

## EAU Congress 2021

### EDITOR'S PICK

Robotic Surgery and Its Application in Urology: A Journey Through Time

### INTERVIEWS

Interviews with Hugh Mostafid, Prokar Dasgupta, Olivier Cussenot, Phillip Stricker, Neil Barber, and Keng Ling Ng



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# *“Prepare yourselves for the latest updates in the field of urology, including a comprehensive review of the 36th Annual Meeting of the European Association of Urology (EAU) 2021.”*

Spencer Gore, CEO

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# NOT FOR Welcome

Dear Readers,

Welcome to this latest issue of *EMJ Urology*. Within this eJournal you will find trail-blazing content in the form of peer-reviewed articles, interviews with expert clinicians, and our independent review of the congress for the European Association of Urology (EAU) 2021, the 36<sup>th</sup> annual congress for urology. Gathering the latest advances in the field, *EMJ Urology* presents summaries of the exciting abstracts presented at EAU 2021 in topics such as computational fluid dynamic modelling of renal stones, characterisation of pudendal neuropathy, and relapses of urogenital tract tuberculosis. We are eager to spotlight the latest high-quality developments in urology, in line with our goal of providing clinicians with current ground-breaking information.

The peer-reviewed articles selected cover safe approaches to non-papillary percutaneous puncture, the influence of microbiota upon graft in kidney transplantation, and pathogenesis and treatment of refractory oedema in nephrotic syndrome. These in combination with the editor's pick by Zaman et al. discussing robotic surgery and its application in urology.

EMJ had the pleasure of speaking with Prokar Dasgupta about his impressive career and research works in urology, as well as Hugh Mostafid concerning the EAU congress and his influential position as a member of the guidelines panel.

Shared in our review of EAU 2021 is an informative feature exploring the avenues to improve prostate cancer screening. Alongside this, our congress research highlights outline interesting topics such as MRI screening and targeted biopsy for prostate cancer screening, developing urine tests for nicotine biproducts to detect bladder cancer recurrence, and testosterone therapy reducing the risk of heart attack and stroke. The online environment at EAU 2021 maintained the usual high-level of collaboration and knowledge sharing, bringing urologists together and hurdling the barriers to face-to-face interaction and international travel.

Finally, I would like to thank the Editorial Board, authors, and interviewees for their contributions, which allow us to provide the latest key progress in urology for healthcare professionals.



Spencer Gore

**Spencer Gore**

Chief Executive Officer, EMG-Health

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# Foreword

Dear Colleagues and Friends,

It is a great pleasure for me to introduce you to the new issue of *EMJ Urology*.

In this issue, we again have a variety of very interesting papers.

The European Association of Urology (EAU) Congress is organised every year and attracts great attention worldwide. Many sessions, debates, presentations, and courses are included in this congress, where the latest developments of every urology subspecialty are presented and discussed. In this issue, you will also have the chance to read some information that was shared at the Virtual EAU Congress, held on 8<sup>th</sup>–12<sup>th</sup> July 2021, which is one of the biggest urology meetings in the world. Due to the COVID-19 pandemic, this year's EAU Congress had to be organised virtually and was a great success, with excellent technical support.

My chosen article for the Editor's Pick in this issue is 'Robotic Surgery and Its Application in Urology: A Journey Through Time' by Zaman et al. Robotic surgery is increasingly being performed worldwide, particularly in the

*"In this issue, you will also have the chance to read some information that was shared at the Virtual EAU Congress, held on 8<sup>th</sup>–12<sup>th</sup> July 2021, which is one of the biggest urology meetings in the world"*

management of oncological cases, and has decreased the learning curve compared to laparoscopy. It has various other advantages, including decreased estimated blood loss, complications, duration of hospital stay, and improved functional outcomes for certain subjects. The future generation of young surgeons are attracted to the robotic surgery, particularly with new robotic platforms that will soon be on the market.

I would like to take this opportunity to invite you all to submit your work to *EMJ Urology*.

I hope you enjoy reading the new issue!

Kind regards,



**A. Erdem Canda**

Professor of Urology, Department of Urology, School of Medicine, Koç University, Istanbul, Turkey

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## EMJ NEPHROLOGY

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### ERA-EDTA Congress Virtual and Berlin 2021



#### EDITOR'S PICK

Blood Volume Monitoring: A Clinical Tool to Guide Ultrafiltration in Volume Control and Optimisation of Intradialytic Blood Pressure

#### INTERVIEW

With Kenar D.

## EMJ

Home > Nephrology

### EDITOR'S PICK: BLOOD VOLUME MONITORING: A CLINICAL TOOL TO GUIDE ULTRAFILTRATION IN VOLUME CONTROL AND OPTIMISATION OF INTRADIALYTIC BLOOD PRESSURE

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## Congress Review

Review of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Virtual Congress 2021

## Congress Features

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# Congress Review

## Review of the European Association of Urology (EAU) Annual Meeting 2021

Location: EAU Virtual meeting  
Date: 8<sup>th</sup>–12<sup>th</sup> July 2021  
Citation: EMJ Urol. 2021;9[1]:12-24. Congress Review.

**H**ILVERSUM the modern architectural city in Netherlands was the chosen location for the live studio that hosted the European Association of Urology (EAU) virtual congress on 8<sup>th</sup>–12<sup>th</sup> July 2021. The city is also known media city of the Netherlands, as it populated with headquarters of several broadcast studios, news stations, television, and newspaper companies. With its rich broadcasting history and influence, it is no wonder that it was scouted by the EAU central office to host this outstanding annual meeting.

The opening ceremony began with the Christopher Chapple, EAU Secretary General welcoming the attendees to the virtual event. The travel restrictions and social distancing due to the ongoing COVID-19 pandemic meant that the event could not be held in person as initially planned. However, with the adoption of modern technology in media the event, although long distance, was able to carry on as a hybrid event. The EAU was packed with education programmes, lectures,

poster presentations, and even a scavenger hunt competition. Chapple stated that there were over 6,000 delegates from 150 countries. There was a clear representation of the global urology collaboration in this event with several joint sessions with EAU and international societies: Korean Urological Association (KAU); Japanese Urological Association (JUA); Pakistan Association of Urological Surgeons (PAUS); Iranian Urological Association (IUA); Urological Society of India (USI); Arab Association of Urology (AAU); Société Internationale d'Urologie (SIU); Pan-African Urological Surgeons Association (PAUSA); Confederación Americana de Urología (CAU); Canadian Urological Association (CUA); Urological Society of Australia and New Zealand (USANZ); Russian Society of Urology (RSU); and Taiwan Urological Association (TUA).

Chapple thanked Arnulf Stenzl, University of Tübingen Medical Center, Germany, and Peter Albers, Universitätsklinikum Düsseldorf, Germany, as well as the overall



EAU central office for their hard work in developing the programme for this annual meeting. According to Stenzl, there were 1,268 selected abstracts out of 4,500 submissions, 65 sessions in total, with 43 poster sessions, and 22 video sessions. He shared that there would be a question-and-answer function that allowed the attendees to also participate in sessions ahead. "One of the things that we always do at our Welcoming Ceremony is to acknowledge the enormous contribution of colleagues to the field of urology, both eminent established colleagues as well as young urologists," said Chapple.

There were combinations of videos, put together by the EAU team, of the winners receiving their awards. The awards were for both EAU 2020, that did not take place, and EAU 2021. Manfred Wirth, former treasurer of the EAU, was the 2020 winner of the Willy Gregoir Medal for a significant contribution to the development of the urological specialty in Europe. Hendrik Van Poppel, EAU Adjunct Secretary General, responsible for Education, was the 2020 winner of the Frans Debruyne Lifetime Achievement Award. Jelle Barentsz, The Prostate MRI Reference Center, Nijmegen, the Netherlands, received the EAU Innovators in Urology Award. Mike Moran,

University of South Carolina, USA, received the EAU Ernest Desnos Prize for Medal for his remarkable contributions to urology history. Derya Tilki, Martini-Klinik, Hamburg, Germany, was awarded the 2020 EAU Crystal Matula Award, which is usually given to young European urologist, aged 40 or under, who have the potential to become future leaders in academic European urology. Véronique Phé, Pitié-Salpêtrière Hospital, Paris, France, received the 2021 EAU Crystal Matula Award. Alessandro Larcher, San Raffaele Hospital, Milan, Italy, received 2020 EAU Hans Marberger Award which is given to the best published European paper on minimally invasive surgery in urology. Andrea Gallioli, Fundació Puigvert hospital, Barcelona, Spain, was the 2021 EAU Hans Marberger Award winner. Daniël Osses, Erasmus University Medical Center, Rotterdam, the Netherlands, was the winner of the 2020 EAU Prostate Cancer Research Award. Wolfgang Fendler, University Hospital Essen, Germany received the 2021 EAU Prostate Cancer Research Award.

In conclusion, the 36<sup>th</sup> Annual EAU Congress, had several remarkable sessions covering the

*"One of the things that we always do at our welcoming ceremony, is to acknowledge the enormous contribution of colleagues to the field of urology, both eminent established colleagues as well as young urologists."*

latest updates on important trial results and other breakthrough developments. Patients were also heavily involved this year, there were patient information sessions, patient poster sessions, and an androgen deprivation therapy educational programme. The EAU 2021 had an extensive coverage of the various aspects of the field of urology. ■



## Low Testosterone and COVID Severity: Cause or Symptom?

**I**NCREASED RISK of severe COVID-19 resulting in intensive care, intubation, and even death has been linked to lower levels of testosterone in males. A study carried out in Milan, Italy and presented at the EAU21 virtual congress on July 8<sup>th</sup> to 12<sup>th</sup> found that those with symptomatic COVID-19 who were found to have low testosterone were more likely to become severely ill and die from the disease.

*"The relationship is clear; the lower the testosterone, the higher the severity of the condition and the likelihood of death."*

Andrea Salonia, a specialist in urology and Endocrinology at San Raffaele University Hospital compared levels of testosterone in 286 male patients with COVID-19 who attended the emergency department; the study included 305 healthy male volunteers. The threshold for low testosterone is deemed 9.2 (nmol/L) or below, 90% of the patients with COVID-19 had

testosterone below this level, compared to just 17% of the healthy volunteers. Furthermore, patients with mild symptoms tended to have slightly higher testosterone levels (3-4 nmol/L) than patients who were admitted to the ICU or died of the disease (0.7-1.0 nmol/L).

Salonia stated: "The relationship is clear; the lower the testosterone, the higher the severity of the condition, and the likelihood of death. I've never seen anything like it in my 25 years in the field."

As the team did not have access to data on the testosterone levels of patients prior to contracting COVID-19, the research does not reveal whether the low testosterone was a pre-existing condition or whether the virus itself induces the acute reduction in the hormone. Other research has indicated that the virus can reduce the number of Leydig cells, the cells responsible for producing testosterone. Furthermore, testosterone is understood to play a role in protecting males from disease. Salonia has called for further research following changing levels of hormones in patients over a longer period in order to answer these questions. ■





## Urinary Incontinence Linked to Poor Mental Health Among Females

**F**EMALE urinary incontinence is a relatively common condition, especially among older females; however, there has been very little research into its effect on their mental health. For this reason, Margarida Manso and colleagues at the University Hospital Centre of São João, Porto, Portugal, analysed data from a population-based survey conducted by the Portuguese Health Ministry every 5 years, which asks respondents about various aspects relating to health and wellbeing. The principal results were presented at this year's 36<sup>th</sup> Annual EAU Congress, 8<sup>th</sup>–12<sup>th</sup> July 2021.

Manso and collaborators investigated the responses of approximately 10,000 females aged  $\geq 18$  years, comparing addictive behaviours (e.g., smoking and alcohol consumption), the dimensions of mental health disease, the prevalence of depression diagnosis, and the use of mental health consultations between women who did and did not report urinary incontinence.

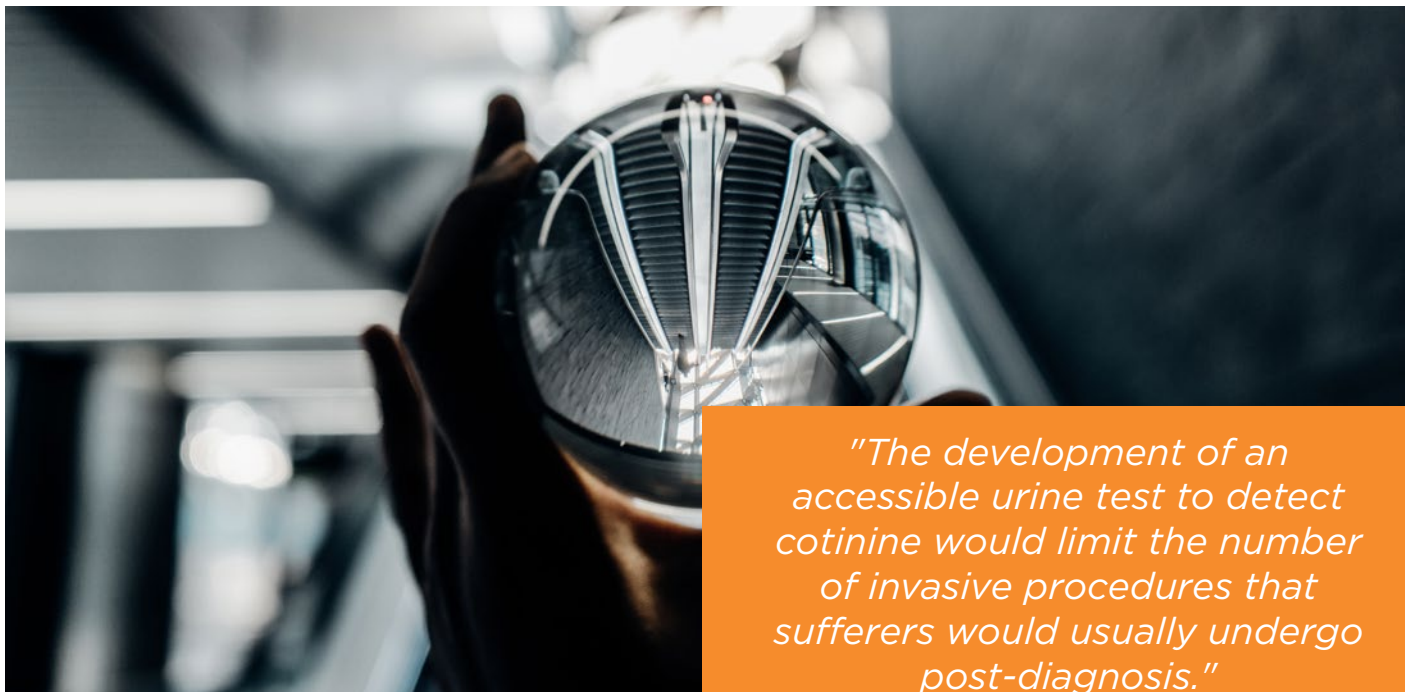
Overall, around 10% of females reported having urinary incontinence, rising to 40% for females aged over 75 years. Individuals who reported

incontinence were 66% more likely to be diagnosed with depression and saw their doctor more frequently for mental health-related issues. In addition, females with incontinence were 65% more likely to classify their health status as 'bad', reported greater difficulty concentrating, and had more feelings of guilt and lower self-worth relative to those without the disorder. Interestingly, no substantial differences in smoking or alcohol consumption between the two groups were observed.

Manso highlighted the wider relevance of the research findings: "We believe the conversation between patients and their urologists needs to change. Clinicians should be asking patients about their mental health when discussing treatments, because treating their physical challenges could help with the psychological cost of the condition." Manso added: "Personally, I will be emphasising this more with my patients and trying to understand better the mental burden of living with incontinence." Going forward, the team behind this study are imploring healthcare practitioners to ask women with incontinence about their mental health and to offer potential treatments. ■

*"Going forward, the team behind this study are imploring healthcare practitioners to ask females with incontinence about their mental health and to offer potential treatments."*





*"The development of an accessible urine test to detect cotinine would limit the number of invasive procedures that sufferers would usually undergo post-diagnosis."*

## Could Nicotine By-Product Predict Cancer Return?

PROMISING new evidence has emerged suggesting that cotinine, a by-product of nicotine, can be used as a biomarker to detect the recurrence of bladder cancer. This information was presented by researchers at the virtual 2021 EAU Congress, who found that those with high levels of cotinine present in their urine were four times more likely to experience a return of bladder cancer. The development of an accessible urine test to detect cotinine would limit the number of invasive procedures that sufferers would usually undergo post-diagnosis.

Bladder cancer is one of the most common forms of the disease, particularly in the older generation. Although it is widely known that smoking increases the risk of developing this type of cancer, this study is the first of its kind. Cotinine is a chemical that is produced by the body when nicotine is metabolised, and is usually used as a marker of tobacco smoke exposure.

Maher Abdessater and Raghid El Khoury from the Notre Dame de Secours University Hospital focused their study on low-risk, non-invasive bladder cancer, in which sufferers undergo surgery to remove cancerous tissue of the bladder lining. Following surgery, no additional treatment is required, and patients are monitored

through regular cystoscopies. The study involved 135 patients who were undergoing these regular checks over a period of 18 months, received no additional treatments and had no urinary conditions likely to compromise the results.

Results showed that 80 of the patients had cotinine levels of 550 ng/ml, which were consistent with heavy smoking. 75% of these patients experienced a return of their cancer, whilst only 18% of moderate smokers developed bladder cancer again. Abdessater explained: "One of the major advantages of using cotinine is that it can be detected using a simple urine test, which is a cheaper and less invasive alternative to cystoscopy." Cotinine detection is also a useful technique to identify where patients are not accurately disclosing their smoking habits.

Those involved in this study are currently seeking out other hospitals around the globe who may be interested in co-operating to expand this research to a wider range of patients. Arnulf Stenzl of the University of Tübingen Medical Center and Secretary-General Adjunct of the EAU stated: "We now need to test this in a larger trial, and also look at more precise indications of smoking levels and the type of cigarettes involved." ■

# MRI Screening and Targeted Biopsies to Halve Overdiagnosis of Prostate Cancer

SUBSTITUTING traditional prostate biopsies with MRI and targeted biopsies, in a Swedish study, has halved overdiagnoses and reduced both unnecessary biopsy and identification of low-risk tumours. This new method is just as effective in detecting clinically significant tumours, and is of great interest when it is considered 1.4 million males develop prostate cancer globally and at least 375,000 die as a result of the disease.

