HR: 0.68; 95% CI: 0.57-0.80;  $P < 0.0001$ .<sup>1,2</sup>

In **nmCRPC**, NUBEQA + ADT reduced the risk of death by nearly a third vs ADT alone (OS was a secondary endpoint); HR: 0.69; 95% CI: 0.53-0.88;  $P = 0.003$ . MFS was the primary endpoint.<sup>1,3</sup>

**ARAMIS Study Design:** 1509 nmCRPC patients on ADT\* with a PSA doubling time of  $\leq 10$  months were randomized 2:1 to receive concurrent 600 mg NUBEQA twice daily (n=955) or placebo (n=554) in a multicenter, double-blind, phase III trial. Treatment continued until radiographic disease progression as assessed by CT, MRI, <sup>99m</sup>Tc bone scan by BICR, unacceptable toxicity, or withdrawal. MFS was statistically significant with a median of 40.4 months vs 18.4 months for placebo; HR: 0.41; 95% CI: 0.34-0.50;  $P < 0.0001$ . The final analysis of OS was statistically significant vs placebo; HR: 0.69; 95% CI: 0.53-0.88;  $P = 0.003$ . MFS was the primary endpoint and OS was a key secondary endpoint.<sup>1,3,4</sup>



**HAVE A PATIENT IN MIND?**  
Scan the QR code to request a sample.

**CHOOSE NUBEQA 1<sup>ST</sup> FOR SURVIVAL**

## A JAPANESE UROLOGY RESIDENT'S PERSPECTIVE

→ Continued from page 12

Even advanced and effective diagnostic and treatment methods may not be accessible due to financial constraints. Japan's health care system is characterized by universal health coverage, which ensures that all citizens have access to medical services and significantly reduces the financial burden on patients. This system creates an environment where patients can more

easily access the medical care they need. However, it is important to be aware of the problem of overmedicalization. It is crucial to determine what medical care is truly necessary for each patient, as exemplified by the practice of active surveillance.

At the President's Reception held on the evening of May 5, I had the opportunity to converse with doctors from various international exchange

programs. The event featured Tex-Mex cuisine unique to Texas, allowing us to enjoy food and drinks while communicating with many doctors.

## Conclusion

My first attendance at the AUA Annual Meeting 2024 was a profound experience that not only provided exposure to the latest ad-

vances in urology, but also a comparative perspective on health care practices between the United States and Japan. I will work diligently in my daily medical practice, surgeries, and research so that I can participate in future AUA Annual Meetings as a presenter and engage in discussions with various individuals. I look forward to seeing all readers at future AUA Annual Meetings. ■

## INDICATIONS

NUBEQA® (darolutamide) is an androgen receptor inhibitor indicated for the treatment of adult patients with:

- Non-metastatic castration-resistant prostate cancer (nmCRPC)
- Metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel

## IMPORTANT SAFETY INFORMATION

### Warnings & Precautions

**Ischemic Heart Disease** – In a study of patients with nmCRPC (ARAMIS), ischemic heart disease occurred in 3.2% of patients receiving NUBEQA versus 2.5% receiving placebo, including Grade 3-4 events in 1.7% vs. 0.4%, respectively. Ischemic events led to death in 0.3% of patients receiving NUBEQA vs. 0.2% receiving placebo. In a study of patients with mHSPC (ARASENS), ischemic heart disease occurred in 3.2% of patients receiving NUBEQA with docetaxel vs. 2% receiving placebo with docetaxel, including Grade 3-4 events in 1.3% vs. 1.1%, respectively. Ischemic events led to death in 0.3% of patients receiving NUBEQA with docetaxel vs. 0% receiving placebo with docetaxel. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue NUBEQA for Grade 3-4 ischemic heart disease.

**Seizure** – In ARAMIS, Grade 1-2 seizure occurred in 0.2% of patients receiving NUBEQA vs. 0.2% receiving placebo. Seizure occurred 261 and 456 days after initiation of NUBEQA. In ARASENS, seizure occurred in 0.6% of patients receiving NUBEQA with docetaxel, including one Grade 3 event, vs. 0.2% receiving placebo with docetaxel. Seizure occurred 38 to 340 days after initiation of NUBEQA. It is unknown whether anti-epileptic medications will prevent seizures with NUBEQA. Advise patients of the risk of developing a seizure while receiving NUBEQA and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others. Consider discontinuation of NUBEQA in patients who develop a seizure during treatment.

**Embryo-Fetal Toxicity** – Safety and efficacy of NUBEQA have not been established in females. NUBEQA can cause fetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception during treatment with NUBEQA and for 1 week after the last dose.

