



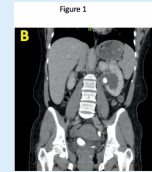
THE OFFICIAL NEWSMAGAZINE OF THE AMERICAN UROLOGICAL ASSOCIATION

## The Future of Urolithiasis Measurement: Determining Stone Volume

Andrei D. Cumpanas, MD; Roshan M. Patel, MD; Jaime Landman, MD; Ralph V. Clayman, MD



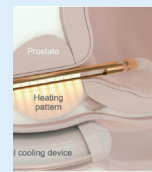
## INSIDE THIS ISSUE



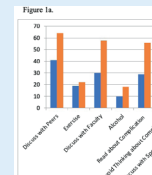
The Dreaded Retained Stent: Our Approach

## COMING SOON in May

### AUANews<sup>Extra</sup>



Transurethral Ultrasound Ablation Procedure vs Robotic-Assisted Laparoscopic Radical Prostatectomy



An Analysis of Urology Trainees and Surgical Complications

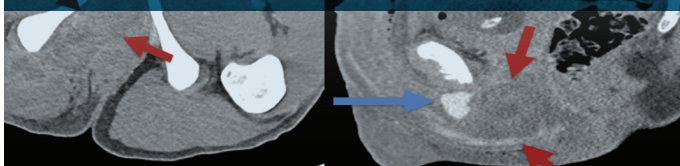
## A Sustainable Model to Provide “Free-of-Cost” Tertiary Care to Disenfranchised in Low-Income Countries

Syed Adibul Hasan Rizvi, FRCS



## Ruptured Penile Artery Branch Pseudoaneurysm Embolization After Perineal Ballistic Injury

Benjamin Taber, BS  
Brandon Waddell, BS  
Michael Uhouse, MD  
Sarah Kantharia, MD  
Michael Whalen, MD



## Ball Security: Are Male Athletes Wearing Protective Cups?

Andrew Allen, BS  
Jared Bieniek, MD



## Workplace Violence: Post-COVID Trends, Risk Factors, and Mitigating Strategies

Ly Hoang Roberts, MD  
Raevti Bole, MD, MS  
Hadley Wood, MD



Is YouTube an Effective Patient Resource? Analysis of the Top Benign Prostatic Hyperplasia Videos

Investigation of Penile Suspensory Ligaments Using Epoxy Sheet Plastination and Confocal Microscopy

Artificial Urinary Sphincter Erosion: Which Patients Are at Risk?

Female Cystectomy: Pelvic Floor Considerations and Quality of Life

End-Stage and Chronic Kidney Disease in Classic Bladder Exstrophy: A Retrospective Multi-Institutional Study

Buccal Mucosa for Urethral Reconstruction: Has It Stood the Test of Time?

HLA-B\*5801 Screening Before Allopurinol Administration to Prevent Allopurinol Hypersensitivity Syndrome

Panel Discussion: Post-Ureteroscopy Stents

A Case in Point for Relevance of Point-of-Care Ultrasound Imaging in Urology Practice

Digging for Data: Driving Health Equity With Science

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May 2024, Volume 29 | Issue 5

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# The Future of Urolithiasis Measurement: Determining Stone Volume

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*Measurement is the first step that leads to control and to improvement.*

*If you can't measure something, you can't understand it.*

*If you can't understand it, you can't control it.*

*If you can't control it, you can't improve it.*

**H. James Harrington**

Maximum linear stone measurements continue to be the standard of care for stone burden characterization according to the AUA and European Association of Urology's guidelines. Previous studies have highlighted the inherent limitations of linear measurements among the growing number of stone patients globally.<sup>1,2</sup> Patel et al noted that when comparing the linear measurements of the same stone across 3 different board-certified radiologists, the average interobserver error was 26.3%.<sup>3</sup> This discrepancy is concerning because the efficacy of maximum linear measurements in predicting actual stone volume diminishes significantly as stone size

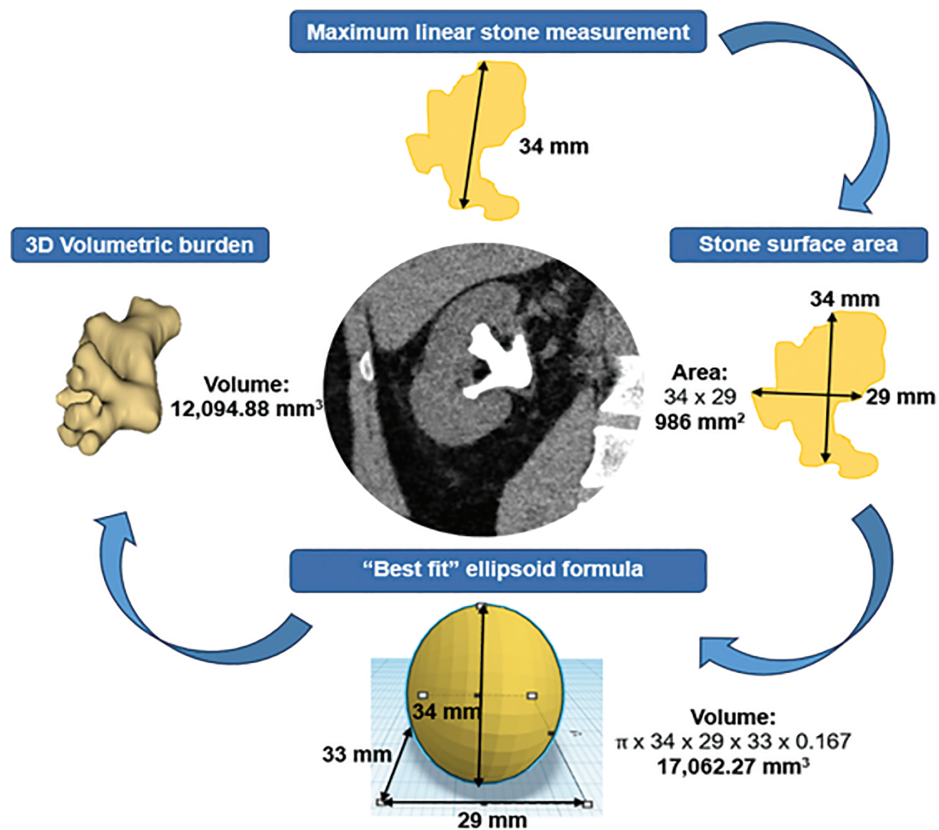
“Specifically, for stones < 10 mm, the maximum stone diameter predicts 76% of the actual stone volume, whereas for > 20-mm stones, the volumetric predictive capacity of maximum diameter drops to only 10%.<sup>4</sup>”

“Clearly, kidney stones are 3D structures, and the 2D kidney, ureter, and bladder x-ray measurements of the past, when applied to CT scans, do not accurately reflect the true stone burden (Figure 1).”

increases.<sup>4</sup> Specifically, for stones < 10 mm, the maximum stone diameter predicts 76% of the actual stone volume, whereas for > 20-mm stones, the volumetric predictive capacity of maximum diameter drops to only 10%.<sup>4</sup>

Clearly, kidney stones are 3D structures, and the 2D kidney, ureter, and bladder x-ray measurements of the past, when applied to CT scans, do not accurately reflect the true stone burden (Figure 1). To address the challenge of accurately quantifying stone volume, Finch et al proposed the utilization of “best-fit” ellipsoid formulas.<sup>5</sup> These formulas incorporate 3 linear measurements of the stone.<sup>5</sup> They found that smaller stones (<9 mm) were more suitably characterized by the prolate ellipsoid formula, while medium-sized stones (9-15 mm) correlated with an oblate formula, and larger stones (>15 mm) aligned best with the scalene formula.<sup>5</sup> Due to the complex, irregular shape of renal calculi, especially as they become larger, the various ellipsoid formulas become less accurate as the stone's size increases (determined through water displacement or gas pycnometry).<sup>5-7</sup> Indeed, even using the best-fit ellipsoid formula, the actual stone volume is overestimated by 27% for stones < 9 mm and by 89% for stones 20 mm or larger.<sup>4</sup>

To overcome these inaccuracies, we developed a 3D stone



**Figure 1.** Variations with regard to linear measurement, 3D measurement to calculate a best-fit ellipsoid formula, and true volume measurement using 3D slicer volume determination are depicted. In this case, the ellipsoid formula overestimated the true stone volume, as determined by 3D slicer measurement, by 41%.

volume artificial intelligence (AI) algorithm.<sup>4</sup> The 16-layer contracting-expanding convolutional neural network technology facilitates 1- to 2-minute volume compilation while ensuring accuracy (R Pearson correlation coefficient = 0.99) and precision (Dice 3D overlap score = 0.88) when compared to the manually calculated 3D characterization of stone burden using the 3D slicer program.<sup>4</sup> The AI algorithm obviates the need for manual measurements, negates interobserver variability, eliminates the inaccuracies of the ellipsoid formulas, and provides a rapid, accurate volume assessment.