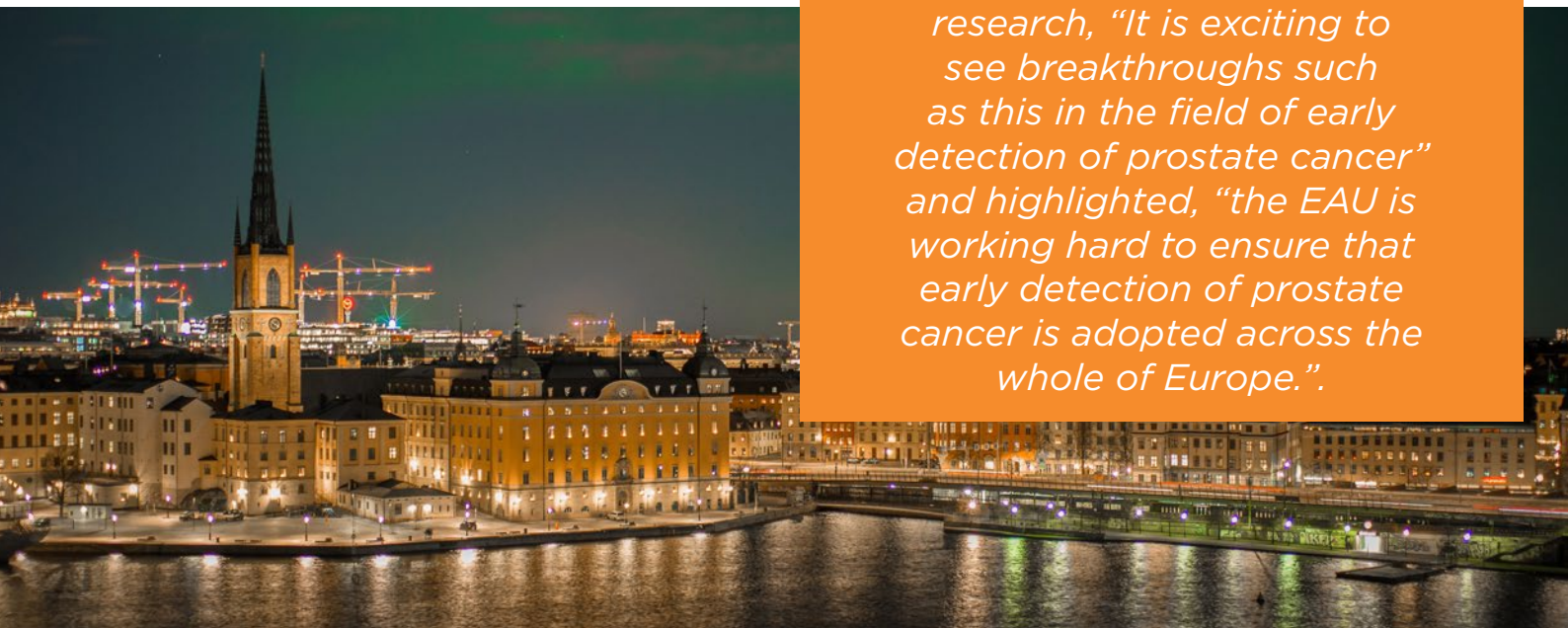
Adding to the existing literature, which demonstrates organised screening can reduce risk of prostate-cancer death due to earlier detection, one of the researchers, Tobias Nordström stated, “Our results from a large, randomised study show that modern methods for prostate cancer screening maintain the benefits of screening, while decreasing the harms substantially.” Labelled the STHLM3MRI study, conducted between 2018 and 2021, the participant cohort included 12,750 males subject to a prostate specific antigen (PSA) blood sample analysis and Stockholm3 test analysing protein and genetic markers for predictive risk of prostate cancer. Elevated scores in these tests stratified the participants for randomly selected traditional biopsy or MRI to detect prostate cancer, with biopsy conducted strictly on tumours identified by MRI in this second group.

The current PSA test and traditional biopsies result in frequent unnecessary invasive procedure and diagnoses, the strength and necessity of this

new method can be seen through its specificity; “refined screening methods are required to reduce overdiagnosis and overtreatment of low-risk tumours, and prevent unnecessary biopsies and biopsy-related side-effects,” was the statement made by Martin Eklund, another associated investigator. Further successes to carry forward can be observed in the large sample size and randomised design of study, the next steps in research were mentioned as nationwide screening efforts at early cancer detection.

Nordström concluded, “We will soon present the second of the two main reports from the STHLM3MRI trial where we assess the role of a novel blood test as adjunct to MRI in prostate cancer screening. The future of prostate cancer diagnostics probably includes both improved blood-tests and MRI.” With the take home message, “We will finally be able to show that men can also reduce their risk of malignant cancer through nationwide prostate-cancer screening that utilises modern methods.” Hendrik Van Poppel, Adjunct Secretary General at EAU, showed his support for the research, “It is exciting to see breakthroughs such as this in the field of early detection of prostate cancer” and highlighted, “the EAU is working hard to ensure that early detection of prostate cancer is adopted across the whole of Europe.” ■

*“Hendrik Van Poppel, Adjunct Secretary General at EAU, showed his support for the research, “It is exciting to see breakthroughs such as this in the field of early detection of prostate cancer” and highlighted, “the EAU is working hard to ensure that early detection of prostate cancer is adopted across the whole of Europe.”*





# Testosterone Therapy Linked to Reduced Heart Attack and Stroke Risk

**R**ECENT evidence has surged linking testosterone therapy to a significantly lowered risk of heart attacks and strokes in males with a deficiency of the hormone. The 10-year study included over 800 people from Germany and Qatar displaying abnormally low levels of testosterone. Males involved in the study were at an increased risk of both heart attacks and strokes due to family history and diabetes profiling and were encouraged to make lifestyle changes to improve their cardiovascular health.

Of the 412 people who opted for testosterone therapy, 16 died, but none suffered a heart attack or stroke. The remaining 393 individuals who opted for no treatment saw 74 deaths, 70 people suffering a heart attack, and 59 a stroke. Testosterone therapy reduced the risk of both heart attacks and strokes in males under 55 by 25% and reduced this risk in over 60s by 15%. Males on testosterone therapy also saw an overall improvement in their health including weight loss and lowered blood pressure.

Although significant improvements were seen following testosterone therapy, scientists have emphasised that this treatment should not be seen as a 'silver bullet' and can only be used in patients matching given criteria. Omar Aboumarzouk from Hamad Medical Corporation revealed "Testosterone can be seriously harmful if taken by men with normal levels, or who function perfectly well with reduced levels of the hormone." Aboumarzouk went on to explain the advantages of normalising testosterone levels in deficient males, which has been seen to improve the beneficial effects of actions taken to improve their health.

This non-randomised study saw positive outcomes, however those involved were at medium-risk of a heart attack or stroke, and those receiving testosterone therapy were slightly younger than those who went untreated. Although these factors present limitations, a new trial is currently progressing involving 6,000 participants, which will allow solid conclusions to be drawn as to the benefits of hormone therapy in men with low testosterone. ■

*"Males on testosterone therapy also saw an overall improvement in their health including weight loss and lowered blood pressure."*



# Virtual Reality Setting of Icelandic Landscape Could Reduce Pain During Uncomfortable Cystoscopy Procedure

**B**LADDER cancer diagnosis and treatment requires patients to undergo an uncomfortable and painful cystoscopy procedure. A new study carried out at Wrocław Medical University, Poland, presented at the EAU annual meeting on 11<sup>th</sup> July 2021, showed that a virtual reality (VR) goggles and headphones could alleviate pain in patients undergoing this medical imaging procedure.

Rigid cystoscopy involves the insertion of a rigid telescope into the bladder via the urethra and is an effective method used in the diagnosis and treatment of bladder cancer. However due to the painful and unpleasantness of this procedure, some patients opt out by avoiding a follow-up and this could lead to the progression and further irreversible development of bladder cancer. Rigid cystoscopy can be carried out under local anaesthesia. General and spinal anaesthesia could also be used; however, these approaches may lead to further risk of complications. Technology advancements, such as VR technology, used in different aspects of medicine have proven to be an important tool in improving patients experiences and overall patient outcomes.

Wojciech Krajewski and his team selected 103 patients undergoing rigid cystoscopy with just

local, intraurethral anaesthesia, with a mean age of 66 years. The participants, either first time diagnosis or requiring a follow up, were randomly selected to undergo classic cystoscopy or the procedure with VR goggles and headphones displaying an image of the Skógafoss waterfall, Iceland. The patients completed a questionnaire on anxiety and depression prior to the procedure. The researchers measured blood pressure, oxygen saturation, and heart rate during the cystoscopy and a measurement score called FLACC that's involves observing face, legs, consolability, and cry was also utilised. Following the procedure, patients rated the pain perception and nausea. The pain scores were lower in the VR group compared to the score, however, the VR group experienced higher levels of nausea and vertigo. Increased blood pressure and heart rates was noted in all patients but was lower in the VR group. The findings were the same in male, female, in both first and follow-up cystoscopies.

Krajewski said that “patients reported less pain, and this was also reflected in our observations of their experience. VR is certainly an option for pain reduction in cystoscopies and we are looking into whether it will have the same effect in other medical interventions such as lithotripsy to break down kidney stones or prostate biopsy.” ■

*“VR is certainly an option for pain reduction in cystoscopies and we are looking into whether it will have the same effect in other medical interventions such as lithotripsy to break down kidney stones or prostate biopsy.”*





# Patients Classed as Being Obese Have a Higher Survival Rate of Advanced Prostate Cancer

A new study presented at the EAU annual meeting on the 11<sup>th</sup> July 2021 says that patients classed as being obese could survive a metastatic castration resistant prostate cancer. A metastatic castration resistant prostate cancer is an advanced form of prostate cancer whereby the disease no longer responds to treatments that lower the levels of the testosterone hormones.

There is evidence in a few cancers of a survival superiority in patients with high BMI, despite the fact that obesity is linked to an increased risk of death from several cancers and other chronic diseases, this occurrence is known as the obesity paradox. The investigation was carried out by researchers from San Raffaele University, Milan, Italy, and Mount Sinai Hospital, New York, USA,

who followed 1,577 patients diagnosed with the advanced cancer over a period of 3 years. The aim of the study was to assess whether the obesity paradox phenomenon applied to patients diagnosed with metastatic castration resistant prostate cancer. The researchers observed the survival rates of patients, with an average age and BMI of 69 years and 28 respectively, who took part in three different clinical trials.

*"This obesity paradox has been seen in some other cancers, possibly due to the relationship between tissue fat and cancer genomes, and more research is needed in this area. It's also possible that improved survival may be due to the interaction of chemotherapy with other drugs"*

The results revealed the higher BMI had a protective factor of 29% higher overall survival probability and 35% cancer-specific survival probability. Over the period of 36 months, up to 30% of patients classed as obese survived compared to 20% of individual who were considered overweight and of normal weight. Overall, patients that are classified as obese, having a BMI of over 30, had a higher survival rate of 10%.

Nicola Fossati, a urologist at San Raffaele University, Milan, Italy, stated that, "this obesity paradox has been seen in some other cancers, possibly due to the relationship between tissue fat and cancer genomes, and more research is needed in this area. It's also possible that improved survival may be due to the interaction of chemotherapy with other drugs. Obese patients in this older age group tend to be taking medication for other conditions and we do not fully understand how these medicines interconnect. ■



## Using Old Drugs for Kidney and Bladder Cancer Treatment



**A**BSENCE of treatment for reoccurring kidney cancer is a vital gap in cancer research that needs to be urgently addressed. Unfortunately, there is a high risk of kidney cancer returning in patients even after undergoing surgery. An exciting Phase III trial, however, showed that an old drug, pembro, which is used to treat other cancers including late-stage kidney cancer, could reduce the risk of kidney cancer returning if used earlier.

The trial took place across 20 countries and involved approximately 1,000 patients with kidney cancer who had undergone surgery. Patients were either given pembro, usually reserved for late-stage kidney cancer, or a placebo. After 2 years, the scientists evaluated the results and found that patients taking pembro reduced their risk of cancer developing again by a third compared to patients on placebo. Promisingly, the side effects from pembro were like other cancer drugs on the market.

Thomas Powles, co-investigator of the trial, from Barts Cancer Institute at Queen Mary University of London, UK, concluded, "There are signs as well that the drug may improve survival rates, but we can't be sure of that for another few years. We're hopeful that this trial, when complete, will provide a strong case for this

*"After 2 years, the scientists evaluated the results and found that patients taking pembro reduced their risk of cancer developing again by a third compared to patients on placebo."*

drug to be approved for use by the medicines regulator." The next steps for this study involve evaluating the results from the ongoing follow-up with patients after 5 years to determine the efficacy of pembro on survival rates.

Further to this research, Powles also shared findings from another trial that took a similar novel approach of using an existing cancer drug for advanced bladder cancer. The DANUBE study involved using darvalumab typically used for lung cancer for late-stage bladder cancer instead. Overall, however, the study showed this drug did not increase survival compared to standard treatment. Nonetheless, for patients unable to take chemotherapy drug cisplatin, this could provide an alternative treatment and further research is warranted. The promising results suggest that one day, scientists may be able to approve the use of existing cancer drugs for kidney and bladder cancer treatment. ■



# Promising New Treatment for Late-Stage Metastatic Prostate Cancer

**P**ROSTATE cancer (PCa) is the leading cause of cancer-related deaths in males, with one patient dying every 45 minutes. Cancer can go undetected for several years and can be very difficult to treat once the tumour metastases. Metastatic castration resistant PCa is currently incurable and life-threatening. Therefore, there is a desperate need to improve therapeutics and develop novel drug targets. A recent Phase III trial orchestrated by Johann de Bono from the Institute of Cancer Research, London, Ken Herrmann, University Hospital Essen, Germany, and a team of researchers analysed the efficacy of a new treatment, Lu-PSMA-617, discussed at the EAU21 congress.

Lu-PSMA-617 targets the molecule PSMA, which can be found elevated on the surface of PCa tumour cells. This unique treatment involves using beta radiation to destroy PSMA and the surrounding microenvironment. The researchers aimed to discover whether Lu-PSMA-617 was more effective than standard care. To begin with, they recruited 831 patients with metastatic

and castration resistant PCa. The patients were randomised to receive Lu-PSMA-617 plus standard care or standard care only.

Interestingly, the patients treated with Lu-PSMA-617 had significantly improved survival time. The median survival time was 15.3 months in patients treated with Lu-PSMA-617 and 11.3 months in individuals receiving standard care only. Overall, survival time improved by an average of 4 months. Additionally, progression-free survival also showed promising results and became longer with Lu-PSMA-617 treatment (8.7 months versus 3.4 months). What is more, the safety profile showed that the quality of life was not negatively impacted.

This novel treatment could be valuable in patients where standard treatment has been ineffective or in individuals with high levels of PSMA. Herrmann concluded, "Lu-PSMA-617 can improve the lives of many men with advanced prostate cancer and their families." Due to the positive results, this treatment is being reviewed by the NHS in England and Wales for approval. ■

*"Patients treated with Lu-PSMA-617 had significantly improved survival time."*



# Monitoring Low-Risk Prostate Cancer Proves More Effective Than Active Treatment



*"It was revealed that males under the age of 60 benefit very little from active surveillance in terms of survival, whereas those over 60 were seen to survive for at least 10 years with no additional treatment."*

ENCOURAGING evidence has surged proving that men over 60 diagnosed with low-risk prostate cancer could benefit from monitoring their disease with no additional treatment. This method of 'active surveillance' involves close monitoring of their cancer, and was presented at the EAU Congress, which took place on 8<sup>th</sup> to 12<sup>th</sup> July 2021 following its success in two recent studies.

Due to the novel nature of active surveillance, scientists from the University of Gothenburg and Uppsala University, Sweden, developed a new statistical technique to combat the lack of available long-term data. Researchers began looking at the number of patients on active surveillance who progressed to other forms of treatment, rather than focusing on those who died of prostate cancer. Due to the wide use of treatments such as radiotherapy and surgery, existing long-term follow-up data allowed scientists to predict the outcomes for patients on active surveillance up to 30 years following diagnosis. The model showed the percentage of sufferers who died from the disease, as well as the number of years they spent without treatment.

The principal aim was to identify those who benefitted the most from active surveillance. Eugenio Ventimiglia, a urologist from San Raffaele Hospital, and a PhD student from Uppsala University explained "the older you are and the lower risk your cancer, the greater the benefit. But

we saw a real divide at age 60." It was revealed that males under the age of 60 benefit very little from active surveillance in terms of survival, whereas those over 60 were seen to survive for at least 10 years with no additional treatment.

The method of active surveillance also reduces the risk of side effects, including incontinence and erectile dysfunction, which are commonly experienced with radiotherapy and surgery. Research from the Europa Uomo Patient Reported Outcome Study (EUPROMS), which included around 3,000 males saw 45% of those on active surveillance experience erectile problems, compared to 70-90% on other treatments. The importance of this statistic was explained by Lionne Venderboc, a postdoctoral researcher at Erasmus MC "Lack of sexual function affects patients' quality of life more than any other reported side effect. The survey shows that active surveillance has the least impact on sexual function of all possible treatment options." There is hope that this method encourages men to overcome their reluctance to be tested for prostate cancer, as the later the disease is diagnosed, the more severe the impact of treatments on quality of life. ■



# 36<sup>th</sup> Annual European Association of Urology (EAU) Congress Attracts Global Audience

The European Association of Urology (EAU) held a five-day virtual congress for online participants: EAU21



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## INTRODUCTION

The European Association of Urology (EAU) held its 36<sup>th</sup> Annual Congress, EAU21, on 8<sup>th</sup>–12<sup>th</sup> July. The global pandemic required the organisers to hold EAU21 virtually, with a small number of session chairs and moderators travelling to the Netherlands to host sessions in a studio setting (Figure 1).

The congress attracted over 6,200 unique participants from 120 countries. During the congress days, 52,000 live views were logged for the 180 sessions. The five-day EAU21 Scientific Programme featured 1,600 faculty members and speakers discussing all of the latest developments in urology. The European School of Urology (ESU) hosted special courses during congress hours, and a special programme for urology patients was also introduced this year. The European Association of Urology Nurses (EAUN) will hold its own virtual meeting in September.

What follows is an extremely condensed overview of some of the highlights of the EAU21.<sup>1</sup>

## FULL DAY OF SEMI-LIVE SURGERY

'Technology development never ends!' was the catch-all title for the nearly eight-hour flagship,

semi-live surgical session at the EAU21. The session, or more accurately, the Meeting of the EAU Section of Uro-Technology (ESUT), Robotic Urology Section (ERUS), and Section of Urolithiasis (EULIS) was designed to take up most of the first day of the EAU21, lasting from 10 a.m. to 7 p.m., with an hour-long break at noon. Ali Serdar Gözen and Jochen Walz chaired the day's sessions.

The first five blocks of presentations covered a wide range of innovations in urological technology, including flexible ureteroscopy with thulium fibre laser, several new kinds of laser technology (including a demonstration of mini-PCNL with MOSES 2.0), and the demonstration of a new kind of ureteral stent, the JFil, by Andrea Bosio. The JFil led to a lot of questions from the audience, who were clearly interested in the potential of the innovative 'pigtail' stent and its potential for reducing stent-related symptoms.

A real scoop in this first series of talks was the participation of Ruben Olivares, who was the first to use the Medtronic Hugo RAS system to perform a prostatectomy on June 19<sup>th</sup> at the Clinica Santa Maria in Chile. Olivares highlighted the system's modular nature, its flexible upgradeability, the advantages of its open console, and the support for standard surgical tools.



**Figure 1: The European Association of Urology (EAU) 2021 studio set in Hilversum, the Netherlands.**

Some moderators and sessions chairs were able to travel to 'host' the congress and lead discussions.

This historic first procedure would mark the start of a registry and data collection on the performance of the system.

## NIGHTMARE SESSION

The first Plenary Session of the EAU21 was the Nightmare Session on Friday morning, which was about early detection of prostate cancer. Roderick van den Bergh, Isabel Heidegger, and Armando Stabile each gave a case presentation, which were discussed and then cross-examined by medical lawyer Bertie Leigh afterwards. Besides Leigh, the session was chaired by Chris Bangma and Walz.

van den Bergh described his case as a situation that "started as a fairy tale and ended as a nightmare." He alluded to it as a perfect case of active surveillance that ended in a "possible metastatic lesion." Leigh said: "There is nothing wrong with active surveillance. It is a great advance in modern urology. It is about the way you do it and that is what went wrong in this case."