### Adverse Reactions

In ARAMIS, serious adverse reactions occurred in 25% of patients receiving NUBEQA vs. 20% of patients receiving placebo. Serious adverse reactions in  $\geq 1\%$  of patients who received NUBEQA included urinary retention, pneumonia, and hematuria. Fatal adverse reactions occurred in 3.9% of patients receiving NUBEQA vs. 3.2% of patients receiving placebo. Fatal adverse reactions in patients who received NUBEQA included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%). The most common adverse reactions ( $>2\%$  with a  $\geq 2\%$  increase over placebo), including laboratory test abnormalities, were increased AST, decreased neutrophil count, fatigue, increased bilirubin, pain in extremity, and rash. Clinically relevant adverse reactions occurring in  $\geq 2\%$  of patients treated with NUBEQA included ischemic heart disease and heart failure.

In ARASENS, serious adverse reactions occurred in 45% of patients receiving NUBEQA with docetaxel vs. 42% of patients receiving placebo with docetaxel. Serious adverse reactions in  $\geq 2\%$  of patients who received NUBEQA with docetaxel included febrile neutropenia (6%), decreased neutrophil count (2.8%), musculoskeletal pain (2.6%), and pneumonia (2.6%). Fatal adverse reactions occurred in 4% of patients receiving NUBEQA with docetaxel vs. 4% of patients receiving placebo with docetaxel. Fatal adverse reactions in patients who received NUBEQA included COVID-19/COVID-19 pneumonia (0.8%), myocardial infarction (0.3%), and sudden death (0.3%). The most common adverse reactions ( $\geq 10\%$  with a  $\geq 2\%$  increase over placebo with docetaxel) were constipation, rash, decreased appetite, hemorrhage, increased weight, and hypertension. The most common laboratory test abnormalities ( $\geq 30\%$ ) were anemia, hyperglycemia, decreased lymphocyte count, decreased neutrophil count, increased AST, increased ALT, and hypocalcemia. Clinically relevant adverse reactions in  $<10\%$  of patients who received NUBEQA with docetaxel included fractures, ischemic heart disease, seizures, and drug-induced liver injury.

### Drug Interactions

**Effect of Other Drugs on NUBEQA** – Combined P-gp and strong or moderate CYP3A4 inducers decrease NUBEQA exposure, which may decrease NUBEQA activity. Avoid concomitant use.

Combined P-gp and strong CYP3A4 inhibitors increase NUBEQA exposure, which may increase the risk of NUBEQA adverse reactions. Monitor more frequently and modify NUBEQA dose as needed.

**Effects of NUBEQA on Other Drugs** – NUBEQA inhibits breast cancer resistance protein (BCRP) transporter. Concomitant use increases exposure (AUC) and maximal concentration of BCRP substrates, which may increase the risk of BCRP substrate-related toxicities. Avoid concomitant use where possible. If used together, monitor more frequently for adverse reactions, and consider dose reduction of the BCRP substrate.

NUBEQA inhibits OATP1B1 and OATP1B3 transporters. Concomitant use may increase plasma concentrations of OATP1B1 or OATP1B3 substrates. Monitor more frequently for adverse reactions and consider dose reduction of these substrates.

Review the Prescribing Information of drugs that are BCRP, OATP1B1, and OATP1B3 substrates when used concomitantly with NUBEQA.

\*Concomitant GnRH analog or prior bilateral orchiectomy.

**References:** **1.** NUBEQA (darolutamide) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc.; October 2023. **2.** Smith MR, Hussain M, Saad F, et al; ARASENS Trial Investigators. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. *N Engl J Med.* 2022;386(12):1132-1142. **3.** Fizazi K, Shore N, Tammela T2, et al. Nonmetastatic, castration-resistant prostate cancer and survival with darolutamide. *N Engl J Med.* 2020;383(11):1040-1049. **4.** Fizazi K, Shore N, Tammela TL, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med.* 2019;380(13):1235-1246.

Please see the following page(s) for the brief summary of Prescribing Information.



© 2023 Bayer. All rights reserved. Bayer, the Bayer Cross, and NUBEQA are registered trademarks of Bayer.  
PP-NUB-US-2879-1 11/23

AUA2024 RECAPS

# The Meaning of Mentorship

Amanda C. North, MD  
Children's Hospital at Montefiore, Bronx, New York

The mission of the Society of Women in Urology (SWIU) is “to support the professional develop-

ment and career advancement of women urologists and urologic researchers through education, advocacy, and mentorship.” SWIU offers many different opportunities for mentorship including the annu-

al clinical mentoring conference in January, speed mentoring, a longitudinal mentor-mentee program, and resident travel awards to help residents in urology attend the annual conference. In recognition

of the importance of mentorship to the mission of SWIU, a mentorship award is given every year at the annual meeting. The Christina

→ Continued on page 15

NUBEQA® (darolutamide) tablets, for oral use  
Initial U.S. Approval: 2019

**BRIEF SUMMARY OF PRESCRIBING INFORMATION  
CONSULT PACKAGE INSERT FOR  
FULL PRESCRIBING INFORMATION**

**1 INDICATIONS AND USAGE**

NUBEQA is indicated for the treatment of adult patients with:

- non-metastatic castration resistant prostate cancer (nmCRPC)
- metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel.