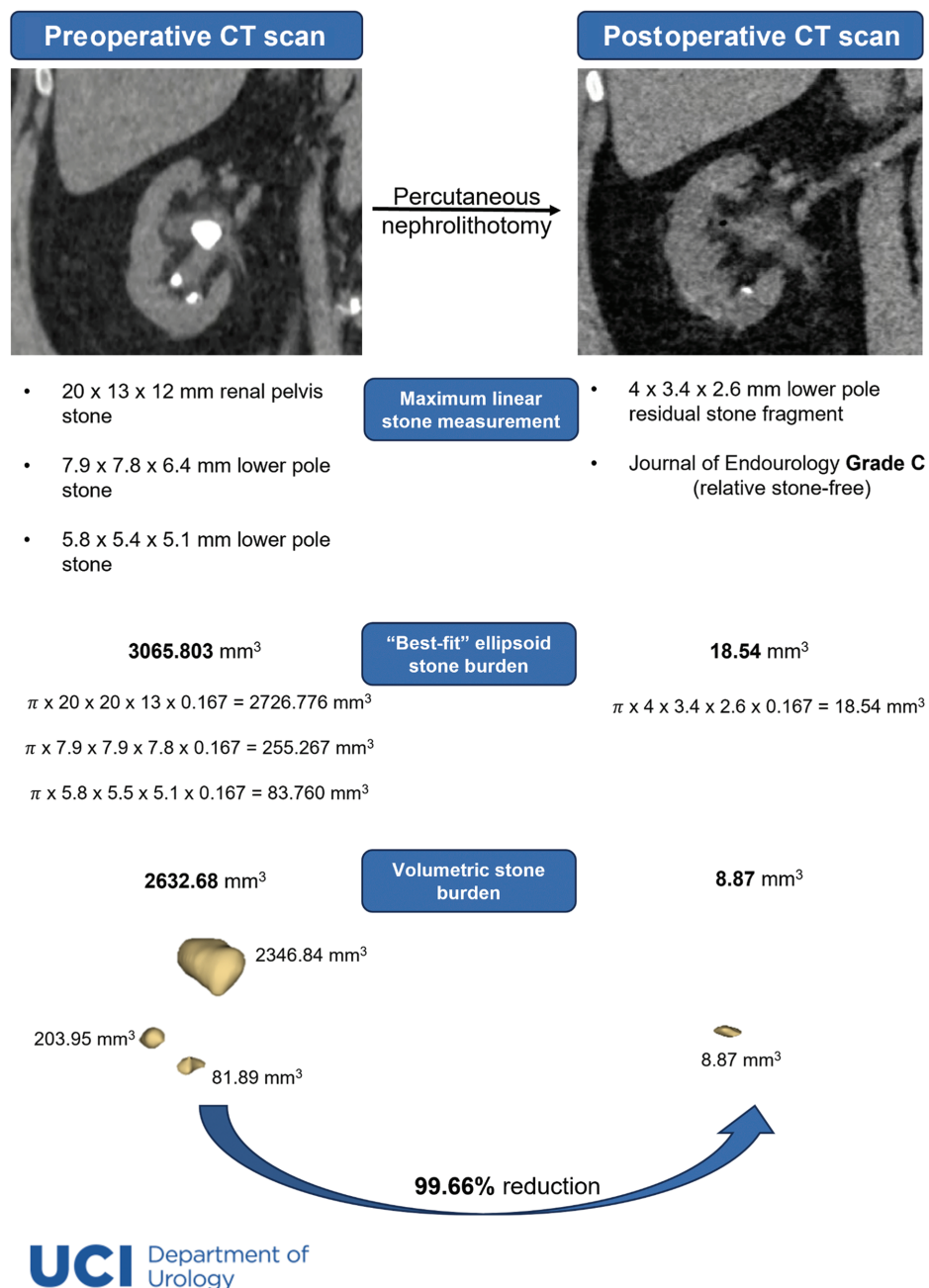
From this work, several important questions have arisen. First: How does/should stone volume impact the choice of surgical management? Although current guidelines recommend percutaneous nephrolithotomy as the first-line option for the management of stones > 2 cm, is clearing a 20- × 7- × 2-mm stone percutaneously reasonable when one would use a ureteroscopic approach for a 15- × 10- × 8-mm stone, given the

“In fact, any residual stone fragment, irrespective of its size, has the potential to serve as a nidus for stone growth, eventually leading to recurrence and necessitating further intervention.”

fact that the latter has a 4-fold larger volume? Further investigation is warranted to elucidate whether differences in volumetric stone burden among subgroups with equivalent 1D linear sizes have discernable effects on surgical outcomes and patient management.

## THE FUTURE OF UROLITHIASIS MEASUREMENT: DETERMINING STONE VOLUME

→ Continued from page 3



**Figure 2.** The importance of reporting both 3D slicer volumetric stone burden reduction and the maximum linear size of any residual stone fragments is depicted. Relying solely on percent stone volume clearance is misleading; as in this case, despite a 99.66% stone clearance by volume, the remaining 3.8-mm fragment (*Journal of Endourology* evaluation of relative stone-free status—Grade C) has a high likelihood of growing and/or resulting in symptoms leading to another surgical procedure within the next 2 to 4 years.

Second: Is volumetric stone clearance a reliable metric of successful surgery? Although volumetric stone clearance (cubic millimeters of stone per minute of surgery) allows for a more standardized means of reporting operative outcomes, it is essential to exercise caution when relying solely on volume reduction when assessing outcomes. For example, a 95% reduction in stone burden, although commendable, could trivialize the presence of a residual 3- to 4-mm stone fragment (Figure 2).

According to the CT-based grading scale proposed by the *Journal of Endourology*,<sup>8</sup> a fragment of this size would correspond to a relative stone-free Grade C (2.1- to 4-mm fragments). These fragments are not “clinically insignificant” as previously thought.<sup>9,10</sup> Indeed, at a median postoperative follow-up of only 7 months, fragments 4 mm or smaller carry a considerable risk of reintervention (16%) and complications (11%). In fact, any residual stone fragment, irrespective of its size, has the potential to serve as a

“Incorporation of preoperative and postoperative standardized volumetric stone burden outcomes into current clinical urolithiasis research would help to further optimize guidelines-based treatment options.”

nidus for stone growth, eventually leading to recurrence and necessitating further intervention. Clearly, achieving absolute stone-free status (*Journal of Endourology* Grade A, no fragments present on a 2- to 3-mm noncontrast CT scan) is the goal in order for our patients to have the very best outcome from their stone surgery.

Third: What are the implications of volumetric stone burden follow-up for patients who have undergone a metabolic evaluation and are on medical management for their stone disease? To date, surveillance of urolithiasis patients primarily relies on correlating 24-hour urine parameters with the linear size growth of stones. Yet, as underlined by Eisner et al, the average interobserver variability when comparing linear stone measurements ranges between 1.2 and 1.9 mm.<sup>11</sup> With such low reproducibility, the reliance on linear stone size growth is problematic given that a 1- to 2-mm size change can be attributed to various factors: measurement error, change in the stone’s orientation within the collecting system, or true stone growth. This uncertainty significantly impacts the medical management of nephrolithiasis, as the detection of true stone growth usually prompts further patient evaluation and modification in both diet and medical therapy. This becomes even more important when dealing with patients with multiple stones, such as individuals

with nephrocalcinosis due to medullary sponge kidney disease.

In summary, it is our belief that integrating volumetric stone burden assessment into routine clinical practice would be helpful with regard to nephrolithiasis surveillance and management, with implications extending to both surgical treatment planning as well as long-term follow-up care. Incorporation of preoperative and postoperative standardized volumetric stone burden outcomes into current clinical urolithiasis research would help to further optimize guidelines-based treatment options. ■

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AUA AWARD WINNERS

# A Sustainable Model to Provide “Free-of-Cost” Tertiary Care to Disenfranchised in Low-Income Countries

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Sindh Institute of Urology and Transplantation,  
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I am honored and humbled to receive the Urology Care Foundation™ Humanitarian Recognition Award for 2024. I am also thankful to the AUA for giving me this opportunity to highlight our model of free care to the poor in low-income countries.