Later in the session, the focus shifted to low-grade cancers: "The frequent problem of over-treatment," as Walz put it. The over-treatment case presented was quite unique as the patient had put pressure on his urologist to perform a radical prostatectomy, which raised the question: what if a patient keeps pushing for surgery? Leigh stated: "When your patient asks you to do something that you think will do him harm and will not do him any good, you should rarely comply with his wishes."

## MANAGEMENT OF INCONTINENCE

Centred on the optimal management of incontinence in elderly patients, Plenary Session 2, which took place on Friday, also covered what drug interactions to be aware of when using pharmacotherapy for urgency urinary incontinence. According to Martin Michel, complete medication history is key to the prevention, detection, and management of drug-drug interactions.

EAU Secretary General, Chris Chapple, discussed that new mesh materials need to be more like a fascia-mimetic material, which is made of three layers of polyurethane electro-spun fibres. Polyurethane materials cope well with repeated distension and are well-tolerated in animals, inducing little inflammation.

Mary Lynne van Poelgeest-Pomfret underscored the importance of listening to patients with regard to treatment goals and evaluation tools.

## ADVANCED BLADDER CANCER IN 2021

Plenary Session 3, 'Advanced bladder cancer in 2021: Going forward?' on Saturday morning, looked into the future of advanced bladder cancer treatment. Chaired by Maria De Santis, Joan Palou, Morgan Rouprêt, and Arnulf Stenzl, the session went into technical advances and personalised and targeted therapeutic strategies.

James Catto kicked-off the session with his state-of-the-art lecture 'Safe and optimal management of muscle-invasive bladder cancer (MIBC) in the time of SARS-CoV-2.' He said: "In terms of cure [for MIBC], we have two choices: surgery or radiotherapy." He went on to present the pros and cons of each of these approaches in light of COVID-19 (Figure 2).

The second state-of-the-art lecture was given by Lars Dyrskjød, who answered the question of whether it is possible to use molecular markers to decide treatment for MIBC. One of his conclusions was that "ctDNA [circulating tumour DNA] has many opportunities across the patient disease course to inform clinical practice."

The final state-of-the-art lecture of the session was Enrique Grande's 'Does every metastatic patient need immunotherapy in a first-line setting?' pertaining to metastatic urothelial carcinoma. Grande started his lecture by answering his central question with a "probably not;" he ended with a "definitely not."

## RENAL CANCER

Plenary Session 4 addressed updates on localised and metastatic renal cancer. W. Marston Linehan kick-started the session with his Society of Urologic Oncology (SUO) lecture on the

discovery, oxygen sensing, and therapy using the von Hippel-Lindau (VHL) kidney cancer gene.

To find the gene for clear cell renal cell carcinoma, Linehan and his team conducted genetic linkage in families affected with VHL disease. They localised the gene to the short arm of chromosome 3 and, with physical mapping, identified the VHL gene, which is a two-hit, loss-of-function, tumour-suppressor gene. Linehan also cited the relevance of the findings of the Nobel Prize-winning study on how cells can sense and adapt to changing oxygen availability.

Covering immunotherapy-based management of metastatic clear cell and variant renal cell carcinoma, Ignacio Duran stated that immunotherapy-based combinations can provide a long-term benefit in a substantial percentage of patients with metastatic clear cell renal cell carcinoma.

Moderated live from the EAU21 studio, Umberto Capitanio, Marc-Oliver Grimm, and Peter Mulders chaired Plenary Session 4.

## METASTATIC PROSTATE CANCER

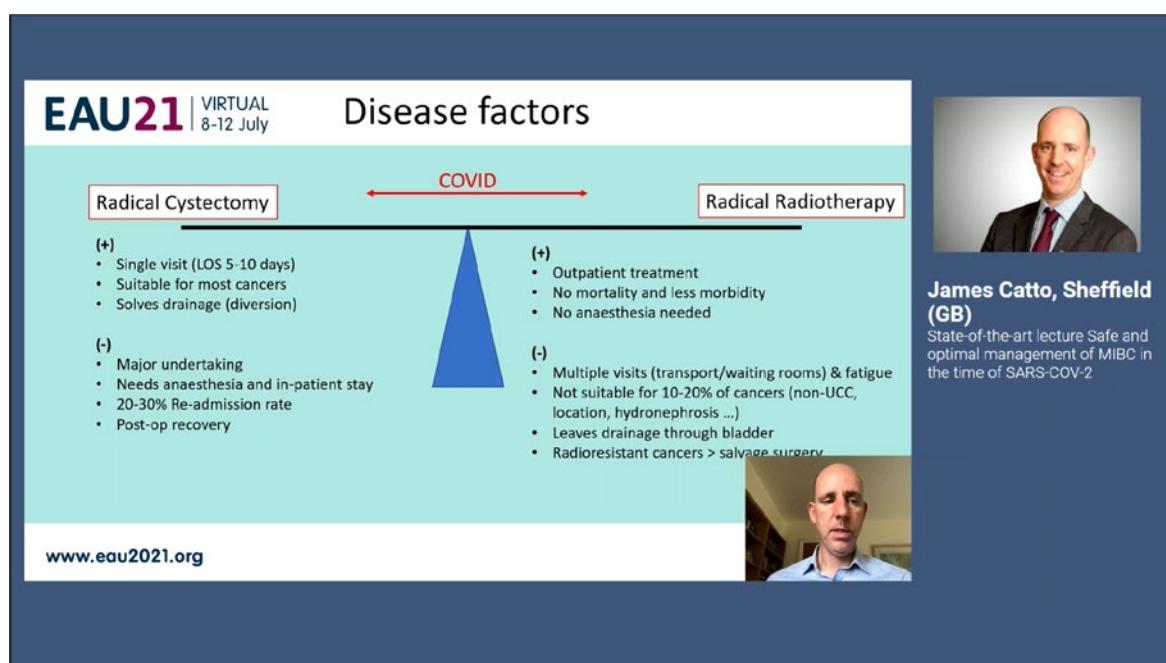
On Sunday, Plenary Session 5 commenced and focused on the treatment for metastatic hormone-sensitive prostate cancer. The session was led by Alberto Briganti, Karim Fizazi, Silke Gillesen Sommer, and Arnould Villers.

During his state-of-the-art lecture, Declan Murphy emphasised that in the *de novo* setting, the accuracy of prostate-specific membrane antigen PET/CT is superior to conventional imaging.

Later in the session, Christopher Sweeney said that there is evidence to support the hypothesis that men with metastatic hormone-sensitive prostate cancer have a wide array of prognoses, which can be easily defined by clinical variables.

In discussions on the role of imaging-guided treatments such as radiotherapy, Pierre Blanchard stated there is a low level of evidence for metastases-directed therapy in the oligometastatic recurrent prostate cancer setting, although metastases-directed therapy is widely used.





**Figure 2: The pros and cons of radical cystectomy versus radical radiotherapy in light of COVID-19.**

LOS: late-onset sepsis; UCC: urothelial cell carcinoma.

## EVER-INCREASING APPLICATIONS FOR ROBOTIC SURGERY IN UROLOGY

Robotic urology is a rapidly evolving field, with many studies underway and results coming in the next few years, but some careful conclusions were already drawn by the speakers at the EAU21 on Sunday. Plenary Session 6, chaired by Alex Mottrie, Maarten Albersen, and Timothy O'Brien, examined if the surgical robot is starting to take over reconstructive surgery, traditionally the field for open or laparoscopic techniques, and all signs are pointing to a shift to robotic-assisted surgery.

As departing Chairman of the EAU Robotic Urology Section (ERUS), Mottrie is, understandably, extremely enthusiastic about the potential of robotic surgery and advanced surgical technology in general: "This session proves that everything is becoming robotised. We started with prostate, prostatectomy, then kidney, and bladder, but now everything that we do with our bare hands is going more and more towards robotics. There are new robotic systems coming to market: microsurgery, and so on. This will very probably soon include urethral reconstruction and whatever else. As the expenses come down, also due to increased competition, there are very few drawbacks left."

While robotic training is becoming increasingly standardised thanks to ERUS, its curriculum, and the work of training centres like Orsi, how much of the current robotic training is based on a single robotic system, and how useful will it be as the market becomes more diverse?

Mottrie stated: "As it currently stands, we only have one system. Our current training protocols are, let's say, a 'mono-robot training'. But we will, in the coming years, come to a new era where we will have robot-agnostic training. When you buy a car, sure, there are differences between brands, but the driver's licence is the same. You might need the company to tell you what each button and switch does, but in terms of surgical technique and approach, it's all basically the same. It's work in progress on our part."

## THE PROSPECTS OF SURGICAL REMOTE LEARNING

The final of seven Plenary sessions at the EAU21 took place on Day 5 of the virtual congress, bringing together stone experts from across the continent for an interesting live session. The session was chaired from the studio by Thomas Knoll and Selçuk Silay, joined by Evangelos Liatsikos remotely.

Amid case discussions that weighed the benefits and drawbacks of extracorporeal shock wave lithotripsy, percutaneous nephrolithotomy, or flexible ureteroscopy, was an update on technique and training. Olivier Traxer summarised his personal experiences of remote training over the past fifteen months.

“With the events of 2020, we have had to rethink education,” said Traxer. “Social media has allowed us to get in touch and spread information, but of course there is little in the way of quality control. The industry has started developing webinars and educational platforms, but we must of course admit that there is a certain amount of bias there.

“International societies like the EAU and the European School of Urology (ESU) perhaps did the most to replace physical meetings, creating evidence-based webinars and learning tracks. This year’s Annual Congress [EAU21] is an excellent example of what we are now able to do, to teach surgical theory. Things like stone composition recognition can easily be done from home.

“The fact remains, however, that we are surgeons and we have so far not been able to replace in-person, hands-on teaching. We need feeling and feedback from our tools. While this is so far irreplaceable, a mix of hands-on and remote training is certainly a future for us.”

Knoll and Liatsikos joined in discussing these realities with Traxer. Perhaps remote ‘coaching’ of more experienced surgeons with a live feed of the procedure (similar to moderation during live surgery sessions) is an option, but only if the surgeon already has a degree of skill. There are also many legal ramifications that need to be examined for this to be considered.

Although the congress might have ended, registration remains open for people who would like to watch all the content on-demand. The EAU21 scientific content remains accredited until 12<sup>th</sup> October 2021, earning participants up to 40 hours of continuing medical education credits.<sup>1</sup>

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# Latest Trials Explore Ways to Improve Prostate Cancer Screening

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THE EUROPEAN Association of Urology 2021 Congress (EAU21) hosted a session where six speakers discussed the latest state-of-the-art prostate cancer screening trials. The experts shared their preliminary results and suggested improvements to the current screening process.

Prostate cancer (PCa) is the leading cause of cancer-related deaths in males. Patients with PCa can go undiagnosed for many years as the symptoms mostly appear when the tumour has grown large enough to put pressure on the urethra. Currently, prostate-specific antigen (PSA) is used as a marker to help detect and predict PCa onset. However, PSA is not specific to PCa, and PSA is also elevated in other prostatic conditions. This lack of specificity in PCa screening can lead to over-diagnosis, invasive biopsies, and anxiety in patients.

This highlights the need for improving PCa screening to get an accurate diagnosis and avoid unnecessary procedures. This year's EAU21 Congress invited experts involved in some of the latest state-of-the-art PCa screening trials

to discuss their results and the implications for future screening strategies. Six speakers shared their preliminary and ongoing data from clinical trials and their methods for implementing a more efficient PCa screening process.

The first speaker, Monique J. Roobol, Erasmus University Medical Centre, Cancer Institute, Rotterdam, the Netherlands, gave an informative introduction on the burden of PCa screening. Roobol's team developed a PCa screening algorithm that assessed the risk of PSA screening in individuals. The algorithm takes into consideration the geography of the patient and individual risk factors such as age. The algorithm showed that only 10% of males aged 50-59 years and only 25% of males aged 60-70 years would move on to risk stratification.

*The algorithm showed that only 10% of males aged 50-59 years and only 25% of males aged 60-70 years would move on to risk stratification.*



The results showed that current methods of PCa testing are not suitable for all individuals, and a tailored approach is urgently needed. Roobol also added that stopping testing in elderly individuals with low PSA levels would reduce unnecessary harm and costs. Finally, Roobol shared the vision of the European Cancer Organisation (ECCO) and explained that they aim to provide all males with access to risk-based screening programmes in Europe by 2027.

The next speaker was Christian Arsov, Department of Urology, University Hospital Dusseldorf, Germany, who discussed the preliminary results from the ongoing PROBASE trial. The randomised study took place in four regions of Germany and involved 46,642 males aged 45 years old. There were two study arms: study arm A had an immediate screening of baseline PSA at age 45 years, and study arm B deferred screening until the age of 50 years.

Overall, 344 men were in the high-risk group as they had PSA levels above 3. The participants underwent a second PSA test to confirm the PSA levels, and 179 men were still at risk. The results of the trial showed a very low prevalence of PCa in 45-year-olds (0.2%). The speaker emphasised that elevated PSA levels should always be confirmed with a second test.

Over the years, PCa screening has evolved, and the screening steps are as follows: PSA test, systemic biopsy, MRI, and finally, targeted biopsy. At each stage, a percentage of individuals can be ruled out, therefore reducing the chance of over-diagnosis.

Anssi Auvinen from Tampere University, Finland, discussed the ongoing PROSCREEN trial. In this trial, the researchers wanted to add another step to PCa screening called the 4K score, a combination of four blood tests, after the PSA test to further eliminate males who are not eligible for an MRI or biopsy. The 4K score eliminated 30% of participants. This trial is still in its infancy and experienced delays due to the pandemic. Calculations show that in 15 years, the researchers should be able to establish the efficacy of adding the 4K score to PCa screening.

The next speaker, Tobias Nordstrom, Karolinska Institute, Stockholm, Sweden, also aimed to improve the risk-adapted screening process by combining a genomic test with MRI-targeted



*The results showed that males with normal genetic risk had a lower chance of repeated PSA tests, and males with high genetic risk were more likely to have elevated PSA, biopsy, and a PCa diagnosis.*

biopsy in the STHLM3 MR Phase II trial. Stockholm-3 (STHLM3) is a blood-based test that involves a combined assessment of PSA, four proteins, 101 genetic markers, and medical history, i.e., earlier biopsies. All 12,750 respondents who took part in this trial had a PSA and STHLM3 test. Participants were randomised to receive either a traditional biopsy or MRI. Interestingly, the results showed that STHLM3 discriminated better than PSA for significant cancer, with an area under the curve of 0.76 compared to 0.60 in PSA. Nordstrom concluded that combining STHLM3 with MRI targeted biopsy reduced over detection yet still effectively detected significant cancer.

This was followed by a presentation by Jacob Fredsoe, Aarhus University Hospital, Denmark. Fredsoe explained the PROCARIS trial, which took a unique approach using genetic markers, specifically single-nucleotide polymorphisms (SNP), to assess PCa risk. To reduce the likelihood of over-diagnosis, Fredsoe's group explored the option of reducing repeated PSA tests depending on an individual's genetic risk.

This study was conducted in central Denmark and involved 146 general practices; n=73 general practices were intervention practices, and n=73 were control practices. Men who visited their general practitioners were given a PSA test and offered a genetic test. If the genetic test showed they were at normal risk, they had no further PSA tests. However, if the genetic test showed they were at high risk, the patient was encouraged to have yearly PSA tests.

The primary endpoint was the proportion of males with repeated PSA tests within 2 years. The results showed that males with normal genetic risk had a lower chance of repeated PSA tests, and males with high genetic risk were more likely to have elevated PSA, biopsy, and a PCa diagnosis.

The final speaker, Robert Nam, Sunnybrook Research Institute, Toronto, Canada, discussed the 'Risk-Adapted Screening with MRI Only: MVP Trial.' In PCa screening, MRI is often used alongside PSA tests or genomic tests. However, Nam's group aimed to explore whether MRI could be used as a stand-alone tool to detect PCa. In this Phase III study, patients aged 50 years or older underwent either prostate MRI or PSA test in a randomised 1:1 ratio.

Collectively, 525 were able to participate in this trial: 246 had an MRI, and 248 had a PSA test. Surprisingly, 18 patients dropped out of the study as soon as they found out they would be getting a PSA test as they were upset and were hoping to be in the MRI group. Preliminary results showed that the MRI arm of the study detected more than double the rate of PCa compared to the PSA arm. Nam concluded that MRI is a lot more selective than PSA tests and avoids over-treatment and over-diagnosis. Regardless of initial expenses, it would work out to be more cost-effective in the long term to have an MRI scan rather than repeated PSA tests.

Despite a variety of clinical trials in PCa screening discussed in this year's congress, there was a common theme: a risk-adapted strategy to screening. The speakers proposed novel approaches to get the best out of the screening process whilst reducing harm and over-diagnosis. Many of these trials were in the beginning stages and only showed preliminary results; however, the speakers agreed this was a step in the right direction. In the future, other unanswered questions may be explored such as cost, convenience, and anxiety. Some of the results from these trials will not be confirmed for another decade, but the researchers are optimistic that there will be exciting improvements in PCa screening in the near future. ■

# Abstract Reviews

Sharing insights and updates from a selection of abstracts presented by leading experts in the field of urology at the European Association of Urology (EAU) Congress 2021.

## How the COVID-19 Pandemic Changed Post-operative Infections in Urology Wards: A Retrospective Cohort Study from Urology Departments

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**Keywords:** COVID-19, infection prevention, multidrug resistance (MDR), nosocomial infection, pandemic, surgery, urology.

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### BACKGROUND AND AIMS

Hospital-acquired infections represent a global healthcare crisis, contributing to patient morbidity and mortality.<sup>1</sup> In response to the COVID-19 pandemic, hospitals had to re-organise wards, postpone elective procedures, and cancel non-urgent activities. Measures to limit the spread of the disease included restrictions to patients' visitors, avoidance of street clothes by healthcare professionals, frequent object disinfection, and improved hand hygiene. Some of these measures have been shown to lower the rate of hospital-acquired infections and, as a result, the authors hypothesised that the occurrence of post-operative infection during the pandemic would be lower.<sup>2,3</sup> The objective of the authors' study was to compare the rate of post-operative infections and patterns of antimicrobial resistance before and during the pandemic in urology departments.

### MATERIALS AND METHODS

This was an observational retrospective cohort study carried out in two Portuguese centres. Data from all elective surgical procedures between April and June 2018 and the homologous period in 2020 were collected.



Table 1: Demographics and characteristics of patients submitted to elective urological surgery.

	Pre-pandemic period (n=425)	Pandemic period (n=273)	p value
Age, median (years, IQR)	65 (55–74)	65 (54–72)	0.361
Sex, Male (%)	319 (75.1)	203 (74.4)	0.858
Hospital stay, median (days, IQR)	3 (2–5)	3 (2–6)	0.806
ASA (%)			
I	29 (6.8)	13 (4.8)	0.125
II	273 (64.2)	168 (61.5)	
III	113 (26.6)	90 (33.0)	
IV	9 (2.1)	2 (0.7)	
Missing	1	0	NA
Antibiotic prophylaxis (%)			
None	5 (1.2)	12 (4.6)	0.024
Standard	225 (54.7)	139 (53.5)	
Prolonged	181 (44.0)	109 (41.9)	
Missing	14	13	NA
Peri-operative devices (%)	171 (40.2)	127 (46.7)	0.100
Pre-operative positive urine culture (%)	33 (24.6)	28 (27.5)	0.654
Post-operative infection (%)	60 (14.1)	33 (12.1)	0.494
Positive cultures	25/60 (47.2)	22/33 (62.9)	0.192
Drug-resistant species	24/25 (92.3)	11/22 (52.4)	0.003
Endoscopic intra-renal surgery	54 (12.7)	33 (12.1)	0.816
Lower urinary tract endoscopic surgery	182 (42.8)	110 (40.3)	0.530
Kidney and ureter surgery	51 (12.0)	34 (12.5)	0.906
Prostate surgery	74 (17.4)	35 (12.8)	0.110
Radical cystectomy	9 (2.1)	13 (4.8)	0.074
Genital surgery	55 (12.9)	48 (17.6)	0.101

ASA: American Society of Anesthesiologists; IQR: interquartile range; NA: not applicable.