**4 CONTRAINDICATIONS**

None.

**5 WARNINGS AND PRECAUTIONS**

**5.1 Ischemic Heart Disease**

Ischemic heart disease, including fatal cases, occurred in patients receiving NUBEQA. In a randomized study of patients with nmCRPC (ARAMIS), ischemic heart disease occurred in 3.2% of patients receiving NUBEQA and 2.5% receiving placebo, including Grade 3-4 events in 1.7% and 0.4%, respectively. Ischemic events led to death in 0.3% of patients receiving NUBEQA and 0.2% receiving placebo. In a randomized study of patients with mHSPC (ARASENS), ischemic heart disease occurred in 3.2% of patients receiving NUBEQA with docetaxel and 2% receiving placebo with docetaxel, including Grade 3-4 events in 1.3% and 1.1%, respectively. Ischemic events led to death in 0.3% of patients receiving NUBEQA with docetaxel and 0% receiving placebo with docetaxel.

Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue NUBEQA for Grade 3-4 ischemic heart disease.

**5.2 Seizure**

Seizure occurred in patients receiving NUBEQA.

In ARAMIS, Grade 1-2 seizure occurred in 0.2% of patients receiving NUBEQA and 0.2% receiving placebo. Seizure occurred 261 and 456 days after initiation of NUBEQA.

In ARASENS, seizure occurred in 0.6% of patients receiving NUBEQA with docetaxel, including one Grade 3 event, and 0.2% receiving placebo with docetaxel. Seizure occurred 38 to 340 days after initiation of NUBEQA.

It is unknown whether anti-epileptic medications will prevent seizures with NUBEQA. Advise patients of the risk of developing a seizure while receiving NUBEQA and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others. Consider discontinuation of NUBEQA in patients who develop a seizure during treatment.

**5.3 Embryo-Fetal Toxicity**

The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy when administered to a pregnant female [see *Clinical Pharmacology*].

Advise males with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA [see *Use in Specific Populations*].

**6 ADVERSE REACTIONS**

**6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

**Non-Metastatic Castration Resistant Prostate Cancer**

The safety of NUBEQA was evaluated in ARAMIS, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, that enrolled patients who had non-metastatic castration-resistant prostate cancer (nmCRPC) [see *Clinical Studies*]. Patients received either NUBEQA at a dose of 600 mg, or a placebo, twice a day. All patients in the ARAMIS study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. Among patients who received NUBEQA, the median duration of exposure was 14.8 months (range: 0 to 44.3 months). Serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions in ≥1% of patients who received NUBEQA included urinary retention, pneumonia and hematuria. Fatal adverse reactions occurred in 3.9% of patients receiving NUBEQA and 3.2% of patients receiving placebo. Fatal adverse reactions in patients who received NUBEQA included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%).

Permanent discontinuation of NUBEQA due to adverse reactions occurred in 9% of patients receiving NUBEQA. The most common adverse reactions requiring permanent discontinuation in patients who received NUBEQA included cardiac failure (0.4%), and death (0.4%).

Dosage interruptions due to adverse reactions occurred in 13% of patients treated with NUBEQA. The most common adverse reactions requiring dosage interruption in patients who received NUBEQA included hypertension (0.6%), diarrhea (0.5%), and pneumonia (0.5%).

Dosage reductions due to adverse reactions occurred in 6% of patients treated with NUBEQA. The most common adverse reactions requiring dosage reduction in patients treated with NUBEQA included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%).

The most common (>2% with a ≥2% increase compared to placebo) adverse reactions, including laboratory test abnormalities, were AST increased, neutrophil count decreased, fatigue, bilirubin increased, pain in extremity, and rash.

Table 1 summarizes the adverse reactions in ARAMIS.