After graduating from Dow Medical College Karachi in 1961, I proceeded to the UK for fellowships in surgery. I was awarded fellowship from The Royal College of Surgeons (London) and The Royal College of Surgeons (Edinburgh) in 1967. I was extremely impressed and influenced by the National Health Service in the UK, where medical treatment was provided free to all. In 1971, I returned to Pakistan and joined an 8-bed urology ward as assistant professor in Civil Hospital, Karachi. Back home, I came face to face with the “poverty” as I treated the im-

poor of our society. Those who could not buy their next meal had to purchase medicines and surgical consumables as they were not provided by the public hospital. I guess humanism was imbibed in my character growing up in a village where rich and poor lived together and poverty was not stigmatized. I decided to engage the community to help these patients in cash and kind, thus leading to the establishment of a community-government partnership to provide “free-of-cost” care to the society. I was lucky as like-minded physicians, surgeons, and allied professionals joined my team on this journey. We all believe that “health is a birthright irrespective of caste, color, creed, or religious belief.” It is important here to give some economic indicators of the Pakistani population. Pakistan is a low-income country where per capita income is \$1658/y, 50% live below the poverty line, and 65% reside in rural settings. The government expenditure on health is 1.2% of the gross domestic product.<sup>1</sup>

Fund (in Million US\$)

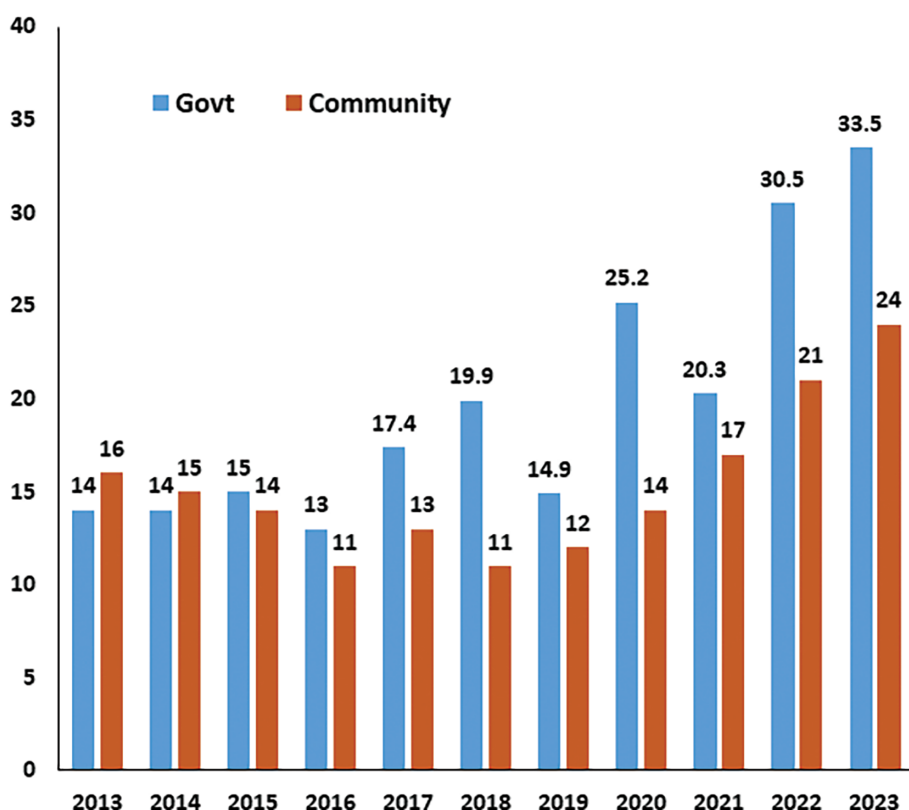
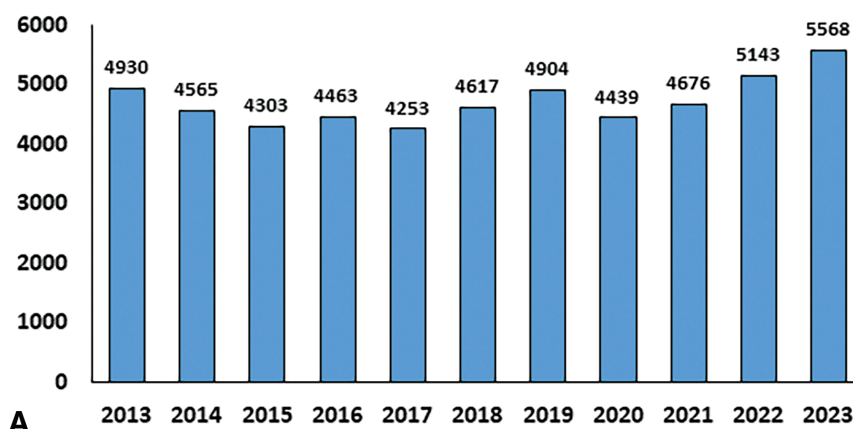


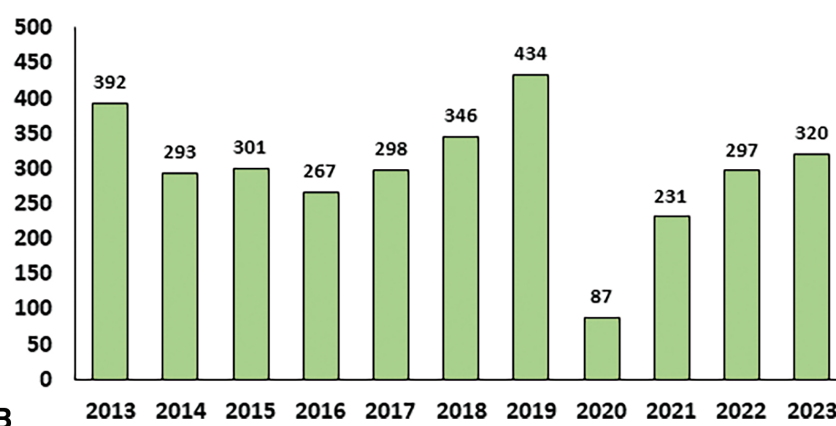
Figure 1. Annual funding by the community and government (Govt).

No of Dialysis patients



A

No of Transplants



B

Figure 2. A, Annual frequency of registered dialysis patients. B, Annual frequency of renal transplant.

## A Model of Community-Government Partnership

The development of this model was gradual. The government provided the infrastructure and staff salaries and the community contributed by cash or in kind to run services. The community was engaged through press, electronic media, and presentations at corporate houses for donations highlighting the free medical services rendered at the urology unit. In recent years, social platforms Facebook, Instagram, and Twitter/X have disseminated the institute’s awareness programs and services. A trust was established in 1986 where government officials and notables of the society were appointed as trustees. For transparency and accountability, the accounts were audited by independent auditing firms. Because of its services,

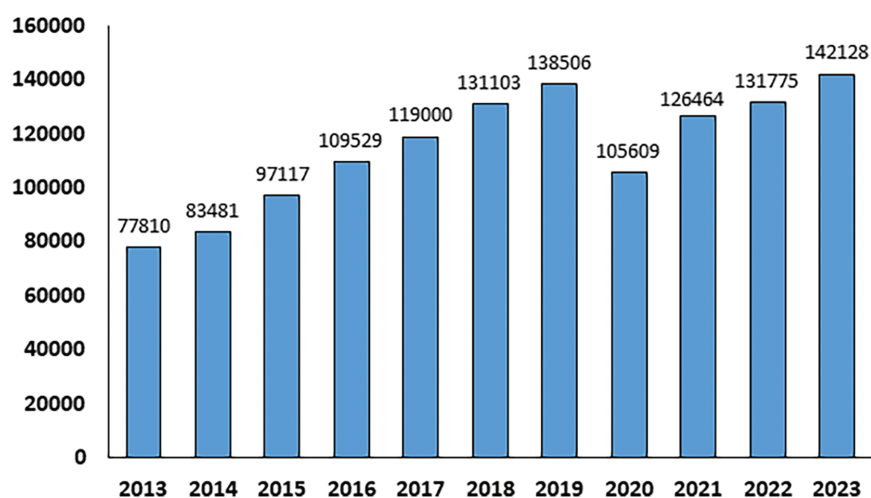
the government helped by elevating the urology ward to Institute of Urology and Transplantation by an act of parliament in 1991. A yearly grant-in-aid was given from the provincial budget.<sup>2,3</sup> Several schemes were initiated to fund treatment and expand facilities: (1) sponsor a patient, (2) fund to purchase equipment, and (3) establish a unit, eg, 20 machine dialysis unit.<sup>4</sup>