Patient data included age, sex, post-operative in-hospital length of stay, American Society of Anesthesiologist (ASA) score, type of procedure, antibiotic prophylaxis, pre-operative urine cultures, peri-operative use of medical devices, post-operative infections, microbial culture, and antimicrobial susceptibility testing. Infection was defined according to the European Centre for Disease Prevention and Control (ECDC) protocol. Multidrug resistant (MDR) organism was defined as a micro-organism resistant to one or more classes of antimicrobial agents tested. The main outcomes were the number of post-operative infections during the pandemic and the number of MDR isolates.

## RESULTS

Baseline characteristics are presented in **Table 1**. The post-operative infection rate during the pre-pandemic period was 14.1% compared with 12.1% during the pandemic ( $p=0.494$ ). Ninety two percent of isolates were MDR in the pre-pandemic period compared with 52% during the pandemic ( $p=0.002$ ). The pandemic period was associated with a reduced risk for MDR isolates on multivariate logistic regression analysis (odds ratio: 0.1; 95%

confidence interval: 0.07–0.57;  $p=0.010$ ), but not with reduced number of infections (odds ratio: 0.84; 95% confidence interval: 0.53–1.34;  $p=0.47$ ).

## CONCLUSION

MDR isolates were lower during the pandemic in urology wards, possibly as an indirect result of COVID-19 preventive measures such as increased hand hygiene, room disinfection, and reduced family visits to inpatients. No statistically significant difference was found between the number of post-operative infections in the authors' sample. Further reports such as those from the ECDC are needed to confirm the authors' results. ■

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# Linguistic and Clinical Validation of the Spanish Acute Cystitis Symptoms Score Questionnaire in Females with Acute Cystitis

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## BACKGROUND AND AIMS

The Acute Cystitis Symptom Score (ACSS) is a patient self-reporting questionnaire for the clinical diagnostics and patient-reported outcome that may assess the symptoms and the effect on the quality of life in women with acute uncomplicated cystitis.<sup>1,2</sup> The current study aimed to create a validated Spanish version of the ACSS questionnaire. The questionnaire was developed in Russian and English by the European Association of Urology (EAU) Section of Infections in Urology (ESIU).<sup>1</sup>

## MATERIALS AND METHODS

The ACCS questionnaire was translated from its original Russian and American English into Spanish by translators with Spanish as their mother language. Then, four urologists from Spain and Latin America reviewed the two translations and established a consensus form. This consensus form was then translated back into Russian by a translator with Russian as their mother language and American English by a translator with American English as their mother language, in order to check and exclude any relevant change of the meaning. This consensus version was then used for all countries with Spanish as their primary language for cognitive assessment processes. All comments were considered, and the study version was established.<sup>3-7</sup> The study version was used for clinical validation in female patients from Spain, Colombia, and Peru.

Clinical evaluation was carried out by 198 female participants (151 with symptoms suspicious of uncomplicated cystitis and 47 controls). Psychometric characteristics of the ACSS were tested using coefficients of Cronbach's  $\alpha$  and split-half reliability. The

diagnostic characteristics were tested using specificity, sensitivity, diagnostic odds ratio, positive and negative likelihood ratios, area under the receiver operating characteristic diagnostic accuracy, and risk ratio. Average point estimates and 95% confidence intervals were used to present the results of the tests.

## RESULTS

The age of the 151 patients (mean: 49.9 years; standard deviation [SD]: 18.6) and 47 control (mean: 53.2 years; SD: 19.0) and their additional conditions at baseline visits such as menstruation, premenstrual syndrome, pregnancy, menopause, and diabetes were compared. Among the isolated pathogens, the most frequent was *Escherichia coli*, present in 94 urine cultures (74.6%). Other micro-organisms isolated were *Klebsiella pneumoniae* in 7 cases (5.5%), *Proteus mirabilis* in 7 (5.5%), Group B *Streptococcus* in 4 (3.1%), *Enterococcus faecalis* in 3 (2.3%), *Staphylococcus saprophyticus* in 3 (2.3%), and others.

ACSS comparative analysis reported a significant difference ( $p < 0.001$ ) between patients and controls at the baseline visit regarding sum score of the typical symptoms (mean: 8.11; SD: 4.31; and mean: 0.70; SD: 1.04), differential symptoms (mean: 1.46; SD: 2.1; and mean: 0.28; SD: 0.58), and quality of life (mean: 4.9; SD: 2.1; and mean: 1.32; SD: 1.9) (Table 1). At the follow-up visit, in the 'Evolution' domain of Part B of the questionnaire, 74.2% of patients were asymptomatic (back to normal), 15.7% much better, and 10.1% somewhat better. None of the patients persisted without clinical changes or had worsened in their symptoms

Cronbach's  $\alpha$  of the ACSS was 0.88 (mean: 0.85; SD: 0.90), and the split-half reliability was 0.89 (mean: 0.78; SD: 0.93). Using a sum score of  $>6$  for typical symptoms, a specificity of 0.98 (mean: 0.89; SD: 1.00) and sensitivity of 0.53 (mean: 0.54; SD: 0.79) were found. The diagnostic odds ratio was 16.33 (mean: 2.08; SD: 128.06); diagnostic accuracy 0.56 (mean: 0.44; SD: 0.62); positive likelihood ratio and negative likelihood ratio were 25.57 (mean: 3.65; SD: 179.13) and 0.48 (mean: 0.39; SD: 0.58), respectively; risk ratio was 1.80 (mean: 1.51; SD: 2.14); and area under the receiver operating characteristic was 0.73 (mean: 0.68; SD: 0.77).



## CONCLUSIONS

The validated Spanish ACSS questionnaire is a reliable, valid, and easy-to-use questionnaire that can evaluate the symptoms and clinical outcomes of patients with acute cystitis. It can be used as a patient's self-diagnosis of acute cystitis, as a patient-reported outcome measure tool and help to rule out other pathologies in patients with voiding syndrome.<sup>2-7</sup> ■

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**Table 1: Acute Cystitis Symptom Score questionnaire scores for each item of the domains: typical symptoms, differential, and quality of life for cases and controls.**

	Severity	Cases		Control		
	(Likert scale)	n	Mean (SD)	n	Mean (SD)	p value
Frequency	0 (no) 1 (mild) 2 (moderate) 3 (severe)	19 35 52 44	1.81 (1.00)	35 7 5 0	0.36 (0.67)	0.001
Urgency	0 (no) 1 (mild) 2 (moderate) 3 (severe)	16 42 52 41	1.78 (0.96)	42 5 0 0	0.11 (0.31)	<0.001
Painful micturition	0 (no) 1 (mild) 2 (moderate) 3 (severe)	43 27 42 39	1.51 (1.16)	45 1 1 0	0.06 (0.32)	<0.001
Incomplete bladder emptying	0 (no) 1 (mild) 2 (moderate) 3 (severe)	56 30 32 33	1.28 (1.17)	45 2 0 0	0.04 (0.20)	<0.001
Suprapubic pain	0 (no) 1 (mild) 2 (moderate) 3 (severe)	66 33 27 25	1.07 (1.13)	44 3 0 0	0.06 (0.25)	<0.001
Visible haematuria	0 (no) 1 (mild) 2 (moderate) 3 (severe)	89 35 17 10	0.66 (0.92)	45 1 1 0	0.06 (0.32)	<0.001

Table 1 continued.

	Severity	Cases		Control		
	(Likert scale)	n	Mean (SD)	n	Mean (SD)	p value
Flank pain	0 (no)	91	0.71 (1.00)	39	0.19 (0.45)	0.011
	1 (mild)	26		7		
	2 (moderate)	21		1		
	3 (severe)	13		0		
Abnormal vaginal discharge	0 (no)	101	0.47 (0.76)	44	0.09 (0.35)	0.005
	1 (mild)	33		2		
	2 (moderate)	13		1		
	3 (severe)	4		0		
Urethral discharge	0 (no)	131	0.19 (0.534)	47	0.00 (0.00)	0.079
	1 (mild)	14		0		
	2 (moderate)	4		0		
	3 (severe)	2		0		
Fever	0 (no)	131	0.19 (0.52)	47	0.00 (0.00)	0.079
	1 (mild)	13		0		
	2 (moderate)	6		0		
	3 (severe)	1		0		
General discomfort	0 (no)	4	1.82 (8.03)	31	0.36 (0.53)	<0.001
	1 (mild)	52		15		
	2 (moderate)	61		1		
	3 (severe)	33		0		
Impact on daily activities/work	0 (no)	14	1.77 (0.82)	30	0.49 (0.75)	<0.001
	1 (mild)	48		12		
	2 (moderate)	65		4		
	3 (severe)	29		1		
Impact on social activities	0 (no)	13	1.76 (0.93)	31	0.47 (0.75)	<0.001
	1 (mild)	49		11		
	2 (moderate)	49		4		
	3 (severe)	39		1		

SD: standard deviation.

# The Importance of Neurophysiological Study and CT-Guided Perineural Injection in the Characterisation of Pudendal Neuropathy

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## BACKGROUND AND AIMS

The diagnosis of pudendal neuropathy is based on a set of five criteria; four of them are clinical and the last one involves the evaluation of the response to CT-guided infiltration of the pudendal nerve.<sup>1</sup> These criteria can be considered as cornerstones in the diagnosis of pudendal neuralgia (PN) and in the indication of decompression surgery (Nantes criteria). The objective of the present study was to analyse the efficacy of CT-guided pudendal nerve infiltration and its role in the PN diagnosis, and to identify predictive factors for response to CT-guided pudendal nerve block.

## MATERIALS AND METHODS

A cross-sectional study was performed. Fifty-two subjects with PN who met the five essential Nantes

criteria were identified. Thirty-seven patients with at least 1-year of follow up and who underwent CT-guided perineural injection were included. Pain response was assessed using a visual analogue scale (VAS). The remaining 15 patients were excluded because of one of the following two reasons: either a short follow-up period (<1 year) or the patient rejected undergoing diagnostic CT-guided injection. Injection responses were categorised as positive or negative, according to self-reported pain relief (VAS score) after the procedure.

Patients were evaluated for treatment outcomes (pain relief, duration, VAS change, and indication for surgical decompression). Mann-Whitney U, chi-squared, or Fisher's exact tests, as well as logistic models were used to assess associations between covariates and positive response to CT-guided perineural infiltration or improvement after surgical decompression.

## RESULTS

Overall, 45/52 (86.54%) patients were female and the mean age was 51.17 years (standard deviation [SD]:  $\pm 14.15$  years). The response rate after CT-guided pudendal injection was 75.68% of patients. The mean duration of pain relief was 9.05 days (SD:  $\pm 11.59$  days). The mean VAS scores were 7.66 (SD:  $\pm 1.50$ ) and 3.00 (SD:  $\pm 2.44$ ) before and after the procedure, respectively.

A diagnostic neurophysiological study was associated with the pain relief after CT-guided nerve block ( $p=0.02$ ) (Table 1).

Multivariate analysis confirmed that a conclusive neurophysiologic testing was associated with the positive response to CT-guided pudendal nerve block (odds ratio: 9.54, range: 1.32–68.83;  $p=0.025$ ).

Twenty-two patients (42.31%) underwent pudendal nerve decompression surgery. Of these, 15/22 (68.18%) patients improved after surgery. A favourable response to injection was associated with the surgical indication ( $p=0.002$ ). In addition, 14/19 (73.68%) of patients who had a good response to CT-guided nerve block improved after surgical decompression, as well as those who had a positive prior neurophysiologic study (12/16; 75%).



Table 1: Association between the efficacy of CT-guided pudendal nerve block and a conclusive neurophysiological study.

	Conclusive neurophysiological study		p value
Response to CT-guided pudendal nerve block	Yes	No	0.036
Yes	22 (88%)	6 (50%)	
No	3 (12%)	6 (50%)	

CONCLUSION

CT-guided pudendal nerve block is an effective treatment option and plays an important role in the diagnosis of PN. The previous conclusive neurophysiological study is associated with the success of the CT-

guided infiltration and can be used as a tool for predicting the response to this technique. ■

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**Keywords:** Fesoterodine fumarate, multiple sclerosis (MS), neurogenic bladder, neurogenic detrusor overactivity (NDO), spinal cord lesion (SCL).

**Citation:** EMJ Urol. 2021;9[1]:40-41. Abstract Review No. AR4.

BACKGROUND AND AIMS

Antimuscarinic drugs are the first-line choice in the treatment of patients with neurogenic detrusor overactivity (NDO), even if the relative literature is still limited.<sup>1,2</sup> Fesoterodine fumarate is the newest antimuscarinic drug. No study has been yet published about the use of fesoterodine fumarate in patients affected by neurogenic lower urinary tract dysfunction. The aim of the authors' study was to determine the efficacy

Efficacy of Fesoterodine Fumarate in Neurogenic Detrusor Overactivity Due to Spinal Cord Lesion or Multiple Sclerosis: A Prospective Study

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of fesoterodine fumarate for the treatment of patients with NDO due to multiple sclerosis (MS) or spinal cord lesion (SCL).

## MATERIALS AND METHODS

The study was designed as an open-label prospective interventional trial without a control group. Eligible subjects for enrolment were considered patients between 18 and 80 years of age affected by NDO, confirmed by urodynamic studies (UDS), secondary to MS or SCL of at least 6 months before their enrolment. All participants provided informed consent and the study had the approval of the scientific and ethics committee of the National Rehabilitation Center, Athens, Greece. It was considered unethical to create a placebo (or a non-therapy) control group as the increased detrusor pressure might harm the unit under test of the patients. On the other hand, previous studies on other antimuscarinics proved that the placebo effect is rather 'limited' in such a cohort of neurological patients.

A 2-week wash-out period was requested prior to enrolment for patients under drug medication for the treatment of NDO. All patients underwent a first confirmatory baseline UDS and fulfilled the SF-Qualiveen as a quality of life (QoL) questionnaire.<sup>3-5</sup> Afterwards, all subjects received a treatment of 8 mg fesoterodine daily for 3 months. At the completion of this period, they repeated the UDS and SF-Qualiveen. Each UDS was performed with the same equipment in the same environment from the same clinician, unaware of the study hypothesis, according to the International Classification for Standards' (ICS) urodynamic practices and terms.<sup>6</sup> The primary endpoint of the study was the change from baseline to end of treatment in maximum detrusor pressure (Pdetmax) during the filling phase of the UDS, and whether the use of fesoterodine fumarate would decrease it. Secondary endpoints included changes from baseline to end of treatment in bladder capacity and compliance. By analysing the questionnaires pre- and post-treatment, patient QoL was evaluated. Statistical analysis was performed using SPSS® Statistics 26 (IBM, Endicott, New York, USA).

## RESULTS

One hundred and thirty-seven patients were recruited and 124 of them, 68 males and 56 females, completed the study. Of the included patients, 95 had SCL (60 paraplegia and 35 tetraplegia) and 29 had MS. The urodynamic parameters Pdetmax, bladder capacity, and compliance were estimated for the whole group before and after treatment and were proved to be statistically different when compared to the baseline ( $p < 0.001$  for all variables), according to the Wilcoxon test for a non-parametric sample. Changes in urodynamics parameters were also significant in each of the paraplegic, tetraplegic and MS groups ( $p < 0.001$ ) (Table 1). According to all the domains of SF-Qualiveen, QoL also improved. There was a significant difference in SF-Qualiveen score after treatment with fesoterodine in all patients, independently of the diagnosis.

## CONCLUSIONS

Fesoterodine fumarate is an efficacious drug in patients with SCL and MS, as it significantly decreases the detrusor pressure, increases the bladder capacity and compliance, and improves the QoL. ■

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**Table 1: Variance of the urodynamic variables after treatment with fesoterodine fumarate.**

	Minimum	Maximum	Mean	Standard deviation	p value
Paraplegia					
Pdetmax PRE (cmH <sub>2</sub> O)	25.00	128.00	68.6500	27.22214	<0.001
Pdetmax POST (cmH <sub>2</sub> O)	13.00	81.00	46.4500	18.20172	
Bladder capacity PRE (mL)	70.00	511.00	268.2167	94.27297	<0.001
Bladder capacity POST (mL)	148.00	685.00	389.6333	115.21917	
Compliance PRE (mL/cmH <sub>2</sub> O)	6.00	340.00	54.0167	58.72501	<0.001
Compliance POST (mL/cmH <sub>2</sub> O)	18.00	350.00	72.3667	62.46815	
Tetraplegia					
Pdetmax PRE (cmH <sub>2</sub> O)	27.00	125.00	64.9143	25.29749	<0.001
Pdetmax POST (cmH <sub>2</sub> O)	13.00	83.00	42.0857	17.17278	
Bladder capacity PRE (mL)	104.00	518.00	260.4286	104.67184	<0.001
Bladder capacity POST (mL)	203.00	660.00	379.0286	130.30744	
Compliance PRE (mL/cmH <sub>2</sub> O)	3.00	160.00	49.6286	37.35370	<0.001
Compliance POST (mL/cmH <sub>2</sub> O)	19.00	220.00	74.0000	51.87428	
Multiple sclerosis					
Pdetmax PRE (cmH <sub>2</sub> O)	18.00	133.00	49.2069	27.57118	<0.001
Pdetmax POST (cmH <sub>2</sub> O)	12.00	97.00	36.7241	21.97222	
Bladder capacity PRE (mL)	76.00	503.00	209.9310	104.58316	<0.001
Bladder capacity POST (mL)	125.00	596.00	293.2069	113.42568	
Compliance PRE (mL/cmH <sub>2</sub> O)	10.00	310.00	63.3793	74.86913	<0.001
Compliance POST (mL/cmH <sub>2</sub> O)	22.00	480.00	80.4138	96.85944	
Total group					
Pdetmax PRE (cmH <sub>2</sub> O)	18.00	133.00	63.0484	27.69252	<0.001
Pdetmax POST (cmH <sub>2</sub> O)	12.00	97.00	42.9435	19.12233	
Bladder capacity PRE (mL)	70.00	518.00	252.3871	101.72062	<0.001
Bladder capacity POST (mL)	125.00	685.00	364.0887	124.72637	
Compliance PRE (mL/cmH <sub>2</sub> O)	3.00	340.00	54.9677	57.80285	<0.001
Compliance POST (mL/cmH <sub>2</sub> O)	18.00	480.00	74.7097	69.00604	

Pdetmax: maximum detrusor pressure; POST: after treatment; PRE: before treatment.



# Relapses of Urogenital Tract Tuberculosis

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**Keywords:** Incidence, kidney tuberculosis, prostate tuberculosis, recurrent tuberculosis, relapse, urogenital tuberculosis (UGTB).

**Citation:** EMJ Urol. 2021;9[1]:43-44. Abstract Review No. AR5.

## BACKGROUND AND AIMS

Tuberculosis (TB) is an infectious disease prone to both a self-healing and chronic or recurrent course.<sup>1-3</sup> The purpose of the study was to analyse the incidence of recurrence of urogenital TB (UGTB) and to identify the characteristics of patients with recurrent disease.