**Table 1: Adverse Reactions (>2% with a ≥2% increase compared to placebo) in Patients with Non-Metastatic Castration Resistant Prostate Cancer in ARAMIS**

Adverse Reaction	NUBEQA (n=954)		Placebo (n=554)	
	All Grades %	Grades 3 or 4 %	All Grades %	Grade 3 or 4 %
Fatigue <sup>1</sup>	16	0.6	11	1.1
Pain in extremity	6	0	3	0.2
Rash <sup>2</sup>	4	0.1	1.4	0

<sup>1</sup> Includes fatigue and asthenia

<sup>2</sup> Includes rash, eczema, rash maculo-papular, dermatitis, erythema multiforme, rash macular, rash papular, rash pustular, skin exfoliation

Clinically relevant adverse reactions occurring in 2% or more of patients treated with NUBEQA included ischemic heart disease (4%) and heart failure (2.1%).

Table 2 summarizes the laboratory test abnormalities in ARAMIS.

**Table 2: Laboratory Test Abnormalities in ARAMIS**

Laboratory Abnormality	NUBEQA (N=954) <sup>1</sup>		Placebo (N=554) <sup>1</sup>	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
AST increased	23	0.5	14	0.2
Neutrophil count decreased	20	4	9	0.6
Bilirubin increased	16	0.1	7	0

<sup>1</sup> The denominator used to calculate the rate varied based on the number of patients with a baseline value and at least one post-treatment value.

**Metastatic Hormone-Sensitive Prostate Cancer**

The safety of NUBEQA, in combination with docetaxel, was evaluated in ARASENS, a randomized (1:1), double-blind, placebo-controlled, multi-center clinical study, that enrolled patients who had mHSPC [see *Clinical Studies*]. Patients were to receive either NUBEQA at a dose of 600 mg, or a placebo, twice a day in combination with docetaxel at a dose of 75 mg/m<sup>2</sup> every 21 days for 6 cycles. All patients in the ARASENS study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. Patients with a medical history of seizure were allowed to enter the study. Among patients who received NUBEQA, the median duration of exposure was 41 months (range: 0.1 to 56.5 months) vs. 16.7 months (range 0.3 to 55.8) with placebo. Eighty-eight percent and 86% of patients received the 6 planned cycles of docetaxel, in the NUBEQA with docetaxel arm and placebo with docetaxel arm, respectively.

Serious adverse reactions occurred in 45% of patients receiving NUBEQA with docetaxel and in 42% of patients receiving placebo with docetaxel, respectively. Serious adverse reactions in ≥ 2% of patients who received NUBEQA with docetaxel included febrile neutropenia (6%), neutrophil count decreased (2.8%), musculoskeletal pain (2.6%) and pneumonia (2.6%). Fatal adverse reactions occurred in 4% of patients receiving NUBEQA with docetaxel and 4% of patients receiving placebo with docetaxel. Fatal adverse reactions in patients who received NUBEQA included COVID-19/COVID-19 pneumonia (0.8%), myocardial infarction (0.3%), and sudden death (0.3%).

Permanent discontinuation of NUBEQA due to adverse reactions occurred in 14% of patients treated in the NUBEQA with docetaxel arm. The most common adverse reactions which resulted in permanent discontinuation of NUBEQA were rash (1.1%), musculoskeletal pain (0.9%), and aspartate aminotransferase (AST) increased (0.9%).

Dosage interruptions of NUBEQA due to adverse reactions occurred in 23% of patients treated in the NUBEQA with docetaxel arm. The most common (>2%) adverse reactions requiring dosage interruption of NUBEQA were alanine aminotransferase (ALT) increased (3.2%), AST increased (3.1%) and febrile neutropenia (2.1%).

Dosage reductions of NUBEQA due to adverse reactions occurred in 9% of patients treated in the NUBEQA with docetaxel arm. The most common (>2%) adverse reactions requiring dosage reduction of NUBEQA were ALT increased (2.8%) and AST increased (2.5%).

The most common (>10% with a ≥2% increase over placebo with docetaxel) adverse reactions are constipation, rash, decreased appetite, hemorrhage, weight increased, and hypertension. The most common laboratory test abnormalities (≥30%) are anemia, hyperglycemia, lymphocyte count decreased, neutrophil count decreased, AST increased, ALT increased, and hypocalcemia.

Table 3 summarizes the adverse reactions in ARASENS.