The success of the model motivated both the government and the community to help expand services. The government increased the yearly grant-in-aid and business houses came forward for infrastructure development. Business houses constructed a 6-story building worth \$5 million in 1990, a 6-story oncology center fully equipped with radiation therapy worth \$7 million in 2000, and

## A SUSTAINABLE MODEL TO PROVIDE “FREE-OF-COST” TERTIARY CARE

→ Continued from page 5

### No of Procedures



**Figure 3.** Annual frequency of surgical procedures performed at the Sindh Institute of Urology and Transplantation.

**Table.** Growth of Services at the Institute (2013 vs 2023)

Name of services	2013	2023
Total patients, No.	1,003,739	3,496,390
Emergency visits, No.	102,879	179,629
Outpatient visits, No.	313,521	545,867
Inpatient admissions, No.	35,777	85,924
Dialysis sessions, No.	226,226	465,490
Minor and major surgical procedures, No.	77,810	142,128
Lithotripsy sessions, No.	2824	7060
Radiotherapy and chemotherapy, No.	7829	26,688
Total transplants from 1985, No.	4141	7090
Radiology tests, No.	234,975	661,977
Laboratory investigations, No.	6,876,515	12,356,021
Medical costs, millions, USD	6.8	13.2
Total staff, No.	1705	3845

Abbreviations: USD, US dollars.

a 14-story fully equipped transplant center worth \$15 million in 2016.<sup>4</sup> The contributions of the community and government on a year-to-year basis exceed \$50 million (Figure 1).

### Expanding Facilities in Response to Patients Need

Initially the bulk of the urological workload was patients with stone

disease. Many presented with neglected stones in renal failure and end-stage kidney diseases. Nephrology services, including dialysis, were initiated to treat these patients. Thereafter, “free dialysis” brought patients to the institute from all over the country, and this increase led to renal transplantation in 1985.

The Sindh Institute of Urology and Transplantation (SIUT) motto has been, “All facilities under one roof and remaining at the cutting edge of technology.” Therefore, today the institute, in addition to urology, nephrology, and transplantation, offers surgical and medical facilities for general surgery, vascular surgery, head and neck surgery, internal medicine, gastrointestinal, hepatobiliary, cardiology, oncology including breast cancer, infection diseases, neurology, pulmonology, critical care medicine, ophthalmology, laboratory medicine, radiology, radiotherapy, and nuclear medicine. Technology allows the treatment of more patients due to the benefits of economies of scale. Minimally invasive surgery and extracorporeal shock wave lithotripsy were initiated in 1988, percutaneous nephrolithotomy in 1995, and robotic surgery in 2020. The institute is now the biggest robotic surgery unit in Pakistan providing training to surgeons from within and abroad.

### Taking Facilities to the Doorstep of the Patient

Poverty restricts frequent travel within our city and from other cities. Given this, the institute established 5 satellite dialysis centers in Karachi 5 to 10 km away from the institute where the buildings were donated by the community. The government helped establish urology and dialysis centers in the cities

of Sukkur, Larkana, and Nawabshah 500 to 600 km away from the institute. Satellite centers have resulted in substantial savings in time and travel costs for the patients. Patients residing near and around Sukkur and Larkana reach these centers within 1 hour, as compared to 7 to 8 hours to Karachi, and travel costs were reduced from \$10 to \$30 to \$1 to \$2 per daily visit.<sup>4</sup>

### Summary

The model has successfully treated over 30 million patients free-of-cost in the last 50 years. The number of patients dialyzed yearly in all the centers exceeds > 5000 (Figure 2, A). Thus far, more than 7000 renal transplants have been performed, an average of 350/y (Figure 2, B). Urological diseases in both adults and children constitute more than 50% of the workload, where yearly patient volume exceeds 3.5 million. Yearly surgical procedures exceed 140,000, 40% of these for stone disease (Figure 3). The growth of services from 2013 to 2023 is summarized in the Table.

### Conclusions

This model of community-government partnership has been sustained for the last 50 years. The hallmark of sustainability is equity and transparency of services and state-of-the-art treatment facilities under one roof. This model has been possible through the generosity of the public, the support of the government, and most importantly, the SIUT team—their dedication and timeless patient care (Figure 4). Our model of community-government partnership may be emulated in other low-income countries to provide free care to the poor of their population. ■



**Figure 4.** The Sindh Institute of Urology and Transplantation (SIUT) team; commitment and ownership of the philosophy that every human being has the right to health care “free with dignity.”

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## RADIOLOGY CORNER

# Ruptured Penile Artery Branch Pseudoaneurysm Embolization After Perineal Ballistic Injury

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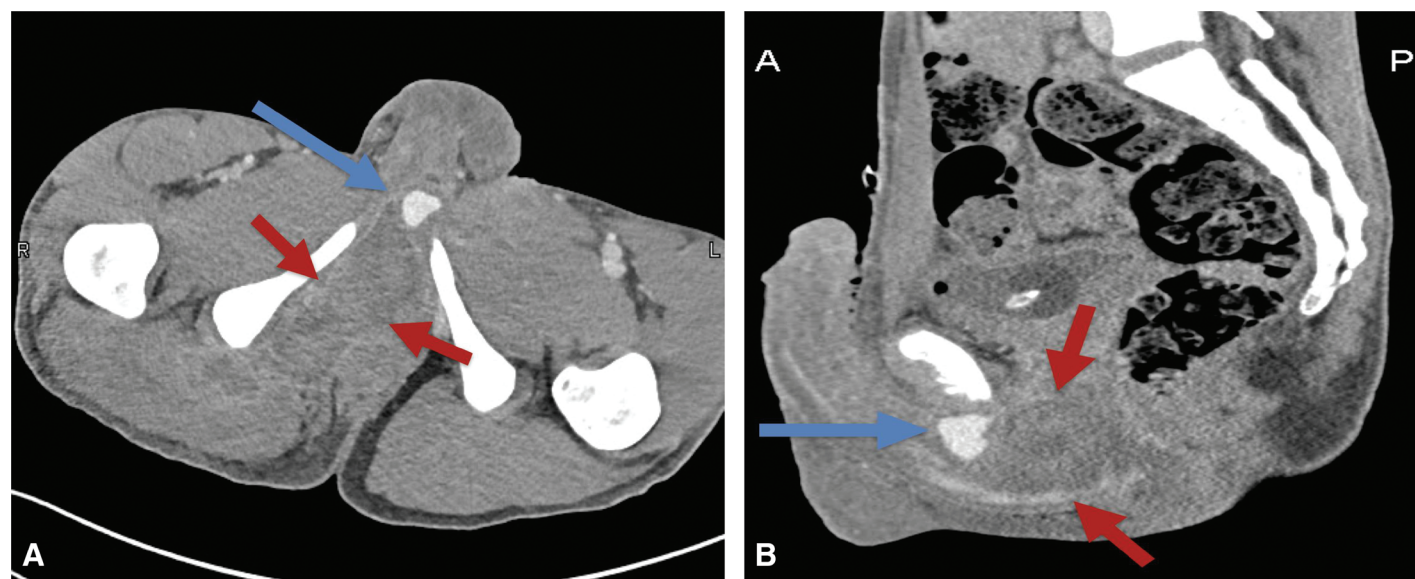
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**Figure 1.** Axial (A) and sagittal (B) CT angiography of the pelvis demonstrates arterial contrast extravasation at the left penile base (blue arrows). Adjacent ischioanal fossa hematoma can also be seen (red arrows).

## Introduction

A pseudoaneurysm is the disruption of an arterial wall, causing a saccular outpouching that communicates with the vessel lumen, contained only by the outermost layer of the arterial wall, the tunica adventitia. Trauma is one of the main etiologies for pseudoaneurysm formation, and early recognition is key as pseudoaneurysm rupture is associated with high morbidity and mortality.<sup>1</sup> Historically, surgical repair was required, but with advancements in image-guided endovascular interventions, angioembolization has become an established treatment

“Trauma is one of the main etiologies for pseudoaneurysm formation, and early recognition is key as pseudoaneurysm rupture is associated with high morbidity and mortality.<sup>1</sup>”

for symptomatic pseudoaneurysm, particularly when the donor artery is accessible and amenable to occlusion. Off-target risks of embolization include inadvertent damage to end-organ structures. This is especially relevant for the very small caliber of the arterial supply to the external genitalia, with concern for significant morbidity from end artery ischemic necrosis.