## MATERIALS AND METHODS

Specially created questionnaires on the spectrum of the incidence of extrapulmonary TB (EPTB) in Siberia were analysed. The histories of 140 outpatients with UGTB were also analysed (TB of the urinary and male reproductive system and female genital TB were excluded), and were observed in the Novosibirsk Regional Tuberculous Dispensary between 2010–2019. Among the whole cohort, cases of relapses were selected and analysed in detail.

## RESULTS

In 2019, a total of 563 patients with isolated forms of EPTB were diagnosed in the Siberia. Of the cohort, 81 patients (14.4%) had UGTB; one was infected with HIV and the remaining patients with UGTB were HIV-negative. In the cohort of patients who were immunocompetent with EPTB, the share of UGTB was 22.1%, and among patients infected with HIV it was 0.5%.

There were three children with UGTB, and all were immunocompetent.

In 99 patients with EPTB (17.6%), the present disease was a relapse. Among all patients with EPTB, relapses of UGTB were diagnosed in 8 patients (8.1%), and all patients with UGTB were HIV-negative. Thus, there was negative correlation between isolated forms of both newly diagnosed and recurrent UGTB and HIV-infection.

In the Novosibirsk region, in a 10-year period, 140 patients were diagnosed with UGTB. One hundred and twenty-seven patients (90.7%) were newly diagnosed, and 13 patients (9.3%) had relapsed. The average age of patients with recurrent UGTB was 53.7. In young patients (30–50 years) this was 46, and in patients older than 50 years this was 54. Among patients with relapse, men predominated (61.5%). The primary focus of TB was located in the organs of the urogenital system in 53.9% of patients. This fact confirms the theory of reactivation of dormant foci. The average relapse time after successful cure of TB was 9.1 years. *Mycobacterium tuberculosis* was found in 38.5% of patients in the debut of UGTB; all strains were susceptible to anti-TB drugs. In patients with recurrent UGTB, *M. tuberculosis* was found in 23.1%, and in one patient drug resistance of pathogen to streptomycin and isoniazid was detected. In general, the kidneys were the most susceptible to relapses: they were involved in 69.2% of cases. In 61.5% of cases, the prostate was affected.

Therapy with anti-TB drugs was effective in 92.3% of the patients with recurrent UGTB. Tolerance was worse than in first episode of TB: in 23.1% of patients, different side effects were registered.

## CONCLUSIONS

Of the patients with UGTB, 8.1–9.3% had TB and successfully recovered from it. When UGTB recurred, the kidneys were affected in 69.2% of cases, and in 61.5% of cases, the prostate was involved. The majority of patients (61.5%) with recurrent UGTB were men. Therefore, sex may be considered as a predictor of recurrence for UGTB. HIV infection was negatively correlated with both newly diagnosed and recurrent UGTB. In patients with combined lesion

(pulmonary TB, HIV infection, and UGTB), the disease course had a prevalence of caseous form, abscesses, and fistulae. ■

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# Development and Validation of the International Female Coital Incontinence Questionnaire

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**Keywords:** Coital incontinence, female sexual dysfunction, questionnaire, women.

**Citation:** EMJ Urol. 2021;9[1]:44-45. Abstract Review No. AR6.

named 'coital incontinence', and thus lead to specific alteration of the sexual life.<sup>3,4</sup> Literature reports that incidence of coital incontinence in females who are incontinent can vary between 10% and 66%.<sup>5-7</sup> Urinary symptoms and female sexual dysfunction are also a dichotomy that is difficult to analyse and distinguish. Coital incontinence is an under-studied and underestimated condition because patients rarely refer spontaneously to their sexual disturbances.<sup>8</sup> For this reason, diagnostic tools would be of fundamental importance, but there are no specific validated questionnaires on coital incontinence.<sup>9,10</sup>

## MATERIALS AND METHODS

The first questionnaire on coital incontinence was presented at the 36<sup>th</sup> Annual European Association of Urology (EAU) Congress in a press release dated 8<sup>th</sup> July 2021. The International Female Coital Incontinence Questionnaire (IFCI-Q) aims to evaluate the presence, severity, and type of coital incontinence, and its impact on quality of sexual intercourse. The self-administered questionnaire, with 8 questions, includes specific questions on coital incontinence, concomitant urinary symptoms, quality of life, quality of sexual intercourse, and psychological status issues. Data from sexually active female patients who complained about coital incontinence were collected.

## RESULTS

The participants average age was 43.4 years and 26.6% of them had no concomitant urinary

## BACKGROUND AND AIMS

Bladder symptoms, particularly urinary incontinence and pelvic floor disorders, may seriously impact on quality of life, self-image, partner relationships, and subsequently sexual life.<sup>1,2</sup> Urinary leakage can specifically occur during sexual intercourse, formally

symptoms. Thirty-six percent of patients complained about coital incontinence during the orgasm, 33% during penetration, and 30% of women had the combined form. Additionally, 43.3% of the participants complained of overactive bladder symptoms, 23.3% had mixed urinary incontinence, and 6.6% had stress urinary incontinence. Approximately 60% of patients reported that this type of incontinence restricts their sexual activity. The patients who participated completed the self-administered IFCI-Q in 8-10 minutes, and the participants were satisfied with the clarity and speed of the questionnaire. To detect test-retest reliability, the questionnaire was administered twice, with an interval of 2 weeks. Internal consistency and replicability of data measured for the questionnaire was found to be good.

## CONCLUSION

Maurizio Serati, Insubria University, Italy, commented: "Coital incontinence is the most devastating female pelvic dysfunction in terms of impact on quality of life. It is mandatory to elaborate an appropriate diagnostic tool to diagnose this neglected problem."

Marilena Gubbiotti, San Donato Hospital, Italy, also added: "The IFCI-Q is important because there are currently no specific validated questionnaires on coital incontinence, and

it is the first tool in this field. The IFCI-Q has been proven to be simple to understand and fast. The IFCI-Q provides a valuable and useful adjunct to clinical care and outcomes research in females with lower urinary tract symptoms and/or sexual dysfunction." ■

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# The Results of Open Ureterocalicostomy for Reconstruction of the Upper Urinary Tract

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**Keywords:** Hydronephrosis of the intrarenal pelvis, ureteric reconstruction, ureterocalicostomy (UC).

**Citation:** EMJ Urol. 2021;9[1]:46-47. Abstract Review No. AR7.

## BACKGROUND AND AIMS

During Poster Session 13 of the 36<sup>th</sup> Annual European Association of Urology (EAU) Congress, the retrospective study 'The Results of Open Ureterocalicostomy for Reconstruction of the Upper Urinary Tract' was presented. The research was focused on the long-term results of ureterocalicostomies (UC) and analysis of the prognostic factors for the successful operation, which is considered to be one of the most complicated types of reconstruction for the upper urinary tract.<sup>1,2</sup>

## MATERIALS AND METHODS

From 2012 to 2019, 37 patients underwent anastomosis between the ureter and the lower

calyx. All surgical interventions were classified into two groups according to the type of kidney resection. Type I, with preserved renal parenchyma (>10 mm), resection was performed in warm ischaemia conditions with exposure and transection of the lower calyx at the level of its fornix or neck, with removal of the entire lower pole of the kidney (n=27; 72.9%). The calyx was divided 3–5 mm distal from the parenchymal resection area. Type II, in cases where the thickness of the renal parenchyma did not exceed 10 mm, the part of the lower pole was removed in the area of maximal thinning of the parenchyma without renal ischaemia in most cases (n=10; 27.1%).

All types of resection, according to the direction of its plane, were additionally classified into transverse, defined as perpendicular to the vertical axis of the kidney (n=17; 45.9%), and oblique, defined as applied at an angle of 45° towards the vertical axis of the kidney (n=20; 54.1%).

## RESULTS

Early post-operative complications were observed in 14 (37.8%) patients. All complications were not severe. The rate of good results was 81.1% (n=30), satisfactory results was 13.5% (n=5), and poor results was 5.4% (n=2). One patient with a solitary kidney underwent repeated UC, and for another patient nephrectomy had to be performed. Only two parameters had a reliable prognostic value in terms of negative results of the operation: the thickness of the renal parenchyma of <10 mm and the use of Type II resection of the renal parenchyma.

Angular deformation of the junction of the ureter with the lower calyx was recorded in 13 (35.1%) patients. In most cases, angular deformation was observed in patients who underwent transverse resection of the lower pole of the kidney (n=10; 58.8%).

## CONCLUSION

A high level of good results of open UC was achieved. The most important predictor of the long-term outcome of surgery was the thickness of the renal parenchyma being <10 mm. Bearing in mind this point, clear

benefits of the oblique resection become obvious. Since the upper third of the ureter and the actual anastomosis area lie on the lumbar muscles, the classical transverse resection of the lower pole of the kidney can be accompanied by the angular deformation of the anastomosis. With active scar tissue formation in the post-operative period, this can lead to its deformation, narrowing, and disruption of blood flow. Whereas, using the oblique resection of the lower kidney pole allows for the isolation of the area of the anastomosis from contact with the lumbar muscles or scar

tissue of the retroperitoneal space to prevent its angular deformation. In this case, the anastomosis is completely covered by the renal parenchyma from below. ■

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# Computational Fluid Dynamic Modelling of Renal Stones in the Renal Calyx

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**Keywords:** Computational fluid dynamics, conservative management, renal calculi, spontaneous stone expulsion, urolithiasis.

**Citation:** EMJ Urol. 2021;9[1]:47-48. Abstract Review No. AR8.

## BACKGROUND AND AIMS

Conventional stone prevention methods attempt to maintain the concentration of urinary substances below solubility to inhibit crystal formation. However, continuous adjustment is difficult and does not provide sufficient preventive effect. Therefore, the authors aim to prevent urolithiasis requiring therapeutic intervention by discharging a renal stone in a minute size that does not cause pain attacks or incarceration in the ureter. For that purpose, it is necessary to calculate the urinary flow and posture required for excreting renal stones from the renal calyx for each calyx and each patient. In this study, the authors initially investigated the effects of urinary flow and posture on the movement of renal stones in the renal calyx using computational fluid dynamics (CFD). CFD is a branch of fluid mechanics used to analyse and solve problems that involve fluid flows. It is applied to a wide range of research fields and industries, including aerodynamics analysis, aerospace analysis, and biomedical engineering.

## MATERIALS AND METHODS

The authors prepared the ideal renal calyx model. The renal stone was placed in each calyx, and the flow analysis around the renal stone was performed. These numerical analyses were conducted using an in-house CFD code whose accuracy had been thoroughly validated.<sup>1,2</sup>

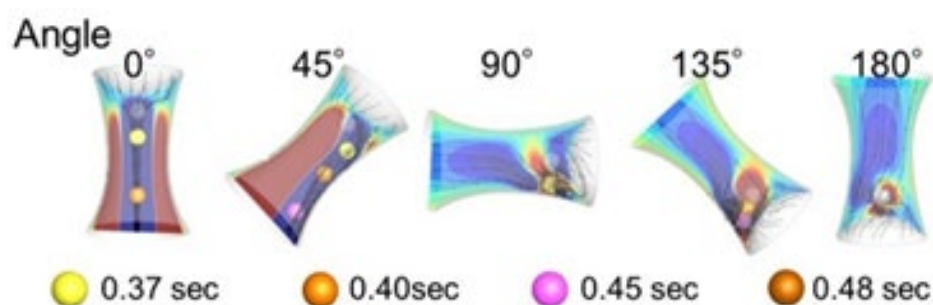


Figure 1: The effect of urinary flow and gravity on the stone movement in the calyx (urine volume 10 L/day).

## RESULTS

It was demonstrated that changing the urinary flow rate in the physiological range (1.5–10 L/day) had little effect on the movement of a renal stone with a diameter of 1.79 mm. Although the tiny stone in the calyx of 135° and 180° angle flowed out, no stone flowed out in the calyx <90° angle (Figure 1). These results suggest that the movement of renal stones was affected more by gravity than by hydrodynamic forces.

## CONCLUSIONS

The authors developed the prediction tool of the renal stone movement in the calyx using CFD. The authors are beginning to apply the

CFD technology to predict stone movement in the whole-kidney model. It will classify the risk of residual stone in each calyx by simulating the trajectory of stones. By adjusting the urinary flow rate and the direction of gravity using the CFD model, residual stones after shockwave lithotripsy and flexible ureterorenoscopy will be discharged efficiently. ■

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# Congress Interview



## Hugh Mostafid

Department of Urology, Royal Surrey County Hospital, Guildford, UK; European Association of Urology (EAU) Non-Muscle-Invasive Bladder Cancer Guidelines Panel



**E** MJ spoke to Hugh Mostafid about his professional journey in urology and his role in the European Association of Urology (EAU) Non-Muscle-Invasive Bladder Cancer Guidelines Panel.

**Q1** With over 30 years of experience as a urologist, what initially sparked your interest to pursue a career in this field and motivated you to progress your career further in this field?

I had originally planned a career in vascular surgery but as part of my junior surgical rotation I had a 6-month urology attachment and I really enjoyed the breadth of conditions that urology covers, everything from paediatric urology to complex voiding problems as well as a number of common cancers. During my urological training in London, I was lucky enough to spend 2 years at the Institute of Urology, which has a long tradition of a scientific approach to urology. It was this that sparked my commitment to academic urology and, once I became a consultant in 2001, I developed an interest in bladder cancer because the management of this condition has remained largely the same for the past 40 years and I could see that there was considerable room for improvement in this area.

**Q2** You currently have more than 100 international publications and written book chapters on bladder cancer, as well as being an invited speaker at national and international meetings on bladder cancer. What do you believe to be the current gaps in literature and what topics merit greater attention?

I think there are two main areas. Firstly, we use a technique to remove bladder tumours (trans-urethral removal of bladder tumour) that is nearly 100 years old, and we need to refine some of the newer techniques such as en bloc resection to improve the quality of the surgery we offer to patients with bladder cancer. Secondly, patients with low-risk non-muscle-invasive bladder cancer (NMIBC) are not at risk of progression or death from the condition but still face invasive surveillance. I think we should investigate alternative options such as active surveillance or surveillance with urine-based biomarkers to reduce the burden of NMIBC on these patients.

**Q3** The Royal Surrey County Hospital, Guildford, UK, is one of the few institutions performing robotic-assisted radical bladder cancer surgery in the UK. What do you think other university hospitals could learn from the approach taken at your current institution?

I think the most important lesson is to adopt a team-based approach. Robotic cystectomy requires a large, dedicated team in order to offer a high-volume service. This, in turn, is critical in terms of offering a timely service for referred patients, improving outcomes, and finally adequate training opportunities. It is not sufficient simply to do a few robotic cystectomies because your institution already has a robot, e.g., for radical prostatectomy.

**Q4** You are a member of the European Association of Urology (EAU) guidelines panel on the NMIBC. Could you please explain what this position entails and how it contributes to the success of the EAU Society?

*"I think the undoubted advantage of a virtual congress has been to widen the field of abstract submissions and improve the scientific quality."*

The EAU NMIBC guidelines panel is one of a large number of guideline panels under the auspices of the EAU Guidelines Office. Each of these panels is responsible for critically appraising new evidence in their field and using this information to produce high quality recommendations. The EAU NMIBC guidelines panel is very active not only in drawing up guidelines on NMIBC but also in carrying out multinational collaborations and systematic reviews in area of NMIBC where there is an unmet need. I think it is clear when speaking to urologists from around the world that the EAU is highly respected, particularly as a result of the EAU Guidelines initiative and this is reflected by their adoption by

many national urological societies around the world.

**Q5** The mission of the EAU society is to "raise the level of urological care throughout Europe and beyond." What is one of the biggest challenges for the EAU in their goal to promote the highest standard of practices in urology in order to benefit patients?

I think the subjects that come up regularly are variations in practice and non-adherence to guidelines. The reasons for this are complex and varied such as a lack of resources but there are other reasons that are poorly understood. A better understanding of these factors would undoubtedly result in improved outcomes for patients.

**Q6** This year's EAU meeting was carried out online due to the on-going COVID-19 pandemic. What do you believe to be the advantages and disadvantages of a virtual congress?

Apart from the obvious benefit of reducing carbon footprint, I think the undoubted advantage of a virtual congress has been to widen the field of abstract submissions and improve the scientific quality. I chaired a poster session with presenters from Taiwan to Houston over 12 time zones. Many of these researchers would not have been able to present in person. On the other hand, it is repeatedly said that video technology cannot fully replicate the interactions that one gets from a live meeting and there is no doubt that some of the discussions that take place outside of the sessions themselves are incredibly useful to develop research ideas.

**Q7** There was a session in the EAU congress this year titled 'Telemedicine in urology'. What impact has the COVID-19 pandemic had on the wellbeing of healthcare professionals in urology. How have you and your team adapted during this time in order to provide highest standard of practices in urology to benefit patients?



Fortunately, urology was not in the ‘front-line’ of the hospital treatment of patients with COVID-19, so we were probably less directly affected than colleagues in other specialities. On the other hand, we do have a high proportion of patients with cancer in urology and trying to maintain our cancer workload has been very challenging. In bladder cancer, the main challenge has been for all patients to receive treatment in a timely manner. One change that has helped has been the increasing use of telephone and video clinics, which has freed up time and space within the department to the benefit of patients with cancer.

**You were the chief investigator for the CALIBER trial, in the recently published study entitled ‘CALIBER: a phase II randomized feasibility trial of chemoablation with mitomycin-C vs surgical management in low-risk non-muscle-invasive bladder cancer’. Could you please highlight to our readers the principal findings and wider relevance of this study?**

The principal findings of the CALIBER trial were that patients with recurrent NMIBC who received 4 instillations of mitomycin tolerated this extremely well and had a 48% complete response rate to this drug saving them the need for surgery. We also found that the surgery-only ‘control’ arm had a 20% recurrence rate at 3 months, a far higher rate than was previously assumed. Overall, the results point to a potential role of neoadjuvant intravesical chemotherapy prior to trans-urethral removal of bladder tumour rather than afterwards, as is currently the case.

**As founder member and past Chair of Action on Bladder Cancer (ABC) UK, a charity that was set up to raise funds for bladder cancer research and improve patient outcomes in the UK, how much of an impact do you believe this organisation has, both directly on urologists and indirectly on patients?**

Cancer charities have an important role in terms of raising public awareness, fundraising, and supporting research. Prior to



*"I welcome and encourage young healthcare professionals into the field of academic urology and specifically bladder cancer research."*

the establishment of ABC UK as well as Fight Bladder Cancer, another UK charity, there were no bladder cancer charities, which was a real impediment to raising awareness and fundraising. I think one specific impact ABC UK has had on urologists directly is to fund bladder cancer specific research projects. Prior to this, bladder cancer researchers had to compete for funding against other well-resourced cancers, which was challenging.

**You have specialised surgical experience in robotic surgery, blue light cystoscopy, and device-assisted intravesical therapy for bladder cancer. What are some of the unique benefits and challenges associated with these novel techniques? Are there any other innovations on the horizon in urological surgery that you think are particularly noteworthy?**

These novel techniques have all shed a spotlight on aspects of our surgical practice and highlighted shortcomings in technique

and outcomes. In this respect, they have proved invaluable. Nevertheless, they also illustrate the importance of proper evidence-based assessment of new techniques in clinical trials before widespread adoption in routine practice.