**Table 3: Adverse Reactions (≥10% with a ≥2% increase compared to placebo with docetaxel) in ARASENS**

Adverse Reaction	NUBEQA with docetaxel (n=652)		Placebo with docetaxel (n=650)	
	All Grades %	Grades 3 or 4 %	All Grades %	Grades 3 or 4 %
Constipation	23	0.3	20	0.3
Rash <sup>1</sup>	20	1.8	15	0.2
Decreased Appetite	19	0.2	13	0.6
Hemorrhage <sup>2</sup>	18	1.4	13	1.4
Weight Increased	18	2.1	16	1.2
Hypertension <sup>3</sup>	14	7	10	3.6

<sup>1</sup> Rash includes rash, rash maculo-papular, palmar-plantar erythrodysesthesia syndrome, eczema, dermatitis, skin exfoliation, dermatitis acneiform, drug eruption, rash pruritic, rash erythematous, erythema multiforme, rash macular, dermatitis exfoliative generalized, penile rash, dyshidrotic eczema, rash papular, dermatitis bullous, rash follicular, rash pustular, rash vesicular, toxic skin eruption

## THE MEANING OF MENTORSHIP

→ Continued from page 14

Manthos Mentoring Award was first given in the year 2000. The award is to remember Dr Christina Manthos, a urologist whose career was cut short by breast cancer, and is given to honor men or women who demonstrate extraordinary mentoring skills in supporting the careers of women urologists. As the 2024 recipient of the Christina Manthos Mentoring

Award, I was invited to speak at the SWIU breakfast at the AUA Annual Meeting in San Antonio, and I want to share my thoughts on this award and on mentorship.

My first SWIU event was in San Francisco in 2004. I was a fifth-year resident in urology and a new mother. While I don't remember the details of the SWIU breakfast that year, I re-

member feeling very inspired. Each resident in my program was required to give a brief summary of our experience at the AUA Annual Meeting at Grand Rounds, and I spoke about the SWIU breakfast. My chairman (who was surprisingly progressive and trained several women residents both before and after me) asked me why there was no Society of Men in Urol-

ogy. I told him that there was indeed. It was called the AUA. (Luckily, he had a good sense of humor, too.) The growth of both women in urology and the influence and impact of SWIU has increased tremendously since that time. I credit the SWIU leadership for their creative and often courageous efforts to support women in urology. I have also been blessed with amazing colleagues—both within and outside of my institution—who have believed in me, supported me, and pushed me. I have also been lucky to train an incredible group of women urologists over the years who continue to amaze me with their clinical skill and academic achievements.

Adam Grant tells us, “We worry about making our parents proud when we should be focused on making our children proud. The responsibility of each generation is not to please our predecessors—it’s to improve the conditions for our successors.”<sup>1</sup> To me, this is one of the core principles of being a mentor or a sponsor. It is not enough to give advice or even to give opportunities. To make the field of urology better for the women who come after us, we must advocate for change. Some of that change has already begun. The American Board of Urology has made it a little bit easier for residents to take parental leave and still be eligible to graduate residency on time. The Annual Meeting is no longer held on Mother’s Day Weekend (I spent my first Mother’s Day at the AUA). Even better, there is now childcare available at the AUA Annual Meeting. None of these changes would have happened without advocacy. Advocacy can mean attending the annual AUA Advocacy Summit in Washington, DC, and going to meetings on Capitol Hill, but it can also mean advocating within your department for equitable distribution of unpaid committee work.

In closing, I owe a huge debt of gratitude to SWIU, my mentors/sponsors, and especially the mentees who have trusted me to support their careers. I am so proud of how far women in urology have come since I first matched in 1999, and I am looking forward to seeing the future of urology filled with women. ■

<sup>2</sup> Hemorrhage includes hematuria, epistaxis, anal hemorrhage, hemorrhoidal hemorrhage, rectal hemorrhage, upper gastrointestinal hemorrhage, hemoptysis, hemorrhage urinary tract, hemorrhagic stroke, subarachnoid hemorrhage, lower gastrointestinal hemorrhage, cystitis hemorrhagic, gastrointestinal hemorrhage, hemorrhage subcutaneous, intra-abdominal hemorrhage, nail bed bleeding, subdural hemorrhage

<sup>3</sup> Hypertension includes hypertension, blood pressure increased, hypertensive emergency and hypertensive crisis.

Clinically relevant adverse reactions in < 10% of patients who received NUBEQA with docetaxel included fractures (8%), ischemic heart disease (3.2%), seizures (0.6%), and drug-induced liver injury (0.3%).

Table 4 summarizes laboratory test abnormalities in the ARASENS study.

**Table 4: Laboratory Test Abnormalities (≥30%) in ARASENS**

Laboratory Abnormality	NUBEQA with docetaxel <sup>1</sup> (N=652)		Placebo with docetaxel <sup>1</sup> (N=650)	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Anemia	72	6	71	7
Hyperglycemia	57	7	53	10
Lymphocyte count decreased	52	12	49	13
Neutrophil count decreased	49	33	44	31
AST increased <sup>2</sup>	40	3.6	35	2.3
ALT increased <sup>2</sup>	37	3.7	31	2.9
Hypocalcemia	31	2.8	28	1.9

<sup>1</sup>The denominator used to calculate the rate varied from 470 to 648 based on the number of patients with a baseline value and at least one post-treatment value.