These risks can be mitigated with selective embolization of the distal-most artery using microcatheters and microwires. There is literature supporting the superselective arterial embolization of the cavernosal artery of the penis with the use of microcoils, which has been demonstrated to be safe and effective while minimizing the risk of long-term erectile dysfunction.<sup>2-4</sup> We present the case of a superselective embolization of a ruptured dorsal penile artery branch pseudoaneurysm following a ballistic injury to the perineum.

## Case Report

### Materials/methods

A 19-year-old male with recent history of a single gunshot wound to the right flank with exit wound in the left anterior thigh status post-flexible sigmoidoscopy and

suprapubic tube placement presented 3 weeks later with acute onset urethral bleeding and dizziness. CT angiography of the pelvis showed a 14- × 4- × 6-cm perineal hematoma with intramuscular extension into the right gluteal and left adductor musculature, and a 2.2-cm pseudoaneurysm with surrounding hematoma near the left penile shaft suspicious for bulbar artery involvement (Figure 1). He was found to have severe hemorrhagic anemia with a hemoglobin of 5.7 g/dL and blood transfusions were initiated. Given the severe anemia and active bleeding, he was taken to the interventional radiology suite for angiogram and selective embolization of a suspected ruptured pseudoaneurysm.

### Results/intervention

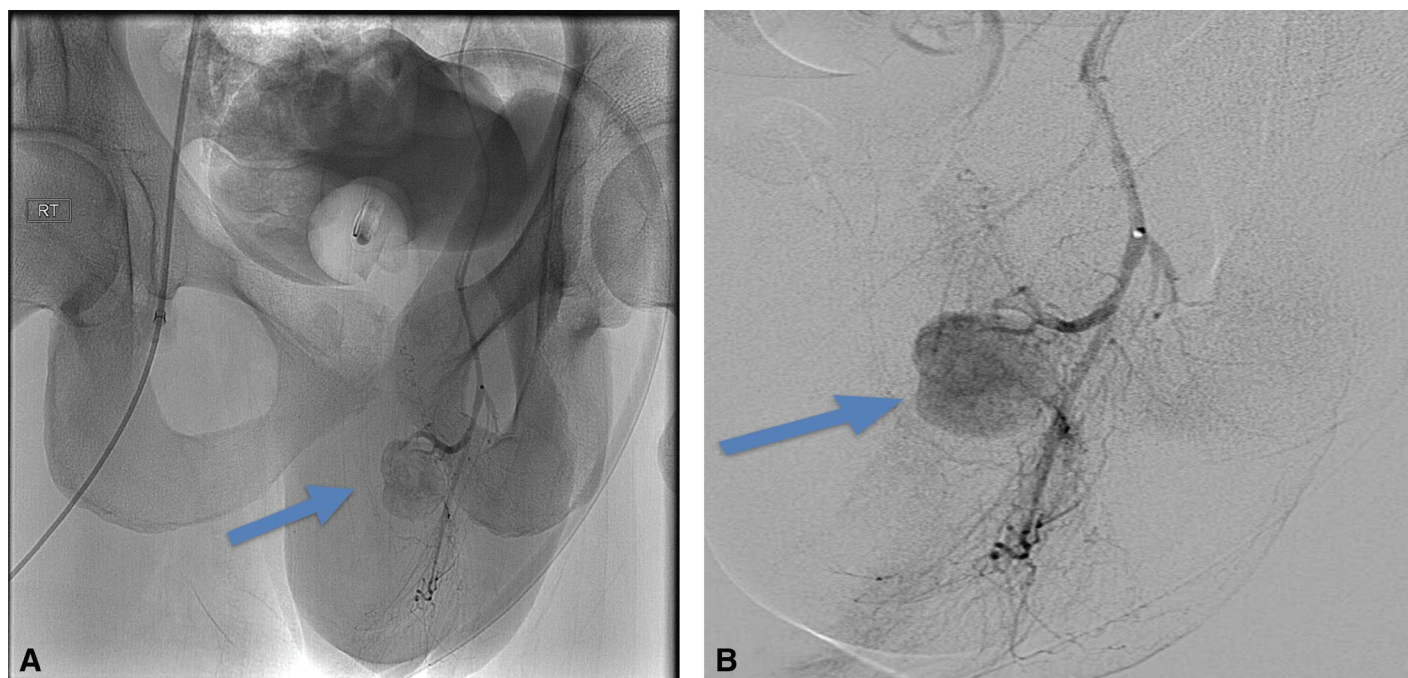
Interventional radiology proceeded with a selective angiogram of the left internal iliac artery, which demonstrated a large pseudoaneurysm off the left internal pudendal/common penile artery, likely the bulbourethral artery. Using a microcatheter and microwire, the left internal pudendal and dorsal penile arteries were sequentially catheterized. Selective angiogram of the terminal branch of the left dorsal penile artery was performed, confirming active extravasation of a bleeding pseudoan-

eurysm (Figure 2). Coil embolization was performed with 2-mm Boston Scientific Interlock microcoils with cessation of contrast filling of the pseudoaneurysm on subsequent ipsilateral and contralateral internal iliac angiograms (Figure 3).

Given the possibility of a superinfected hematoma/perineal abscess given the patient's significant leukocytosis of  $37.74 \times 10^3/\text{mL}$ , the decision was made to perform perineal surgical exploration and contrast studies, which revealed the large ischioanal fossa cavity filled with hematoma. This was evacuated and a Penrose drain was placed. Urology subsequently performed a cystoscopy, which demonstrated a large proximal bulbar urethral cavity with significant blood products and discontinuity with the proximal urethra. Open suprapubic tube exchange was performed given the lack of successful irrigation of the existing suprapubic tube. Antegrade cystoscopy revealed normal prostatic urethra with verumontanum as a visible landmark; the membranous urethra appeared to be relatively intact just distal to the verumontanum, but the proximal bulbar urethra was blind ending, having been obliterated by the gunshot and subsequent

## RUPTURED PENILE ARTERY BRANCH PSEUDOANEURYSM EMBOLIZATION

→ Continued from page 7



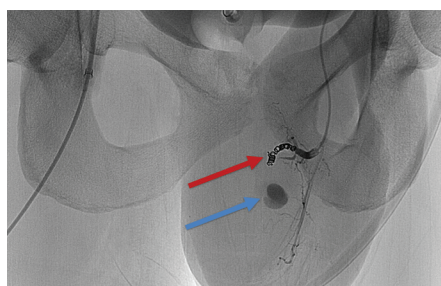
**Figure 2.** Conventional angiography (A) and digital subtraction angiography (B) of the left internal iliac artery shows a large pseudoaneurysm filling off the left dorsal penile artery (blue arrows) with active contrast extravasation.

healing. The patient remained stable and was able to be discharged home with outpatient follow-up and planning for eventual repair of the bulbar urethral stricture.

### Discussion

Timely intervention is crucial for both asymptomatic cases of pseudoaneurysm, to prevent rupture which increases morbidity and mortality, and for symptomatic cases to alleviate associated symptoms and risks.<sup>1</sup> Symptoms such as perineal swelling, generalized pain, and hematuria are indicative of vascular injury. Elective therapy and rapid intervention should be strongly considered in such cases to prevent further deterioration, rupture, and life-threatening hemorrhage.

The precedent for angioembolization in genitourinary trauma



**Figure 3.** Follow-up angiogram following coil deployment (red arrow) demonstrated no further filling of the pseudoaneurysm. Retained contrast is seen within the now excluded pseudoaneurysm (blue arrow).

is well established for both blunt and penetrating renal trauma, with a notable paradigm shift from surgical exploration to angioembolization, even in the setting of high-grade renal trauma (ie, grade 4-5), with resulting reduced rate of nephrectomy.<sup>5</sup> Pelvic angioembolization has been demonstrated as a safe, rapid, and effective intervention for hemorrhage associated with high-impact pelvic injuries in hemodynamically stable and, more recently, unstable patients.<sup>6</sup> Angioembolization avoids the need for invasive surgical access to the pelvis, which is complicated by deeply situated blood vessels that may be avulsed by the mechanism of injury and are prone to torrential hemorrhage upon disruption of the pelvic hematoma during surgical exploration. Angioembolization circumvents the complexity of suture ligation and minimizes the exacerbation of hemorrhage and anatomical insult common with alternative exploratory procedures. Angioembolization may be used as one component of a multistage intervention, first employing an endovascular technique to control hemorrhage and then a later surgical exploration to assess the abdominopelvic viscera.

Regarding technique, percutaneous and endovascular embolization are 2 widely utilized approaches for pseudoaneurysm

appropriate technique based on patient-specific anatomical considerations.