**Finally, what advice would you give to young healthcare professionals pursuing a career in this discipline? Where do you hope they will take the field of urology, and specifically bladder cancer research and developments, over the coming decades?**

I welcome and encourage young healthcare professionals into the field of academic urology and specifically bladder cancer research. I think the role of augmented reality both in the field of genomics and more practically in the day-to-day follow-up of bladder cancer is an especially exciting area, and I think that this is the area that young trainees who are likely to be very computer literate will make the greatest future contribution to our speciality. ■

# Interview



## Prokar Dasgupta

Foundation Professor of Surgery, King's Health Partners, King's College London; Honorary Consultant Urologist, Guy's and St Thomas' Hospitals NHS Foundation Trust, London, UK

**Q1** Your career as a clinician and scientist started when you began studying the immunology of leishmaniasis. How did you transition from researching the immunology of a parasitic disease to the field of urology?

The immunology of leishmaniasis was closely related to the effect of splenectomy to save the lives of patients who were drug resistant. So, it was not difficult to make the transition from surgical science to the sub-specialty of urology. Around this time one of my role models brought a Dornier lithotripter to Kolkata, India, to break kidney stones; this was a game changer as it avoided open kidney stone surgery in most patients, including some members of my own family. It became clear that urology was a fascinating surgical specialty and I was inspired to take it up.

**Q2** What do you consider to be the greatest achievements in your career to date?

The study of C-fibres in the overactive human bladder as a Medical Research Council research fellow and describing the injections of botulinum toxin (Botox) to target these nerves under local anaesthetic.

The introduction of modern robotics, which has transformed the way we practice surgery, particularly with regard to prostate cancer.

The establishment of the Prostate Cancer Research Centre at King's College London, and developing a modified cytotoxic agent for localised immunotherapy for which we have recently received a patent.

Leading the first randomised trial of simulation across 15 nations to show that it makes a difference to patient outcomes and creates better surgeons.

Editing the British Journal of Urology International for 8 years, doubling its impact factor, and achieving a high Altmetric score. I led an international editorial team that revolutionised web-based publishing and the responsible use of social media. We brought innovative design, artificial intelligence, and a new open access platform to the family of journals.

Finally, helping the careers of young researchers and students, many to their own chairs.

**Q3** In 2020 you were appointed as the Foundation Professor of Surgery for King's Health Partners. Could you please explain what this position entails and summarise your vision for the partnership?

This is a big honour for me as we have not had a Professor of Surgery for many years after the retirement of the last Chair. We have a massive opportunity of bringing surgeons across King's Health Partners together irrespective of their specialty and showcasing the fantastic work that they do along with their scientists and educationalists. My vision is to facilitate outstanding surgical science collaborations, support hybrid surgical and implementation trials, improve education for the next generation of surgical trainees, and inspire students wishing to embark on exciting surgical careers.

*We conducted the first clinical trials involving a new surgical technique for micro-injecting botulinum toxin-A directly into the bladder with a flexible cystoscope to suppress C fibres and improve bladder control.*

#### **Q4 Could you provide an overview of the so-called 'Dasgupta technique' for delivering Botox to refractory overactive bladders?**

This was developed nearly 20 years ago in collaboration with Professor Clare Fowler at Queen Square. An overactive bladder affects 8 million people in the UK alone. We conducted the first clinical trials involving a new surgical technique for micro-injecting botulinum toxin-A directly into the bladder with a flexible cystoscope to suppress C fibres and improve bladder control. Compared to other treatments for overactive bladder, botulinum toxin-A directly therapy is more cost-effective and less invasive. The beneficial effect to the patient is maintained for over 20 years. It has been recommended in the National Institute for Health and Care Excellence (NICE) guidelines and international clinical guidelines. Through the guidelines and our teaching and mentorship programmes, this has improved the quality of life of millions of people around the world.

#### **Q5 What is the current status of simulation training in urology and are there any advancements on the horizon that you think are particularly noteworthy?**

Simulation has become an established part of the surgical curriculum, not just technical skills but also non-technical skills training. Urology was the first specialty where it was introduced into the curriculum by our Specialist Training Committee. I think the role of cognitive training will become more important, particularly as functional MRI shows that there are signalling pathways in the brain that can improve performance. This is routinely used by athletes, so why not by surgeons?

#### **Q6 What impact has the COVID-19 pandemic had on urological practice globally and what recommendations have been proposed to overcome these challenges?**

At the height of the pandemic, our surgical output dropped by around 80%. Thankfully, many of the patients with prostate cancer could be managed with hormonal treatment without affecting their final outcomes. Very few of our patients came to see us face-to-face, so we had to rapidly learn the art of teleconsultation. It affected our trainees and students and we tried to reduce that effect by simulation, webinars, and remote learning with augmented reality. We also published guidelines on safe robotic surgery from the European Association of Urology (EAU) Robotic Urology Section (ERUS) and our own outcomes on over 600 patients during the first wave with a mortality rate of 0.2%.

#### **Q7 Could you highlight the key research findings and wider relevance of your recently published review article, "Urinary Biomarkers to Mitigate Diagnostic Delay in Bladder Cancer During the COVID-19 Era"?**

This work was led by my colleague Nikhil Vasdev from the University of Hertfordshire, Lister Hospital, East and North Hertfordshire NHS Trust, Stevenage, UK with whom I also delivered a number of webinars during the Black Lives Matter movement. The article





*"There are three important new developments in robotics: reducing cost with newer robotic systems coming into the market, better connectivity with 5G/6G, and the use of artificial intelligence."*

described a number of exciting biomarkers, especially the role of URO17, a highly sensitive and specific marker for bladder cancer, both new and recurrent. Additionally, URO17 can be used to test patients presenting with haematuria, thereby enabling its integration into clinical practice.

### **Could you outline the benefits of robotic urological surgery? How do you see the field changing over the coming years?**

The benefits of minimal invasion such as less blood loss, less pain, and shorter hospital stays are obvious and attractive to patients. There are three important new developments in robotics: reducing cost with newer robotic

systems coming into the market, better connectivity with 5G/6G, and the use of artificial intelligence.

### **As a researcher, where can we expect to see your focus lie in the coming years?**

We have integrated King's Health Partners Academic Surgery with Surgical and Interventional Engineering at St Thomas' Hospital, led by my colleague, Sebastien Ourselin, and I, along with our highly productive team of engineers and scientists. My main focus will be on surgical data science to make a real difference to patient outcomes and the training of the next generation of surgeons. ■

# Irreversible Electroporation for Patients with Localised Prostate Cancer: Expert Opinion on this Versatile Therapeutic Approach

<b>Interviewees:</b>	Olivier Cussenot, <sup>1</sup> Phillip Stricker <sup>2,3,4</sup>  1. Department of Urology, APHP-Sorbonne University, Tenon Hospital, Paris, France 2. Department of Urology, St Vincent's Private Hospital and Clinic, Sydney, Australia 3. Garvan Institute of Medical Research, Sydney, Australia 4. Australian PC Centre, Sydney, Australia
<b>Disclosure:</b>	Cussenot is an expert for INCa (French National Cancer Institute) and ANSES (French Agency for Food, Environmental and Occupational Health & Safety); he performs workshops on irreversible electroporation (IRE) in partnership with AngioDynamics; he is not receiving any grants from AngioDynamics and is not a paid consultant for the company. Stricker received fees from AngioDynamics for consultancy work.
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## Interview Summary

Irreversible electroporation (IRE) is emerging as a new method of soft tissue ablation, with applications including focal therapy in patients with prostate cancer. IRE can be delivered using the NanoKnife system. To better understand the extent to which the technology can be utilised in the treatment of prostate cancer, the EMJ interviewed two leading figures in urology who have extensive experience with the procedure. These were Olivier Cussenot, Head of the Department of Urology, APHP-Sorbonne University, Tenon Hospital, Paris, France, and Phillip Stricker, Chair of the Department of Urology, St Vincent's Private Hospital, and Clinic and Emeritus Fellow, Garvan Institute of Medical Research, Sydney, Australia.

The article begins with an overview of the current treatment options for prostate cancer and the role of focal therapies, including the NanoKnife system in clinical practice. Research on the NanoKnife system was discussed, followed by clinical experience including patient selection, outcomes, and follow-up. Technical aspects were reviewed such as the skill sets required and the nature of the tissue after the procedure. Finally, the experts provided future perspectives on the use of the NanoKnife system for the management of patients with prostate cancer.

## INTRODUCTION

### Treatment Options for Localised Prostate Cancer

Localised prostate cancers are classified as at low, intermediate, and high risk of progression. Low risk cancers are usually candidates for active surveillance or superactive surveillance (which adds focal therapy to active surveillance). Intermediate risk cancers are considered for active surveillance, superactive surveillance, or curative treatments including radical prostatectomy or radiotherapy. Males without benign prostatic hyperplasia (BPH) criteria could also be treated with brachytherapy at low and intermediate stages. High risk cancers require prostatectomy or radiotherapy with androgen deprivation, or a combination of both.

### Role of Focal Therapy in the Treatment of Prostate Cancer

Focal therapy could be discussed in cases of localised prostate cancers with significant low or intermediate risk of progression, when MRI shows circumscribed lesions. Cussenot said: "Radical treatment is required in about 30–40% of patients under active surveillance because of the potential for tumour growth and/or patient anxiety. Focal therapy aims to reduce the use of radical therapies and its adverse effects."

### What Is Irreversible Electroporation?

IRE is a non-thermal tissue ablation modality based on the apoptotic effect of an electric field which changes the permeability of the exposed cells. Only targeted tissue is destroyed, while sparing critical structures including blood vessels, nerves, and ducts. "It ensures that the architecture of the tissue is respected," explained Cussenot, adding that "NanoKnife is a smart and emerging tool for focal therapy with IRE ablation." It does not rely on heat to achieve cell death, which allows treatment of peripheral or juxta-urethral lesions with maximum safety (including prostate cancer in the distal apex) in contrast to other focal ablation technologies. Moreover, IRE does not prevent iterative local treatment, in cases of asynchronous multifocality. A meta-analysis published this year demonstrated that cryoablation (CA), high-intensity focused ultrasound (HIFU), IRE, and vascular-targeted

photodynamic therapy (VTP) for prostate cancer patients have similar clinical outcomes.<sup>1</sup>

## RECENT STUDIES WITH THE NANOKNIFE SYSTEM

### Safety and Clinical Feasibility of the NanoKnife System as First-Line Treatment

Stricker described his first study on the NanoKnife system in 2014, which examined the safety and clinical feasibility of the technology for the focal treatment of prostate cancer.<sup>2</sup> A total of 34 patients with a mean age of 65 years and a median prostate-specific antigen (PSA) of 6.1 ng/mL were included. Nine (26%), 24 (71%), and one (3%) patients had low, intermediate, and high-risk disease, respectively. After a median follow-up of 6 months, 12 Grade 1 and 10 Grade 2 complications occurred, with no Grade  $\geq 3$  events. Regarding functional outcomes, 100% (24/24) of patients were continent, and potency was preserved in 95% (19/20) of males potent before treatment.

"We showed that the NanoKnife procedure is safe in the primary setting," said Stricker. "We had no major complications and quality of life was excellent. It was a much simpler treatment than radical prostatectomy and radiotherapy, with fewer side effects, done as a day procedure in almost every patient."

### Safety and Feasibility of the NanoKnife System after Previous Failed Radiation

A subsequent study investigated the feasibility and safety of the NanoKnife system as salvage treatment for localised recurrent prostate cancer after previous radiotherapy.<sup>3</sup> A total of 18 patients with median baseline PSA 8.6  $\mu\text{g/L}$  were followed-up for a median of 21 months. Rates of recurrences and side effects were low. The multiparametric MRI (mpMRI) was clear in 11/13 patients, and 8/10 patients were clear of any prostate cancer on follow-up biopsy. Pad-free continence and erections sufficient for intercourse were preserved in 8/11 patients and 2/6 patients at 6 months, respectively.

"The options of treatment after failed radiotherapy are incredibly limited," noted Stricker. "And whilst people do offer salvage surgery in that setting, the side effect profile is incredibly high, with up



to 50% of people being completely incontinent, a small incidence of rectal fistula and almost 100% impotence, with only a 50% cure rate. To find a therapy with a remarkably low side effect profile which could offer these patients a second chance of cure when radiotherapy has failed, which is not uncommon (20–30% of patients), was a real breakthrough.”

## The Importance of Follow-Up

Stricker then highlighted a study with up to 6 years’ follow-up. All 123 patients had an MRI at 6 months and a biopsy at 1 year to assess the control rate of focal ablation with the NanoKnife system as primary treatment.<sup>4</sup> The follow-up biopsy was clear of residual disease in 90.2–97.3% of patients. “The recurrence rate during the ensuing 5 years was 15%,” said Stricker. “These were very good results compared with the focal therapy literature. And I must emphasise that they were accurate because biopsy was a requirement during the follow-up. It suggests that NanoKnife is very successful in getting rid of the primary tumour, but there is some recurrence always in the outfield, so it does mandate regular long-term monitoring, usually with PSA and MRI.”

From a quality of life point of view, the incontinence rate was close to 0% and the impotence rate was initially around 10%, dropping to less than 5% after 1 year. Stricker commented: “This recovery of potency is unique to NanoKnife compared to cryotherapy and HIFU. IRE causes less damage to the erectile nerves because it preserves that type of collateral tissue as long as the cell nucleus is not inside the ablation zone. This study really put NanoKnife on the map as one of the options, alongside cryotherapy and HIFU, to treat focal lesions. There were no major complications, good oncological and functional outcomes, and it was performed as a day procedure in all cases.”

## The NanoKnife System Is a Treatment for Any Area of the Prostate

Stricker noted that, unlike other focal therapies, the NanoKnife system is a treatment which can be used in any area of the prostate. “With other technologies you have to be very careful at the apex because you can destroy the sphincter, which can lead to total incontinence, and you may need to have a safety margin at the apex

which often leaves some cancer behind,” he said. “But we showed that this is not the case with NanoKnife, which can be used around the urethra, in the front of the prostate, at the apex of the prostate, and posteriorly.”<sup>5</sup>

## Quality of Life with the NanoKnife System

“The quality-of-life outcomes with NanoKnife are one of the major reasons to choose the technology for suitable patients, while accepting the need for follow-up,” said Stricker. This was further demonstrated in a study evaluating the effect of robot-assisted radical prostatectomy (RARP) versus focal IRE with the NanoKnife system on patient-reported quality of life and early oncological control.<sup>6</sup> A total of 50 IRE patients were matched to 50 RARP patients by propensity score. IRE patients experienced more early oncological failure than RARP patients. But IRE was significantly superior to RARP in preserving pad-free continence and erections sufficient for intercourse up to 12 months after treatment.

## CLINICAL EXPERIENCE WITH IRREVERSIBLE ELECTROPORATION

### Patient Selection, Outcomes, and Follow-Up

#### Patient selection

For Cussenot, patients are candidates for focal ablation using IRE if they have localised prostate cancer, International Society of Urological Pathology (ISUP) Grade 1 or 2, and an index tumour diameter <15 mm.

Stricker noted that advances in imaging, in particular MRI and more recently prostate specific membrane antigen (PSMA)-positron emission tomography (PET) scans, and the technique of transperineal mapping biopsies and MRI/ultrasound fusion have allowed better prediction of suitability for focal therapy than was possible in the past.

“With really high-grade cancers, such as Gleason 8 to 10, most people still feel that a more aggressive approach is needed because the recurrence and metastatic rates are quite high,” he said. “The ideal candidates for IRE have a Gleason 7 tumour on an MRI or PSMA-PET scan

and pathological concordance confirmed with a transperineal template biopsy. In addition, the patient is keen to avoid the side effects of surgery, radiotherapy, or brachytherapy but very happy to be followed-up carefully."

When Stricker first started using IRE, his age cut-off was about 60 years, but he has since moved towards treating younger patients. "Having done almost 400 procedures now, I'm happy to perform IRE in patients 55 years and over and extremely select patients 50 years and over, with the understanding that they will be monitored for cancer for many, many years," he said. "We also have to acknowledge that we're not really sure whether they truly have a focal problem or whether that's just the presenting edge of a multifocal condition. The ability to confirm the unifocal nature of some tumours should improve as we find more accurate markers (e.g., epigenetic markers) showing that the cancer is truly focal and the rest of the prostate has no abnormalities (i.e., no field defect)."

### **Follow-up after irreversible electroporation**

Regarding follow-up after IRE, Cussenot uses PSA and MRI at 6 and 12 months; if either suggests recurrence, then a biopsy is performed.

Stricker advocates more aggressive follow-up in the first year, with PSA measurements every 3 months, an MRI at 6 months, and a biopsy at 12 months. "The biopsy at 12 months is not universally agreed by the focal therapy pundits because it's invasive. But MRI and PSA are only about 85% accurate, while 15% of recurrent cancers are found by the biopsy alone, so I personally think an aggressive initial assessment is needed. After you've got clearance at 1 year, you can follow-up with PSA and MRI, with a biopsy only if one of those becomes abnormal."

The biopsy at 12 months detects recurrences early and gives the patient an opportunity of early curative whole gland therapy or redo therapy with the NanoKnife system, noted Stricker. "The chance of needing salvage surgery after one or two NanoKnife procedures is only about 5%. We have achieved over 90% negative margin rates with salvage surgery in those cases and I think that is because of our intensive follow-up."

### **Quality of life with focal therapy versus radical prostatectomy**

Cussenot noted that "potentially 70% of localised prostate cancer treated by radical therapies exposes patients to unjustified urinary or sexual side effects. Erectile function and urinary incontinence are preserved with IRE; however, the volume of sperm ejaculation is usually reduced."

Stricker highlighted the findings of a pair-matched comparison of focal IRE versus RARP.<sup>6</sup> "This study showed very clearly that general health, potency, and continence were markedly better with focal therapy compared to even the best nerve-sparing surgery," he said. "The trade-off is that, after surgery in an earlier cancer, there's no need for invasive follow-up. There's always a possibility of a recurrence after focal therapy, and follow-up is essential."

### **Distinguishing features of irreversible electroporation compared with other focal therapies**

Stricker said all focal therapies have similar procedural and recovery times. "The difference is the chance that you get rid of all the cancer," he said. "One of the weaknesses of HIFU is that, because it's a sound wave, it's highly influenced by blood vessels and calcification in the prostate and the position in the prostate which could decrease the chance of clearing the cancer. This is particularly so in the front of the prostate."

The disadvantage with cryotherapy is the need to ensure protection of the urethra and the neurovascular bundles. "That means you protect some of the tissue around the urethra and if there's cancer there, then of course it will recur," he said. "Whereas with NanoKnife therapy you can go right up to the edge of the urethra. And whilst you'll get some swelling, you won't end up getting necrosis of the urethra or a stricture; it will recover. So that's a distinguishing feature."

When comparing brachytherapy and IRE, Stricker said the one big disadvantage of radiation therapy of any type is that it cannot be repeated. "If the cancer recurred in another part of the prostate after focal brachytherapy, you couldn't do another brachytherapy treatment. Whereas NanoKnife therapy is repeatable; I will redo NanoKnife once and if the cancer comes back another time, I think it's time for whole gland treatment."

Laser ablation can be performed within the MRI machine, which is an advantage in terms of accuracy, but like HIFU and cryotherapy it is thermal-based. “That heat or freezing is not selective in its effect on tissues,” said Stricker. “Whereas the NanoKnife is selective, and so it tends to preserve adjacent structures like nerves, and particularly the erectile nerves, and it tends to preserve the blood vessels within the tissue, which the other focal therapies do not do. If you get a nerve inside a cryofield, laser field, or HIFU field, the patient will be impotent. Whereas if you get an erectile nerve in the IRE ablation zone, the patient might become impotent, although it is not inevitable.”