<sup>2</sup>ALT or AST increases to ≥5 x upper limit of normal (ULN) occurred in 5.3% of patients who received NUBEQA with docetaxel. ALT or AST increases to ≥20 x ULN occurred in 0.3% of patients who received NUBEQA with docetaxel. The median time to onset of any grade ALT or AST increases was 2.8 months (range: 0.03 to 46.9).

Clinically relevant laboratory test abnormalities in < 30% of patients who received NUBEQA with docetaxel included blood bilirubin increased (all grades 20%, Grade 3-4 0.5%) compared to placebo with docetaxel (all grades 10%, grades 3-4 0.3%).

### 7 DRUG INTERACTIONS

#### 7.1 Effect of Other Drugs on NUBEQA

##### Combined P-gp and Strong or Moderate CYP3A4 Inducer

Concomitant use of NUBEQA with a combined P-gp and strong or moderate CYP3A4 inducer decreases darolutamide exposure which may decrease NUBEQA activity [see *Clinical Pharmacology*]. Avoid concomitant use of NUBEQA with combined P-gp and strong or moderate CYP3A4 inducers.

##### Combined P-gp and Strong CYP3A4 Inhibitors

Concomitant use of NUBEQA with a combined P-gp and strong CYP3A4 inhibitor increases darolutamide exposure [see *Clinical Pharmacology*] which may increase the risk of NUBEQA adverse reactions. Monitor patients more frequently for NUBEQA adverse reactions and modify NUBEQA dosage as needed [see *Dosage and Administration*].

#### 7.2 Effects of NUBEQA on Other Drugs

##### Breast Cancer Resistance Protein (BCRP) and Organic Anion Transporting Polypeptides (OATP) 1B1 and 1B3 Substrates

NUBEQA is an inhibitor of BCRP transporter. Concomitant use of NUBEQA increases the AUC and C<sub>max</sub> of BCRP substrates [see *Clinical Pharmacology*], which may increase the risk of BCRP substrate-related toxicities.

Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for adverse reactions, and consider dose reduction of the BCRP substrate drug.

NUBEQA is an inhibitor of OATP1B1 and OATP1B3 transporters. Concomitant use of NUBEQA may increase the plasma concentrations of OATP1B1 or OATP1B3 substrates. Monitor patients more frequently for adverse reactions of these drugs and consider dose reduction while patients are taking NUBEQA [see *Clinical Pharmacology*].

Review the prescribing information of the BCRP, OATP1B1 and OATP1B3 substrates when used concomitantly with NUBEQA.

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

##### Risk Summary

The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy [see *Clinical Pharmacology*]. Animal embryo-fetal developmental toxicology studies were not conducted with darolutamide. There are no human data on the use of NUBEQA in pregnant females.

#### 8.2 Lactation

##### Risk Summary

The safety and efficacy of NUBEQA have not been established in females. There are no data on the presence of darolutamide or its metabolites in human milk, the effect on the breastfed child, or the effect on milk production.

### 8.3 Females and Males of Reproductive Potential

#### Contraception

##### Males

Based on the mechanism of action, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA [see *Use in Specific Populations*].

#### Infertility

##### Males

Based on animal studies, NUBEQA may impair fertility in males of reproductive potential [see *Nonclinical Toxicology*].

#### 8.4 Pediatric Use

Safety and effectiveness of NUBEQA in pediatric patients have not been established.

#### 8.5 Geriatric Use

Of the 954 patients who received NUBEQA in ARAMIS, 88% of patients were 65 years and over, and 49% were 75 years and over. Of the 652 patients who received NUBEQA in ARASENS, 63% of patients were 65 years and over, and 16% were 75 years and over. No overall differences in safety or efficacy were observed between these patients and younger patients in both studies.

#### 8.6 Renal Impairment

Patients with severe renal impairment (eGFR 15–29 mL/min/1.73 m<sup>2</sup>) who are not receiving hemodialysis have a higher exposure to NUBEQA and reduction of the dose is recommended [see *Dosage and Administration and Clinical Pharmacology*]. No dose reduction is needed for patients with mild or moderate renal impairment (eGFR 30–89 mL/min/1.73 m<sup>2</sup>). The effect of end stage renal disease (eGFR ≤15 mL/min/1.73 m<sup>2</sup>) on darolutamide pharmacokinetics is unknown.

#### 8.7 Hepatic Impairment

Patients with moderate hepatic impairment (Child-Pugh Class B) have a higher exposure to NUBEQA and reduction of the dose is recommended [see *Dosage and Administration and Clinical Pharmacology*]. No dose reduction is needed for patients with mild hepatic impairment. The effect of severe hepatic impairment (Child-Pugh C) on darolutamide pharmacokinetics is unknown.