By avoiding nonspecific embolization of the internal iliac arteries and opting for super-selective arterial embolization of the common penile artery, risks associated with nontarget embolization, including arteriogenic erectile dysfunction from occlusion of the cavernosal artery, may be significantly reduced.

This case demonstrates the successful application of super-selective arterial embolization for the emergent treatment of a ruptured deep pseudoaneurysm originating from the dorsal penile artery. This approach ensured precise targeting, achieving effective hemostasis while preserving surrounding vasculature and end-organ perfusion, all while mitigating risks of massive pelvic hemorrhage from open surgical exploration.

### Conclusion

Our case highlights the powerful role of interventional radiology-guided angioembolization of a symptomatic pseudoaneurysm of a branch of the penile artery. The success of super-selective arterial embolization in this case emphasizes its potential as a timely and efficacious treatment modality. Careful consideration regarding embolization techniques and minimization of nontarget embolization reduces long-term complications. ■

“By avoiding nonspecific embolization of the internal iliac arteries and opting for super-selective arterial embolization of the common penile artery, risks associated with nontarget embolization, including arteriogenic erectile dysfunction from occlusion of the cavernosal artery, may be significantly reduced.”

treatment. In this particular instance, percutaneous embolization was not considered due to the specific location and tiny caliber of the pseudoaneurysm, highlighting the importance of selecting the most

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## MEDICAL STUDENT COLUMN

# Ball Security: Are Male Athletes Wearing Protective Cups?

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“Clank.” A screaming fastball strikes the groin of Claude Berry, a professional baseball catcher from 1905 to 1915. Astonishingly, he is unfazed. Having secretly fashioned a piece of molded steel to wear in his pants, this novel piece of protective equipment permitted Claude to be comfortable and composed while crouching behind home plate, an otherwise dangerous position on the baseball diamond.<sup>1,2</sup> Eventually seen as a competitive advantage amongst athletes, manufactured athletic cups grew in popularity over the years to come.

Playing catcher myself, I learned to wear a protective cup behind home plate, especially given the frequency of baseballs flying by. In one terrifying instance, I witnessed an umpire struck in the groin with a foul ball, resulting in significant trauma and testicular loss. Despite my regular use of a cup for baseball, I used one much less frequently for other at-risk sports, such as football. Having not personally witnessed a football-related genital injury, and with few teammates wearing cups, there was less motivation to implement the extra protection. Reflecting on my urology interest and personal sports experiences, I wondered: should I have worn a cup for other sports? Did I put myself at risk? And possibly more importantly, are athletes still wearing cups today?

On review of the literature, the short answer is that it appears most athletes are not. A 2014 survey of high school and college athletes by Bieniek and Sumfest found that only 14.7% of high school athletes and 7.2% of college athletes across all sports wore cups.<sup>3</sup> Both groups self-reported similar incidences of prior testicular injury (17.2% and 18.4%, respectively). Baseball and lacrosse players had the highest rates of cup usage (40.6% and 51.5%, respectively), with less than 10% of athletes from other sports wearing cups.<sup>3</sup> Thankfully, sports-related genitourinary injuries requiring med-

ical attention remain relatively rare in adolescent populations.<sup>4,6</sup> There have been no formal studies investigating athletic cup use or groin injury incidence at professional levels.

This begs the question, why aren't athletes wearing cups? The previously mentioned study found that

among high school and collegiate athletes, reasons cited for not using a cup included not owning one, lack of knowledge, and social image. To get a sense of the cup culture at professional levels, online interviews with various athletes and coaches were reviewed. Kevin Greene, for-

mer 15-year National Football League (NFL) defensive end, noted, “I didn't know anyone on the 4 teams I played for who wore a protective cup.” In the same piece broadcasted nationally on ESPN's

→ Continued on page 10



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## BALL SECURITY: ARE MALE ATHLETES WEARING PROTECTIVE CUPS?

→ Continued from page 9

NFL Countdown, current NFL players Christian McCaffery and Austin Ekeler cited comfort, mobility, and a risk they were “willing to take” as reasons for not wearing groin protection.<sup>7</sup> While originally viewed as a competitive edge, a cultural shift has occurred with some of today’s top athletes seeing athletic cups as a disadvantage. Major League Baseball managers have estimated that only 25% of their players wear cups. Former Minnesota Twins 5-time All-Star Torii Hunter reports the cliché and potentially risky “I just take it like a man” approach to protection.<sup>8</sup> Speaking personally, I witnessed this sentiment firsthand, which played a role in some teammates foregoing genital protection. As such, further efforts are needed to engage professional athletes to endorse the importance of genital protection and shift the culture back towards athletic cup acceptance.

Though the use of an athletic cup remains logical to reduce sports-related testicular injuries, the data, or lack thereof, do not provide a definitive answer. There are currently no studies demonstrating the effectiveness of athletic cups in reducing the incidence or severity of testicular injury. Future studies on this topic could include strict enforcement of protective cups for one group of athletes, with no enforcement of cups in a control, followed by analysis of genital injury incidence and severity. Challenges for such a study would include compliance and the need for a large sample size, given the relative rarity of significant testicular injuries.

According to the AUA, boys competing in contact sports should be wearing a hard protective cup as soon as one properly fits them.<sup>9</sup> Similarly, the American Medical Society for Sports Medicine encourages all male athletes to wear a cup when participating in sports that have a “significant risk for testicular injury,” including lacrosse, soccer, baseball, ice hockey, rugby, football, boxing, and mixed martial arts.<sup>10</sup> Like batting helmets or shoulder pads, male athletes of all ages should be wearing a protective cup when playing a contact sport. Health care providers need to emphasize and educate athletes on the importance of genital protection until the data say otherwise. If not for injury risk reduction,

just point out the competitive edge it gave to Claude Berry. ■

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**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>



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# Workplace Violence: Post-COVID Trends, Risk Factors, and Mitigating Strategies

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In 2013, Dr Ronald Gilbert was fatally shot during an office visit because a former patient attributed his erectile dysfunction and incontinence to an operation done 20 years prior.<sup>1</sup> In 2013, Dr Charles Gholoian was killed and Dr Christine Lajeunesse was injured for what the

killer considered a botched vasectomy.<sup>2</sup> In July 2020, Stephanie Horton, a patient service representative, was killed in a urology clinic by an irate family member. Stories like these, of violence towards health care providers (HCPs), are unfortunately becoming more common.

According to the US Bureau of Labor Statistics, from 2011 to 2018, 156 (~20/y) HCPs were killed in the workplace. Alarming, from 2020 to 2022, the annual rate tripled to 51, 57, and 65 deaths, respectively.<sup>4</sup>

→ Continued on page 12

## 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 ≥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 ≥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 ≥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 ≥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 (≥10% with a ≥2% increase over placebo with docetaxel) were constipation, rash, decreased appetite, hemorrhage, increased weight, and hypertension. The most common laboratory test abnormalities (≥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.**



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WORKPLACE VIOLENCE: POST-COVID TRENDS, RISK FACTORS

→ Continued from page 11

However, these fatalities represent only a small portion of the hostile encounters that HCPs face. The incidence of violence against HCPs has steadily increased over time, from a prepandemic rate of 6.4 (per 10,000 full-time employees) in 2011, to 10.4 in 2018, then 14.3 in 2022. This represents a rate 3.3 times higher for HCPs than all other occupations.<sup>5</sup>

Workplace violence (WPV) is defined as “the act or threat of physical violence, harassment, intimidation, or other threatening disruptive behavior.”<sup>6</sup> It is a growing problem that has worsened since the COVID-19 pandemic,<sup>7</sup> nationally and internationally.<sup>8</sup> Postulated reasons for this rise include provider factors (ie, necessary implementation of unwanted

public health measures, intense provider workload, lack of training in de-escalation techniques), patient factors (ie, expectations, history of violence, prior negative health care experiences, psychiatric conditions, substance abuse), or administrative issues (ie, long waiting period, understaffing, lack of staff training, lack of administrative support). Regardless of the caus-

es, the consequences are clear: higher levels of HCP burnout, attrition, post-traumatic stress disorder, depression, and anxiety, which can cascade into negative effects on patient care.<sup>8</sup>

In a 2019 *Urology Times* survey, 62% of urologists reported being threatened by a patient, while 23%

→ Continued on page 13

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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

## WORKPLACE VIOLENCE: POST-COVID TRENDS, RISK FACTORS

→ Continued from page 12

reported being physically assaulted.<sup>9</sup> A 2022 national survey of physicians noted that urology was associated with a higher risk of patient harassment or assault (odds ratio [OR] 1.33) than psychiatry (OR 1.21), general surgery (OR 0.83), or OB-GYN (OR 0.63).<sup>10</sup>

The AUA has published the AUA Workplace Violence Preparedness

Toolkit, which consists of 6 chapters outlining a strategic planning guide and templates on WPV policy, threat assessment, procedures, and training.<sup>11</sup> Other various multifaceted mitigation efforts have been proposed, including enhanced security measures (ie, increased security cameras, security presence, panic buttons), staff training (ie, de-escala-

tion techniques, communication skills, identification of high risk individuals), administrative safety standards (ie, protocols and reporting, zero tolerance policy), and provider recovery (ie, debriefing, psychological assessment).<sup>8,12</sup>

At our institution, we have also witnessed this worrisome trend. In 2018, the Cleveland Clinic Police

Department responded to 5353 Code Violet across all locations. Fifty included assault and 9 with injury. By 2023, this had increased to 6948 with 104 assaults and 892 with injury. Within our department, the incidence was 15 to 18 per year between 2018 to 2023 with 1 to 2 injuries.