Another focal therapy is TOOKAD, which uses an injected chemical that is activated by light. Stricker said: “It is not a thermal based treatment, but it’s cumbersome; the patient becomes photosensitive and must be wrapped in foil for a couple of hours to protect their skin.” A prospective randomised Phase III study compared VTP with padeliporfin (TOOKAD) versus active surveillance in 413 patients with low-risk prostate cancer.<sup>7</sup> After an average follow-up of 2 years, 6% of patients undergoing VTP required radiotherapy or surgery, compared to 29% of patients who received active surveillance ( $p < 0.0001$ ). But Stricker commented: “The trial’s weakness was that many of the patients didn’t need treatment (Grade Group 1). The advantage of NanoKnife compared to TOOKAD is that we’ve shown that we can treat significant cancers (Grade Group 2).”

### **Irreversible electroporation as a primary focal treatment for prostate cancer**

Stricker estimated that about 15% of patients might be suitable for IRE therapy. “The old paradigm was either active surveillance or whole gland therapy with surgery or radiotherapy. I think the new paradigm is active surveillance for low grade tumours, focal therapy for some intermediate grade tumours, and whole gland therapy for the remainder. Focal therapy is filling a niche for patients who aren’t prepared to accept the side effect profile of whole gland therapy when they’ve got a tumour which, on consensus opinion, would suggest that focal therapy might be appropriate.”

Patient views regarding quality of life, invasiveness of treatment, and need for follow-up play a big role in this disease, noted Stricker. “Prostate cancer has a long natural history and slow time to recurrence, while the potential side effects of whole gland therapy, such as incontinence, impotence, and rectal damage, are quite devastating, so that type of discussion has to be had with patients.”

### **Questions that still need to be answered in future studies**

A randomised study comparing surgery and focal ablation would be definitive, but is unlikely to be conducted, said Stricker. Another study that would be worthwhile would be to compare focal therapy versus monitoring only in patients with intermediate grade cancer of the prostate, ending with radical prostatectomy if appropriate. “At that point you would analyse whether the radical prostatectomy was curative or not. In other words, does focal therapy add anything beyond active surveillance in these patients?” An ongoing randomised trial comparing hemiablation with HIFU versus radical prostatectomy will provide important answers on the role of focal therapy compared with whole gland therapy. Regarding patient selection, studies are needed to define better markers of a truly unifocal tumour versus more widespread tumours.

Cussenot would like to see long-term follow-up (over 10 years) data quantifying the quality-adjusted life-year benefit of focal therapies including IRE.

### **The Irreversible Electroporation Procedure**

#### **Duration of the procedure**

Cussenot and Stricker agreed that the NanoKnife prostate treatment typically takes 1 hour, from the time patients are sedated until they regain consciousness. Within that timeframe, the passage of energy takes 20–30 minutes. Skills are required in transperineal biopsy, transrectal ultrasound, and interpretation of imaging, including MRI/ultrasound fusion imaging. “Most urologists worldwide now have those skill sets,” said Stricker. “The procedure takes 2–3 hours initially and the learning curve is around 10–20 patients unless you pick tricky cases, which I don’t recommend in the first 50 cases.”



## IRE as a salvage technique

“IRE can be used as a salvage technique for intraprostatic recurrence, after histological confirmation of the recurrence,” said Cussenot. Selection criteria should be localised recurrence and preferably PSA <4, noted Stricker. “The lower the PSA, the greater the success in eradicating the cancer, so monitoring after radiotherapy, radical prostatectomy, or NanoKnife therapy is equally important to preserve the opportunity for a second cure.”

## Nature of the tissue following irreversible electroporation and the impact on subsequent treatments

One of the distinguishing features of the NanoKnife procedure is that it is non-thermal, and this means that subsequent therapies remain a possibility. “Other treatments including radical prostatectomy could be performed after IRE,” said Cussenot. “The absence of a thermal effect drastically reduces retractile fibrosis, which is observed after HIFU or cryotherapy.”

“The results of salvage radical prostatectomy after IRE are excellent as long as it is performed early,” added Stricker. “As soon as you know that there’s a recurrence and it’s not suitable for redo NanoKnife therapy, you should do early radical prostatectomy. Because you only ablate a small area of the prostate with NanoKnife and the remaining tissue is unaffected, the oncological and functional outcomes of salvage surgery are markedly better than after more extensive treatments such as radiotherapy, brachytherapy, and HIFU.”

## FUTURE PERSPECTIVES

### Vision for Incorporating Irreversible Electroporation into the Management of Patients with Prostate Cancer

“IRE could be discussed currently as an opportunity to adapt the risk-benefit ratio in the management of low and intermediate risk localised prostate cancers,” commented Cussenot.

Stricker sees the technology becoming commonplace. “I think that IRE will form part of the armamentarium of many urologists who offer all the treatment options. My vision is that it will

find a middle ground between active surveillance where patients don’t need treatment and whole gland therapy so that IRE is performed in people with localised Gleason 7 tumours.”

### What Role Could Irreversible Electroporation Play in Combination with Immunotherapy?

“Although immunological responses are enhanced after focal therapies such as VTP or IRE, it’s too early to conclude that combination IRE and immunotherapy could be used in clinical practice,” said Cussenot, adding that “IRE and immunologic management must also be explored for advanced disease.”

Stricker is embarking on two studies. One will investigate whether the NanoKnife system triggers an immune stimulatory effect. The second will examine whether immunotherapy combined with the NanoKnife system boosts the systemic effects of treatment. “It makes sense that if you can release tumour specific antigens with the NanoKnife and then give the appropriate stimulation of immunity, you might get some regression of secondary tumours. But at the moment it is hypothesis generating and there are no data.”

The immune studies are part of Stricker’s larger programme of research on the NanoKnife system, which is also evaluating the technology as salvage therapy. Another line of investigation is the selection of patients for focal therapy using epigenetic markers and imaging with MRI and PSMA-PET scanning. The value of these imaging modalities in the follow-up of patients after IRE is also being explored.

### Closing Remarks

Stricker said that international research on IRE, such as an Australian multicentre study and a U.S. Food and Drug Administration (FDA)-approved clinical trial, plus ongoing training in urology centres, are important steps towards adoption. “I think that will all go towards making this an established treatment that is eventually reimbursed and included in guidelines. While there are long-term data and experience with other focal therapies including HIFU, cryotherapy, and laser therapy, when urologists realise the simplicity of IRE and the potential advantages,

I think that it will organically replace the other technologies with time. Because IRE is not thermal based, it preserves collateral tissues, which is different to the other therapies. As we get better with selection, the results will speak for themselves.”

## Biographies

### Olivier Cussenot

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### Phillip Stricker

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# Considerations for Choosing Treatment Options for Benign Prostatic Hyperplasia

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<b>Disclosures:</b>	Barber has been a proctor/speaker for Teleflex, Olympus Keymed, Boston Scientific, Procept Bio-Robotics, and Cambridge Medical Records (CMR). Ng has declared no conflicts of interest.
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## Interview Summary

Benign prostatic hyperplasia (BPH) is a chronic age-related condition associated with lower urinary tract symptoms (LUTS). Although conservative management and pharmacological treatment is the first choice for the management of LUTS/BPH, a very low adherence to, and satisfaction with, pharmacological management regimens in patients with LUTS/BPH suggests that BPH might frequently be inadequately managed by pharmacological interventions. Both invasive and minimally invasive surgical therapies (MIST) are currently available for the surgical management of BPH not responding to conservative or pharmacological management. The development of novel surgical interventions for the management of BPH is evolving rapidly, and a plethora of different invasive and MIST interventions are now available to treat BPH.

MIST procedures such as the prostatic urethral lift (PUL; utilising the UroLift® System, Teleflex, Pleasanton, California, USA) and Rezum® (Boston Scientific, Marlborough, Massachusetts, USA), have reported low rates of sexual dysfunction relative to transurethral resection of the prostate (TURP), the current gold standard surgical therapy for BPH. The L.I.F.T. pivotal trial for PUL reported no instances of new, sustained erectile or ejaculatory dysfunction, whereas TURP is associated with both erectile dysfunction (0–3% of cases) and ejaculatory dysfunction (5–15% of cases). PUL is currently the only leading MIST that offers rapid, significant, and durable symptom relief of LUTS without causing new, sustained erectile dysfunction or ejaculatory dysfunction.

Recent guidelines issued by the European Association of Urology (EAU), the American Urological Association (AUA), and the UK's National Institute for Health and Care Excellence (NICE) recommend PUL for the treatment of BPH with prostate volume 30–80 mL (NICE, EAU)/<80g (AUA). The procedure is also recommended for men who wish to preserve male sexual function. Additionally, EAU guidelines state that PUL is the only surgical intervention recommended for males who cannot have surgery under anaesthesia.

In conclusion, the MIST PUL is endorsed by EAU, AUA, UK NICE, and guidelines for patients with BPH with notable recommendation for males who wish to preserve sexual function or who are not able to have surgery under anaesthesia.



## INTRODUCTION

BPH is a chronic age-related condition associated with LUTS such as urinary frequency, urgency, and nocturia. BPH affects one-half of all males aged 50–60 years and is estimated to affect 90% of males aged 80 years or above.<sup>1</sup> BPH progression may lead to increasingly obstructed voiding, which may significantly impact quality of life (QoL) through sleep loss, reduced productivity, impaired sex life, social isolation, and depression.<sup>2</sup>

## MANAGEMENT OF BENIGN PROSTATIC HYPERPLASIA

Management options for BPH include conservative management, pharmacological treatment, and surgical interventions.<sup>3</sup>

### Conservative Management

Conservative management, such as watchful waiting, behavioural therapy, and dietary modifications, may be suitable for patients with LUTS that are not troubled enough by their symptoms to require pharmacological or surgical intervention.<sup>3,4</sup>

### Pharmacological Treatment

Pharmacological management, either as mono- or combination therapy, primarily involves the use of drugs that either relax the smooth musculature (e.g.,  $\alpha$ 1-adrenoceptor antagonists, muscarinic receptor antagonists and  $\beta$ 3 agonists, phosphodiesterase 5 inhibitors) or exert anti-androgen effects to reduce prostate cell proliferation (e.g., 5 $\alpha$ -reductase inhibitors).<sup>3</sup>

Monotherapy options include  $\alpha$ 1-adrenoceptor antagonists, which are usually considered the first-line pharmacological treatment due to their rapid onset of action, good efficacy, and low rate and severity of adverse events. However, they may not prevent occurrence of urinary retention or the potential future need for surgery.<sup>3</sup> 5 $\alpha$ -reductase inhibitors may reduce the risk of acute urinary retention and need for surgery but, because of their slow onset of action, they are not suitable for short-term use.<sup>3</sup> Muscarinic receptor antagonists and  $\beta$ 3 agonists may be considered in males with moderate-to-severe LUTS who mainly have bladder storage

symptoms.<sup>3</sup> Phosphodiesterase 5 inhibitors may be considered in those with moderate-to-severe LUTS with or without erectile dysfunction.<sup>3</sup>

Combination therapy in the form of an  $\alpha$ 1-blocker plus a 5 $\alpha$ -reductase inhibitor may be considered in individuals with moderate-to-severe LUTS and an increased risk of disease progression. An  $\alpha$ 1-blocker plus a muscarinic receptor antagonist combination therapy may be considered for patients with moderate-to-severe LUTS if relief of storage symptoms has been insufficient with monotherapy with either drug.<sup>3</sup>

A very low adherence to, and satisfaction with, pharmacological management regimens in patients with LUTS/BPH suggests that BPH might frequently be inadequately managed by pharmacological interventions.<sup>5</sup> In fact, it has been reported that 25–70% of patients managed pharmacologically for BPH are either non-compliant or discontinue pharmacological management altogether because of lack of effectiveness or bothersome side effects such as erectile dysfunction, ejaculatory dysfunction, weakness, fatigue, and dizziness.<sup>6,7</sup>

### Surgical Treatment

Monopolar TURP is considered to be the gold standard reference technique for the surgical management of LUTS/BPH; however, many alternative techniques have recently been developed. Surgical approaches for LUTS/BPH can be broadly classified into five main categories: prostate resection, prostate enucleation, vapourisation, alternative ablative techniques, and non-ablative techniques.<sup>3</sup>

Surgical procedures for BPH/LUTS are also classified based on their level of invasiveness into invasive surgical therapies (e.g., TURP, simple prostatectomy) or MIST. MIST interventions may be further classified into either thermo-ablative or mechanical.<sup>8</sup>

MIST procedures include transurethral incision of the prostate (TUIP); thermo-ablative strategies such as transurethral microwave therapy (TUMT), transurethral electrovapourisation of the prostate (TUVP), or transurethral needle ablation; and mechanical strategies such as PUL (utilising the UroLift System) and intraprostatic stents.

Emerging MIST interventions include prostatic artery embolisation; transurethral water vapour therapy (Rezumi); other forms of interstitial ablation using transurethral and transperineally delivered laser energy; mechanical therapies such as the temporary implantable nitinol device (iTIND; Olympus Medical Systems, Tokyo, Japan), ClearRing™ (ProArc Medical, Pardes Hanna-Karkur, Israel), ZenFlow Spring® (ZenFlow, San Francisco, California, USA), Butterfly (Butterfly Medical Ltd., Yokneam, Israel), and high-frequency ultrasound (histotripsy).<sup>8-12</sup> A summary of key characteristics of different MIST procedures is presented in **Table 1**.<sup>8</sup>

## CONSIDERATIONS FOR THE SELECTION OF SUITABLE MANAGEMENT SOLUTIONS

Factors influencing the choice of a BPH management solution for an individual patient would include patient evaluation; predicted treatment outcomes achievable by available treatment options; patient preferences; expectations from the chosen treatment option in terms of speed of onset, efficacy, side effects, and QoL; and disease progression.<sup>3</sup>

Behavioural modification, with or without pharmacological intervention, is usually the

**Table 1: Characteristics of different minimally invasive surgical therapy procedures.<sup>8</sup>**

Type of MIST	Prostate size requirements	Anaesthetic requirements	Relative contraindications
Intraprostatic injections	N/A	Local anaesthesia and sedation	Urethral stricture; neurogenic bladder
Intraprostatic stents	<100 mL	Local or regional anaesthesia	Penile or artificial urinary sphincters; acute urinary tract infection
Prostatic artery embolisation	>30 mL	Local anaesthesia and sedation	Neurogenic bladder; urethral stricture; coagulation disorders; presence of prostate cancer
Transurethral vapourisation of prostate	N/A	Local anaesthesia and sedation	History of prostate or bladder cancer; history of bladder outlet surgery; neurogenic bladder
Transurethral incision of prostate	<30 mL	Local ± sedation ± regional anaesthesia	Large median lobe; prostate size <30 mL
Transurethral microwave therapy	<100 mL	Local ± sedation	Urethral stricture; history of prostate or bladder cancer; neurogenic bladder;
Transurethral needle ablation	N/A	Sedation ± regional anaesthesia	Urethral strictures; prostate cancer; neurogenic bladder
Prostatic urethral lift (UroLift®, Teleflex, Pleasanton, California, USA)	<100 mL	Local anaesthesia and sedation	Renal insufficiency; previous prostate surgery; acute urinary tract infection; cystolithiasis

MIST: minimally invasive surgical therapy; N/A: not applicable.

first choice of therapy.<sup>3</sup> Surgical intervention is most often considered for patients experiencing bladder stones or diverticula; dilatation of the upper urinary tract due to BPO, with or without renal insufficiency; inadequate relief from LUTS or post-void residual urine by means of conservative or pharmacological management; overflow incontinence; recurrent or refractory urinary retention; recurrent urinary tract infections; and treatment-resistant macroscopic haematuria due to BPH.<sup>3</sup> Multiple factors, including local surgical expertise, the ability to have anaesthesia, patient preferences, comorbidities, and prostate size, affect the types of surgical interventions that are available for individual patients.<sup>3</sup> An individualised, shared decision-making approach is therefore required to determine the ideal treatment option for each patient.<sup>13</sup>

### MINIMISING SEXUAL DYSFUNCTION WITH BENIGN PROSTATIC HYPERPLASIA SURGICAL MANAGEMENT

Sexual activity is an important aspect of many males' QoL<sup>14</sup> and maintenance of sexual function is therefore viewed as a significant attribute by both past and future BPH surgery patients.<sup>15</sup> The importance of considering the impact of BPH interventions on male sexual function has therefore resulted in the AUA and EAU now recommending patient sexual health counselling before and after BPH interventions.<sup>3,16</sup>

Some surgical procedures available for the treatment of BPH are associated with a substantial risk of ejaculatory and erectile dysfunction; TURP is associated with both erectile dysfunction (0–3% of cases) and ejaculatory dysfunction (5–15% of cases).<sup>17</sup> However, several MIST procedures have demonstrated encouraging preservation of post-operative sexual function while also providing significant lower urinary tract symptom relief without compromising efficacy and safety.<sup>13</sup>

Studies on PUL, Rezum, and Aquablation® (PROCEPT BioRobotics, Redwood City, California, USA) have reported lower rates of sexual dysfunction relative to TURP, the current gold standard therapy for BPH.<sup>13</sup> In non-head-to-

head, indirect comparisons, PUL has been found to be superior to pharmacological therapy in preserving erectile and ejaculatory function and sexual satisfaction in males with BPH.<sup>18</sup> These findings are further supported by an indirect comparison using a network meta-analysis model that found that treatment with PUL results in better sexual function domain scores compared to TURP, but not compared to Aquablation.<sup>19</sup>

Furthermore, controlled studies have reported that both PUL and Rezum preserve erectile function, although *de novo* instances of ejaculatory dysfunction have been reported with Rezum.<sup>20</sup> In contrast, the L.I.F.T. pivotal trial for PUL reported no instances of new, sustained erectile or ejaculatory dysfunction,<sup>17</sup> and the PUL procedure is currently the only leading MIST that offers rapid, significant, and durable symptom relief of LUTS without causing new, sustained erectile dysfunction or ejaculatory dysfunction.<sup>17,21–24</sup>

### PROSTATIC URETHRAL LIFT IS RECOMMENDED BY CURRENT GUIDELINES FOR SURGICAL MANAGEMENT OF BENIGN PROSTATIC HYPERPLASIA

The EAU, UK NICE, and AUA have all issued guidelines on the surgical management of BPH by both invasive and MIST procedures and endorse the use of PUL of the management of LUTS due to BPH.<sup>3,16,25</sup>

### PUL is the Only Current MIST Strongly Recommended by EAU Guidelines and the Only MIST Mentioned in the EAU Treatment Algorithm for Bothersome LUTS

The EAU guidelines provide algorithms for the conservative, pharmacological, and surgical management of BPH. EAU guidelines also record the quality and the level of evidence available, and derives from that different levels of recommendations of use within described parameters, such as the size of the prostate.<sup>3</sup>

The EAU guidelines state that factors influencing the choice of treatment include findings from the patient evaluation; the ability of the treatment to change the findings; patient preferences;

expectations regarding speed of onset, efficacy, side effects, and QoL; and disease progression. Behavioural modifications, with or without pharmacological treatments, should be considered as the first choice of therapy.<sup>3</sup>

Surgical intervention is usually required in cases of recurrent or refractory urinary retention, overflow incontinence, recurrent urinary tract infections, bladder stones or diverticula, treatment-resistant macroscopic haematuria due to BPH, or dilatation of the upper urinary tract due to benign prostatic obstruction, with or without renal insufficiency (i.e., absolute operation indications, need for surgery). Additionally, BPH surgery is usually needed when patients have not obtained adequate relief from LUTS or post-void residual urine using conservative or pharmacological treatments (i.e., relative operation indications).<sup>3</sup>

Prostate size, comorbidities, ability to have anaesthesia, patient preferences, willingness to accept surgery-associated specific side-effects, availability of the surgical armamentarium, and the experience of the surgeon with these surgical techniques are key factors determining the choice of surgical interventions available for the patient.<sup>3</sup>

EAU presents a surgical treatment algorithm for bothersome LUTS stratified by the patient's ability to have anaesthesia, the patient's cardiovascular risk, and the size of the prostate. Current standard/first choice surgical treatment options include TUIP (prostate volume <30 mL); TURP (prostate volume 30–80 mL); open prostatectomy, HoLEP, bipolar enucleation (prostate volume >80 mL); and laser vapourisation.<sup>3</sup>

PUL is the only MIST to be recommended with a 'strong' strength rating for the treatment of LUTS in the EAU guidelines. PUL is the only MIST mentioned in EAU's treatment algorithm for bothersome LUTS, and is recommended for all patients, regardless of level of risk, for prostate volumes between 30 and 80 mL. The EAU algorithm also positions PUL as the only surgical procedure recommended for patients not able to have surgery under anaesthesia (Figure 1).<sup>3</sup>

### **NICE Recommends PUL for the Management of LUTS Due To BPH**

In May 2021, UK's NICE published guidelines on PUL for the management of LUTS due to

BPH.<sup>25</sup> NICE recommends PUL for treating LUTS due to BPH, as PUL relieves lower urinary tract symptoms, avoids risk to sexual function, and improves QoL. NICE guidelines also highlight that PUL constitutes a minimally invasive procedure, and that PUL should be considered as an alternative to TURP and HoLEP. The NICE guidance also states that the PUL procedure is suitable as a day-case or outpatient procedure for males aged 50 years and older who have a prostate volume between 30 and 80 mL.