### 10 OVERDOSAGE

There is no known specific antidote for darolutamide overdose. The highest dose of NUBEQA studied clinically was 900 mg twice daily, equivalent to a total daily dose of 1800 mg. No dose limiting toxicities were observed with this dose.

Considering the saturable absorption and the absence of evidence for acute toxicity, an intake of a higher than recommended dose of darolutamide is not expected to lead to systemic toxicity in patients with intact hepatic and renal function [see *Clinical Pharmacology*].

In the event of intake of a higher than recommended dose in patients with severe renal impairment or moderate hepatic impairment, if there is suspicion of toxicity, interrupt NUBEQA treatment and undertake general supportive measures until clinical toxicity has been diminished or resolved. If there is no suspicion of toxicity, NUBEQA treatment can be continued with the next dose as scheduled.

### 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information)

#### Ischemic Heart Disease

Inform patients that NUBEQA has been associated with an increased risk of ischemic heart disease. Advise patients to seek immediate medical attention if any symptoms suggestive of an ischemic heart disease event occur [see *Warnings and Precautions*].

#### Seizure

Inform patients that NUBEQA has been associated with an increased risk of seizure. Discuss conditions that may predispose to seizures and medications that may lower the seizure threshold. Advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Inform patients to contact their healthcare provider right away if they have loss of consciousness or seizure [see *Warnings and Precautions*].

#### Embryo-Fetal Toxicity

Inform patients that NUBEQA can be harmful to a developing fetus and can cause loss of pregnancy [see *Use in Specific Populations*].

Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA [see *Warnings and Precautions and Use in Specific Populations*].

#### Dosage and Administration

Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with NUBEQA.

Instruct patients to take their dose of two tablets (twice daily). NUBEQA should be taken with food. Each tablet should be swallowed whole.

Inform patients that in the event of a missed daily dose of NUBEQA, to take any missed dose, as soon as they remember prior to the next scheduled dose, and not to take two doses together to make up for a missed dose [see *Dosage and Administration*].

#### Infertility

Advise male patients that NUBEQA may impair fertility [see *Use in Specific Populations*].

**Manufactured by:** Orion Corporation, Orion Pharma, FI-02101 Espoo, Finland

**Manufactured for:** Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ 07981 USA

© 2019 Bayer HealthCare Pharmaceuticals Inc.

For more information, call Bayer HealthCare Pharmaceuticals Inc. at Bayer at 1-888-842-2937 or go to www.NUBEQA-us.com

6711103BS

1. Grant A. *Hidden Potential: The Science of Achieving Greater Things*. Random House; 2023.

## AUA AWARD WINNERS

# Understanding the Relationship Between Biofilms and Calcium Stones

Daniel Massana Roquero, PhD  
Stanford University, California

Daniel Massana Roquero, PhD, was one of the recipients of the 2024 Urology Care Foundation™ Research Scholar Awards. These awards provide \$40,000 annually for mentored research training for clinical and postdoctoral fellows or early-career faculty. The Endourological Society sponsored Dr Massana Roquero's award.

Kidney stone disease is highly prevalent and most commonly caused by calcium stones. In most cases, calcium stones are present in patients without any apparent metabolic disorder or systemic disease.<sup>1</sup> It has long been thought that calcium stones originate from an imbalance in the urine salts, leading to supersaturation and precipitation in the form of crystals. While still seen as a contributing factor, research indicates that mineral supersaturation is not more prevalent in stone formers than in control groups.<sup>2,3</sup> In our experience, we have found that approximately 35% of calcium stones freshly collected from stone surgeries harbored a wide range of gram-positive and gram-negative uropathogens. This prompted us to consider the connection between bacteria and calcium stones from a different perspective. Assessing whether the connection between bacteria and calcium stones is causative or coincidental is essential to identify risk factors for stone formation and guide prevention and therapy. In the last decade, the association of bacteria with calcium stones has been under heavy scruti-

“While still seen as a contributing factor, research indicates that mineral supersaturation is not more prevalent in stone formers than in control groups.<sup>2,3</sup>”

“We hypothesize that biofilms may play a role in inducing calcium crystal aggregation and encrustation and also promote the mineralization of calcium salts in their interface with the urine microenvironment.”

ny by several research groups, which have shown that various types of bacteria can induce or aggravate calcium stone disease.<sup>4,5</sup>

In this proposal, we aim to study the influence of bacteria in calcium stone, with a particular focus on the role that bacterial biofilms play in contributing to mineralization and overall stone growth. Bacteria can adhere to solid substrates, such as stones or calcium oxalate crystals, by encasing themselves in a self-produced polymeric matrix, forming biofilms. We hypothesize that biofilms may play a role in inducing calcium crystal aggregation and encrustation and also promote the mineralization of calcium salts in their interface with the urine microenvironment. In addition, we hypothesize that calcium stones with significant bacterial burdens have specific chemical constituents and structural domains that are not found in abiotic, pure metabolic calcium stones.