At Cleveland Clinic, WPV is taken seriously and addressed in a multilayered fashion. Our current organizational approach involves reporting and appropriate review through SERS (Safety Event Reporting System), training modules for health care workers, and enhanced workplace awareness and security. That said, one of the top requests from our urological workforce in 2022 was to improve support to address these incidences. In April 2023, a procedure reporting and documenting such incidents in the urology department was developed. Providers were educated on proper documentation, required patient communication, and escalation of events departmentally through leadership and organizationally through our Ombudsman's office and security. Every incident is reviewed and triaged by the department and the Ombudsman's office. Future appointments are adjusted if necessary while the investigation is completed. Incidents are tracked in SERS, with the Ombudsman office, and by our departmental patient experience officer to monitor the progress until resolution. From October 2022 to January 2023, before the policy was re-evaluated, there were 8 known incidences, including threats to a provider and his family (1), threat of gun violence (1), and sexual harassment (2). After staff was educated on the new policy in April 2023 to present, 7 incidents—6 verbal harassment, 1 sexual harassment—have been reported and resolved.

At times, the situation calls for the termination of the patient-physician relationship. When considering this, most state oversight and accrediting bodies require the organization to: (1) provide the patient with written certified notice, (2) provide a brief explanation for termination, (3) continue emergency care for 30 days, (4) recommend another physician, and (5) transfer records to the new physician when requested.<sup>13,14</sup>

<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*].

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

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## WORKPLACE VIOLENCE: POST-COVID TRENDS, RISK FACTORS

→ Continued from page 13

Special consideration must also be given for certain vulnerable populations of providers. Caruso and colleagues note that a physician's "younger age, inexperience, and gender (ie, female)" are risk factors.<sup>8</sup> Anecdotally, we have observed more concerns from our advanced practice provider team than our physician providers. Female HCPs are particularly at risk for workplace harassment or violence by patients (OR 2.33).<sup>10</sup> A 2020 thematic analysis of female internal medicine providers revealed an array of shared experiences of sexual harassment, stalking, and solicitation by patients.<sup>15</sup> All developed methods to reduce risk by avoiding the physical exam, avoiding certain clothing (skirts, dresses), keeping physical distance from the patient, and limiting the duration of the visit. For the female urologist, many of these strategies are difficult to implement, particularly in androl-

ogy, as genital exams are required for accurate diagnosis, and history-taking involves personal details. Female trainees, who tend to be younger and less empowered to confront inappropriate patients relative to faculty, are particularly vulnerable.<sup>16</sup> Chaperone policies have been developed at many institutions; however, the availability of staff to assist during an exam is variable in practice and can contribute to increased provider burden. The intent and execution of chaperone policies at most institutions are aimed at protecting patient interests and vulnerabilities, not providers.

Addressing WPV not only protects health care workers, it also protects the patients and the quality of care they receive and helps maintain the integrity of the patient-physician contract. ■

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## The Dreaded Retained Stent: Our Approach

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Retained ureteral stents are one of the most frustrating and feared scenarios following endourologic surgery. Failure to remove or exchange a ureteral stent in a timely manner can lead to stone formation anywhere along the stent, making them impossible to remove,<sup>1</sup> in addition to complications such as infections and loss of renal function. Attempts to aggressively retrieve a heavily encrusted stent can lead to stent fracture and even complete ureteral avulsion as the proximal coil may not release. Risk factors for stent encrustation include prolonged stent dwell time, history of nephrolithiasis, smaller stent diameter, and pregnancy.<sup>2</sup> Vulnerable populations for retained stents

include those with psychiatric illnesses, incarcerated patients, and individuals with limited medical insurance.

Multiple scoring systems have been developed to classify degrees of stent encrustation. One of the earliest is the FECal (forgotten, encrusted, calcified) model, which grades the pattern of encrustation based on CT or kidney, ureter, and bladder x-ray and suggests appropriate endourologic management.<sup>3</sup> This system is useful to structure one's approach to the encrusted stent and stratifies the approach into 3 components: (1) proximal coil, (2) distal coil, and (3) ureter. The distal coil can typically be released by laser cystolitholapaxy, while the proximal coil can be released by either extracorporeal shockwave lithotripsy or percutaneous nephrolithotomy (PCNL). Depending on the approach, ureteral calcifications can be lasered with either retrograde or antegrade ureteroscopy. Failure to completely mobilize the stent can

“A preoperative percutaneous nephrostomy tube (PCN) placed by interventional radiology should be strongly considered if a patient with a retained stent presents with signs of infection or stone burden on the coils is severe enough to potentially hinder obtaining intraoperative percutaneous access if a PCNL is planned.”

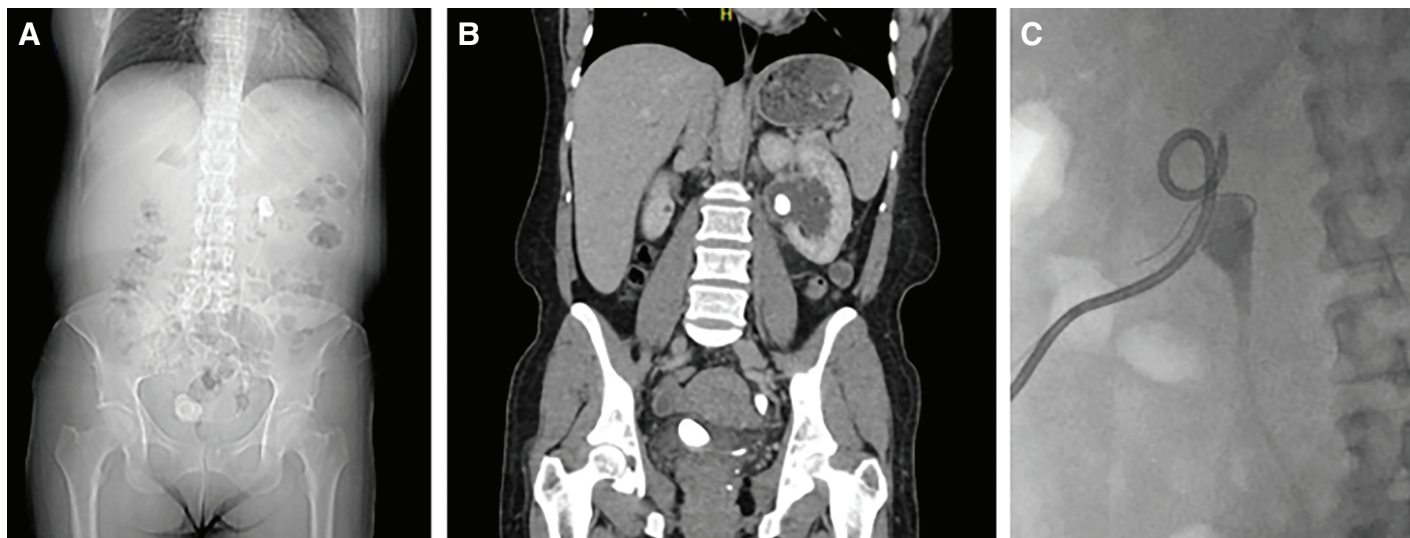
lead to ureteral avulsion during stent removal. After the stent has been removed, additional procedures may be required to address residual stone burden. Of note, if the kidney with the retained stent has poor function, nephrectomy can be considered instead.