Our hypotheses find strong support in naturally occurring bacterial-induced calcium stones within aqueous ecosystems. These formations, known as microbialites, arise from the intricate interplay between microbial activities, specifically bacterial metabolisms, and the heightened saturation of ions in water.<sup>6,7</sup> Furthermore, numerous recent studies have illustrated that bacteria can stimulate the biomineralization of calcium carbonates and calcium phosphates.<sup>8,9</sup>

Our objective is to gather robust evidence of these occurrences through an in vitro model simulating supersaturated urine and by performing a thorough biochemical exam of human-derived stones ex vivo.

Employing a rigorous in vitro model simulating hypercalciuria, we will examine the influence of patient-derived uropathogen biofilms on the processes of crystal aggregation, encrustation, and mineralization by optical and electron microscopy. Further, we aim to identify the chemical and biological constituents of patient-derived calcium stone fragments and their distribution within the stone. We will perform a high-resolution characterization of the stone's chemical and microbial composition by combining advanced characterization and imaging techniques. In addition, we will conduct an extensive mesoscopic and microscopic characterization of whole stone fragments to understand the 3D distribution of different biological and chemical constituents as well as crystal phases.

We are confident that the meticulously crafted experiments, coupled with high-resolution techniques, will yield intriguing and insightful information on the connection between biofilms and calcium stones. I am sincerely grateful to the urology community for their support, which will enable me to continue my work and grow as a young scientist on my path to becoming an independent investigator. I am thankful to my advisor, Dr Joseph Liao, for his support and the opportunity to

“We will perform a high-resolution characterization of the stone's chemical and microbial composition by combining advanced characterization and imaging techniques.”

“We are confident that the meticulously crafted experiments, coupled with high-resolution techniques, will yield intriguing and insightful information on the connection between biofilms and calcium stones.”

leverage my background in chemistry in both translational medical device development and basic science research, both related to benign urological diseases. Additionally, I would like to extend my gratitude to the Department of Urology at Stanford University and external collaborators for their support. ■

1. Coe FL, Worcester EM, Evan AP. Idiopathic hypercalciuria and formation of calcium renal stones. *Nat Rev Nephrol.* 2016;12(9):519-533. doi:10.1038/nrneph.2016.101
2. Borghi L, Guerra A, Meschi T, et al. Relationship between supersaturation and calcium oxalate crystallization in normal and idiopathic calcium oxalate stone formers. *Kidney Int.* 1999;55(3):1041-1050. doi:10.1046/j.1523-1755.1999.0550031041.x
3. Curhan GC, Willett WC, Speizer FE, Stampfer MJ. Twenty-four-hour urine chemistries and the risk of kidney stones among women and men. *Kidney Int.* 2001;59(6):2290-2298. doi:10.1046/j.1523-1755.2001.00746.x
4. Chutipongtanat S, Sutthimethakorn S, Chiangjong W, Thongboonkerd V. Bacteria can promote calcium oxalate crystal growth and aggregation. *J Biol Inorg Chem.* 2013;18(3):299-308. doi:10.1007/s00775-012-0974-0
5. Barr-Beare E, Saxena V, Hilt EE, et al. The interaction between enterobacteriaceae and calcium oxalate deposits. *PLoS One.* 2015;10(10):e0139575. doi:10.1371/journal.pone.0139575
6. Jung J, Bowles JA. A feasibility study of microbialites as paleomagnetic recorders. *Front Earth Sci.* 2021;9:603805. doi:10.3389/feart.2021.603805
7. Foster JS, Reid RP, Visscher PT, Dupraz C. Characterizing modern microbialites and the geobiological processes underlying their formation. *Front Microbiol.* 2019;10:02299. doi:10.3389/fmicb.2019.02299
8. Bai Y, Guo X, Li Y, Huang T. Experimental and visual research on the microbial induced carbonate precipitation by *Pseudomonas aeruginosa*. *AMB Express.* 2017;7(1):57. doi:10.1186/s13568-017-0358-5
9. Zorzetto L, Scoppola E, Raguin E, Blank KG, Fratzl P, Bidan CM. Induced mineralization of hydroxyapatite in *Escherichia coli* biofilms and the potential role of bacterial alkaline phosphatase. *Chem Mater.* 2023;35(7):2762-2772. doi:10.1021/acs.chemmater.2c02969