Our approach to retained stents is to first obtain a CT scan to gauge the severity of encrustation and plan the extent of lithotripsy required. Ideally, we aim to perform total endoscopic management under a single anesthetic. When encrustation is present at both ends, we begin with the patient in dorsal lithotomy and perform cystolitholapaxy on the distal coil. The ureter is next cleared by advancing a semirigid ureteroscope alongside the stent and performing laser lithotripsy. A flexible ureteroscope can also be used, but this can be challenging depending on the degree of encrustation and mucosal inflammation. If the proximal coil can be reached with the

→ Continued on page 15

## THE DREADED RETAINED STENT: OUR APPROACH

→ Continued from page 14



**Figure 1.** This is a 45-year-old female with history of chronic hepatitis C and narcotic abuse. She presented to an outside hospital with urosepsis and an obstructing left ureteral stone. A ureteral stent was placed with plans for subsequent extracorporeal shock wave lithotripsy; however, she was lost to follow-up. She sought medical attention 1 year later with lower abdominal pain and worsening urinary symptoms. CT scan demonstrated a severely encrusted stent with a 3-cm calcified distal coil as well as ureteral and proximal coil stones (A, B). A left nephrostomy tube was placed for temporary renal drainage (C). The patient was then managed with concurrent cystolitholapaxy, retrograde semirigid ureteroscopy, and prone percutaneous nephrolithotomy. Postoperative CT scan showed no residual stone fragments.

ureteroscope, it can be freed so that the stent can be removed entirely in a retrograde manner. Alternatively, the distal coil can be amputated and removed via the urethra, or in the case of a female, withdrawn to the meatus and cut externally. The patient is then positioned prone to obtain percutaneous renal access. A preoperative percutaneous nephrostomy tube (PCN) placed by interventional radiology should be strongly considered if a patient with a retained stent presents with signs

of infection or stone burden on the coils is severe enough to potentially hinder obtaining intraoperative percutaneous access if a PCNL is planned. Depending on the stone burden, we either perform standard or mini-PCNL. The rigid nephroscope is used to perform lithotripsy on the proximal coil. Antegrade flexible ureteroscopy is then used to mobilize the ureteral portion of the stent so that the stent can be retrieved through the percutaneous tract. Residual stones are then

cleared and either a PCN or new ureteral stent is left in place with the shortest possible dwell time. Figures 1 and 2 show example cases of patients with retained stents managed using this approach.

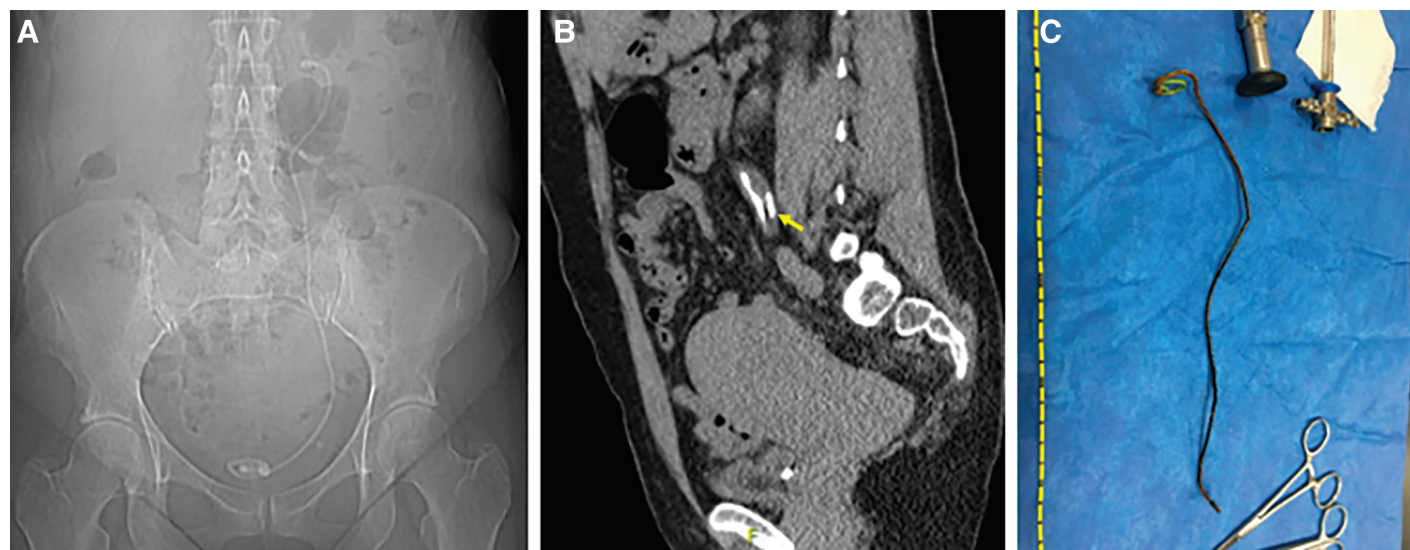
Pais et al reported the largest North American series on PCNL for management of retained stents.<sup>4</sup> Eighty percent of cases required either concurrent cystolitholapaxy or ureteroscopy to mobilize the stent. Overall stone-free rate was 63% and one-third needed a second-stage

“The majority of cases can be addressed using a combination of cystolitholapaxy, ureteroscopy, and PCNL, preferably under 1 anesthetic.”

PCNL. The top reason for retained stents was that the patient was “unaware,” highlighting the importance of patient education.

Multiple initiatives for preventing retained ureteral stents have been proposed including electronic medical record modules, cellular applications, and wrist bands.<sup>5</sup> These proposals helped identify instances where there was a failure to arrange and/or confirm timely follow-up for stent removal. However, the incidence of patients missing stent removal appointments is consistently low (<1%) and none of the above strategies have demonstrated a reduction in postoperative morbidity.

In summary, retained stents are rare but can lead to significant morbidity including loss of the renal unit. The majority of cases can be addressed using a combination of cystolitholapaxy, ureteroscopy, and PCNL, preferably under 1 anesthetic. Given the complexity of management, careful patient counselling is essential. ■



**Figure 2.** A 55-year-old female underwent left ureteroscopy with stent placement at an outside hospital but did not follow up for stent removal. She presented to the emergency department 7 years later with flank pain and intermittent fevers. Preoperative CT demonstrated a 15-mm cluster of stones in the midureter without significant proximal or distal coil calcifications (A, B). However, the distal and proximal coils were noted to be calcified intraoperatively. Cystolitholapaxy was performed on the distal end, and the ureteral stones and calcifications on the proximal coil were fragmented with a holmium laser using a semirigid ureteroscope advanced alongside the stent. Once the stent was liberated and removed (C), flexible ureteroscopy was performed to retrieve residual stone fragments in the kidney. Postoperative ultrasound showed no residual stone fragments or hydronephrosis.

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**NEJM Evidence** | Published November 30, 2022 | DOI: 10.1056/EVID2200167

**ORIGINAL ARTICLE**

**IL-15 Superagonist NAI in BCG-Unresponsive Non-Muscle-Invasive Bladder Cancer**

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**Abstract**

**BACKGROUND:** Patients with Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle-invasive bladder cancer (NMIBC) have limited treatment options. The immune cell-activating interleukin-15 (IL-15) superagonist Nappendostilb alfa inhalate (NAI), also known as N-803, may act synergistically with BCG to elicit durable complete responses (CR) in this patient population.

**METHODS:** In this open-label, multicenter study, patients with BCG-unresponsive bladder carcinoma in situ (CIS) with or without T1/T1 papillary disease were treated with intravesical NAI plus BCG (cohort A) or NAI alone (cohort B). Patients with BCG-unresponsive high-grade T1/T1 papillary NMIBC also received NAI plus BCG (cohort C). The primary end point was the incidence of CR at the 3- or 6-month assessment visit for cohorts A and C, and the disease-free survival (DFS) rate at 12 months for cohort B. Secondary end points included progression-free survival, disease-specific survival (DSS), and overall survival were secondary end points for cohort A.

**RESULTS:** In cohort A, CR was achieved in 58 (74%) of 82 patients (95% confidence interval [CI] 56.6 to 80.5; median follow-up, 25.9 months), with a median duration of 26.6 months (95% CI 15.9 months to upper bound not reached). At 24 months in patients with CR, the Kaplan-Meier estimated probability of avoiding recurrence and of DFS was 89.2% and 30.0%, respectively. In cohort B (n=72), the Kaplan-Meier estimated DFS rate was 58.4% (95% CI 42.0% to 68.8%) at 12 months, with median DFS of 39.3 months (95% CI 15.4 months to upper bound not reached). Most treatment-emergent adverse events for patients receiving BCG plus NAI were grade 1 to 2 (86%), three grade 3 immune-related treatment-emergent adverse events occurred.

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