### **AUA Guidelines Recommend PUL for BPH with Prostate Volume <80 g**

The AUA guideline amendment 2019 on the surgical management of LUTS attributed to BPH states that PUL may be offered as an option for patients with LUTS caused by BPH, provided that the prostate size is less than 80 g, and that there is a verified absence of an obstructive middle lobe.<sup>16</sup> The AUA guidelines also highlight that PUL or water vapour thermal therapy may be offered to eligible patients who desire preservation of erectile and ejaculatory function (Figure 2).<sup>16</sup>

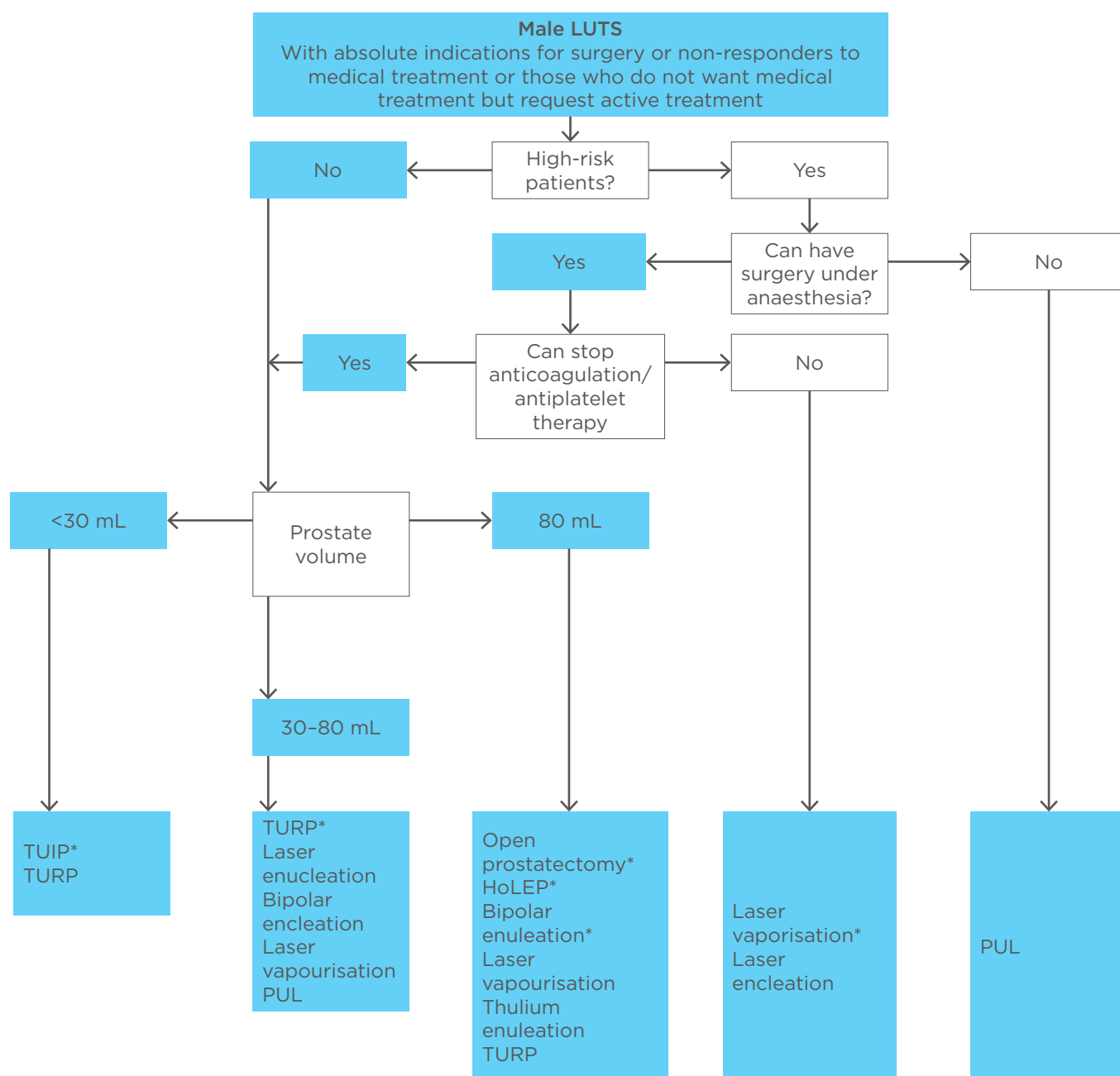
### **PROSTATIC URETHRAL LIFT GUIDELINE RECOMMENDATIONS ARE SUPPORTED BY A STRONG CLINICAL EVIDENCE BASE**

With more than 28 peer-reviewed clinical publications, complemented by real-world evidence studies, PUL is one of the most well-characterised MIST interventions for LUTS/BPH. As a complement to clinical trial data on PUL spanning up to 5 years of follow-up,<sup>17</sup> a real world retrospective study of PUL including 3,226 patients across 22 international sites has been conducted.<sup>26</sup> Analyses to date suggest that the real world outcomes are largely comparable with the outcomes from previously published PUL clinical studies.<sup>18,24,26,27</sup>

### **CONCLUSIONS**

The development of novel surgical interventions for the management of BPH is evolving rapidly, and a plethora of different invasive and MIST interventions are now available to treat BPH. Preservation of sexual function is viewed as an important patient consideration when selecting treatment options for BPH, and interventions





**Figure 1: EAU algorithm for the treatment of bothersome lower urinary tract symptoms refractory to conservative/ pharmacological treatment or in cases of absolute operation indications.<sup>3</sup>**

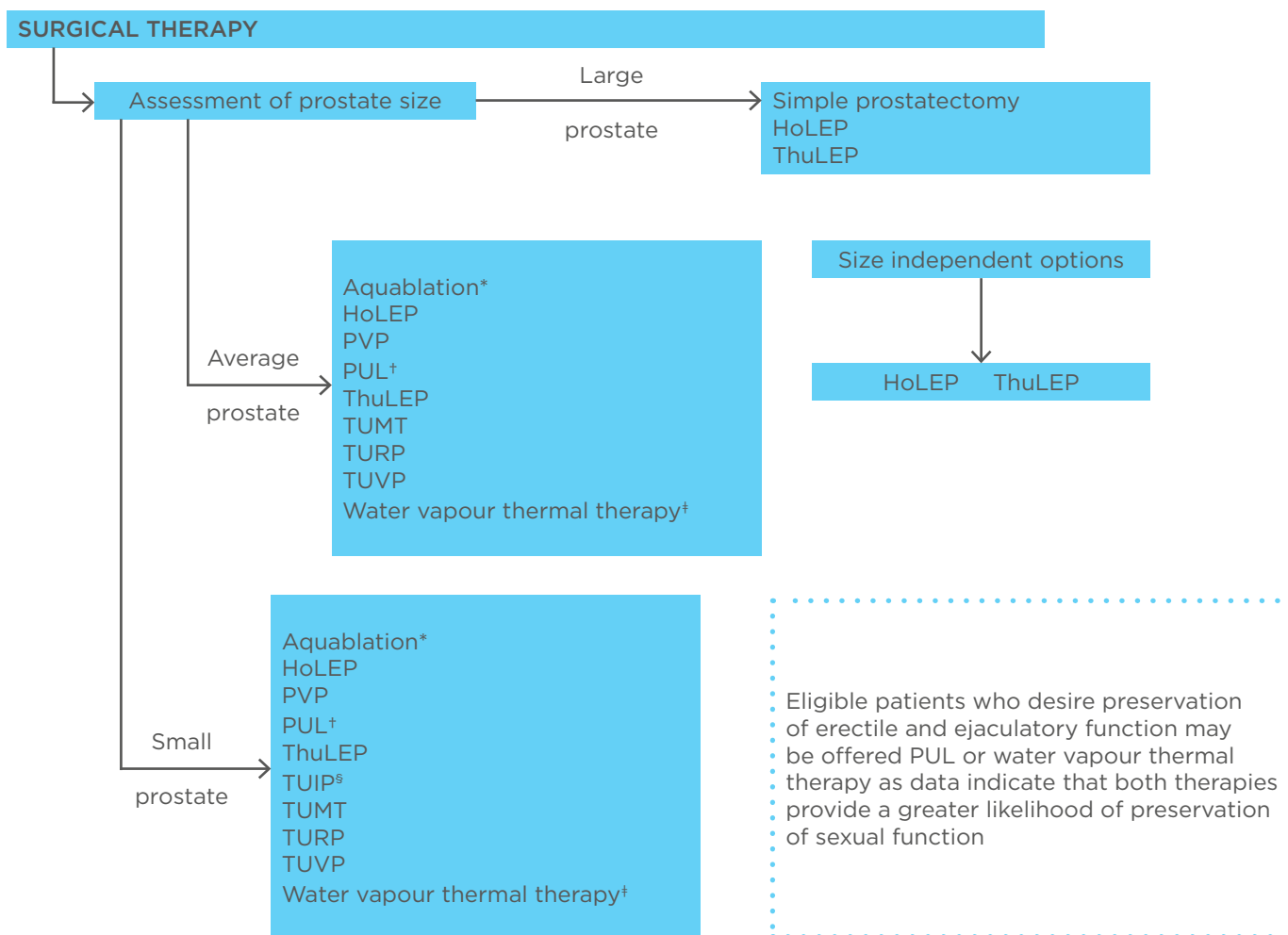
\*Current standard/first choice. Alternative treatments are presented in alphabetical order.

Laser vapourisation includes GreenLight™ (Boston Scientific, Marlborough, Massachusetts, USA), thulium, and diode laser vaporisation. Laser enucleation includes holmium and thulium laser enucleation.

EAU: European Association of Urology; HoLEP: Holmium laser enucleation; LUTS: lower urinary tract symptoms; PUL: prostatic urethral lift; TUIP: transurethral incision of the prostate; TURP: transurethral resection of the prostate.

such as PUL, Rezum, and Aquablation have reported lower rates of sexual dysfunction relative to TURP, the current gold standard surgical intervention for BPH. With more than 28 peer-reviewed clinical publications, complemented by real world evidence, PUL

is one of the most well-characterised MIST interventions for LUTS/BPH, and PUL is currently the only leading MIST that offers rapid, significant, and durable symptom relief of LUTS due to BPH without causing new, sustained erectile dysfunction or ejaculatory dysfunction.



**Figure 2: AUA algorithm for the surgical management of lower urinary tract symptoms attributed to benign prostatic hyperplasia.<sup>16</sup>**

\*Eligibility for an Aquablation® (PROCEPT BioRobotics, Redwood City, California, USA) procedure is dependent upon prostate volume >30 and <80 g.

†Eligibility for a PUL procedure is dependent upon absence of obstructing midline prostate tissue and prostate volume <80 g.

‡Eligibility for a water vapour thermal therapy procedure is dependent upon prostate volume <80 g.

§Eligibility for a TUIP procedure is dependent upon prostate volume <30 g.

AUA: American Urological Association; BPH: benign prostatic hyperplasia; HoLEP: holmium laser enucleation of the prostate; LUTS: lower urinary tract symptoms; PUL: prostatic urethral lift; PVP: photoselective vapourisation of the prostate; ThuLEP: thulium laser enucleation of the prostate; TUIP: transurethral incision of the prostate; TUMT: transurethral microwave therapy; TURP: transurethral resection of the prostate; TUVF: transurethral electrovaporisation of the prostate.

PUL is the only MIST with a 'strong' strength rating for the treatment of LUTS in the EAU guidelines, and is the only MIST mentioned in the EAU algorithm for bothersome LUTS. EAU guidelines endorse PUL for the treatment of BPH with prostate volumes between 30 and 80 mL and highlights that PUL is the only surgical

intervention recommended for patients not able to have surgery under anaesthesia. Due to its minimally invasive nature and documented preservation of male sexual function, PUL is also recommended by UK NICE and AUA guidelines for BPH with prostate volume not exceeding 80 mL/80 g.

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# Robotic Surgery and Its Application in Urology: A Journey Through Time

EDITOR'S  
PICK

My chosen article for the Editor's Pick in this issue is 'Robotic Surgery and Its Application in Urology: A Journey Through Time' by Zaman et al. Robotic surgery is increasingly being performed worldwide, particularly in the management of oncological cases, and has decreased the learning curve compared to laparoscopy. It has various other advantages including decreased estimated blood loss, complications, duration of hospital stay, and improved functional outcomes for certain subjects. The future generation of young surgeons are attracted to the robotic surgery, particularly with new robotic platforms that will soon be on the market.

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## Abstract

**Objectives:** To evaluate an overview of the past, present, and future of robotic surgery. To provide insight and focus on the current status of the field of robotic systems for urological surgery with outcomes and discuss future perspectives in terms of other operative techniques and new robotic platforms.

**Evidence acquisition:** The authors undertook a non-systematic literature review using PubMed, Medline, and Google search. They used the search terms "robotic uro-surgery", "laparoscopic", "minimally invasive surgery", "future of robotics", "global robotic market growth", "geographical distribution", and "cost-effectiveness".

**Evidence synthesis:** Robotic surgery has embraced and extended almost all aspects of uro-surgical fields since its introduction three decades ago. There are definite advantages of robots to the surgeons and patients. It has become new standard of care for many surgical procedures. Innovation and technological advances are continuing and new with more precise robots are emerging. The major downside is cost. Despite the high cost, robot market is growing.

**Conclusion:** Over the past decade, minimally invasive approaches have virtually revolutionised surgery and robotic surgery has accelerated these changes. Without doubt, robotic urologic surgery is here to stay and will expand further in all surgical disciplines. Utilisation of robotics should be coupled with a reduction in costs to healthcare systems, and improved clinical outcomes for the general population rather than a privileged few. Therefore, making this expensive technology more affordable must be part of the equation.

## INTRODUCTION

Urology has long been recognised as a specialty that embraces technologic advances. From the earliest cystoscopes and resectoscopes to flexible ureteroscopes and laparoscopy, urologists have always been at the forefront in adopting and applying surgical technology. Hence, use of surgical robots to date has been dominated by urologists. Following the success of robot-assisted laparoscopic prostatectomy in the 1990s, robotic surgery has expanded into other domains of urological procedures worldwide. However, despite its acceptance and advantages, cost reductions are still needed.

This article explores the evolution of robotic surgery in urology over a timeline spanning the pre- and post-millennium periods. The authors also discuss potential future aspects in terms of technology, market expansion, cost, and geographical distribution.

## EVIDENCE ACQUISITION

A non-systematic literature review was performed using PubMed/Medline and Google. The authors used the search terms “robotic”, “laparoscopic”, “minimally invasive uro-surgery”, “future of robotics”, “global robotic market growth”, “geographical distribution”, and “cost-effectiveness”.

## EVIDENCE SYNTHESIS

### Evolution of Robots and Robotic Surgery in the Pre-millennium Era (1950–2000)

The concept of robotic intervention in medicine is not new. The Industrial Revolution of the late 18<sup>th</sup> century became the instrumental phase in robotic advancement because it led to the development of key factors, including complex

mechanics and electricity. In 1950, telepresence robotic arms were developed, which were direct precursors of today's surgical robots. They were initially used in hazardous environments, such as the bottom of the ocean or in space. Further rapid advances occurred in the 1980s, with development of technologies such as microelectronics, computing, digital imaging, video electronics, and display technology. The vision of a remote surgery programme targeted towards battlefield triage, funded by the USA Defense Advanced Research Projects Agency (DARPA), was the basis for the development of surgical robots.

The very first use of a surgical robot was by Kwoh et al.,<sup>1</sup> who used the Programme Universal Machine for Assembly (PUMA) 560 robotic system to perform neurosurgical biopsies. Subsequently, Davies et al.<sup>2</sup> performed a transurethral resection of the prostate by PROBOT, which was designed by using a rotating blade to complete prostatic resection.<sup>3</sup> Despite initial success, the PROBOT failed to achieve widespread acceptance. Later, ROBODOC was designed to improve the precision of hip replacement surgery<sup>4</sup> and then a robotic-assisted percutaneous access to the kidney device was developed to facilitate stone surgery<sup>5,6</sup> (Table 1).

However, none of the above systems were designed for laparoscopic procedures, which first derived from a collaboration between the National Aeronautics and Space Administration's (NASA's) Ames Research Center (Mountain View, California, USA) and researchers from SRI International (formerly Stanford Research Institute; Menlo Park, California, USA). To reduce the mortality and morbidity of service personnel in conflict zones, the USA military recognised the concept of linking surgeons (distance from battlefield) to patients (on the battlefield). Computer Motion, Inc., (Santa Barbara, California, USA) developed the Automated Endoscopic System for Optimal Positioning (AESOP) robotic

**Table 1: Surgical robots in the pre-millennium era (non-laparoscopic and laparoscopic-assisted), post-millennium era, and current advanced versions.**

<b>Surgical robot (non-laparoscopic) in pre-millennium era</b>		
Arthrobot (the world's first surgical robot)	For orthopaedic procedures	Canada (1983)
PUMA 560 robotic system	Accurate and precise neurosurgical biopsy	Kwoh et al. (1988)
PROBOT (Integrated Surgical Supplies Ltd. Mesa, Arizona, USA)	Transurethral resection of the prostate (did not gain clinical appeal); first robot in urology	Imperial College London, UK (1988)
ROBODOC (first active system)	Precise hip replacement surgery	FDA approval (1988), first active system
Robotic PAKY-RCM	For percutaneous access of kidney	1998
<b>Surgical robot (laparoscopic-assisted) in pre-millennium era</b>		
AESOP	Robotic arm to assist laparoscopy	Computer Motion (1994)
ZEUS robotic system	Three robot arms with surgical control centre, FDA-approved	Computer Motion (1998)
da Vinci system	3D vision, EndoWrist technology, Intuitive Motion technology, FDA-approved	Intuitive Surgical, Inc. (2000)
<b>da Vinci surgical systems (2000–2010): post-millennium</b>		
Standard da Vinci (retired in 2019)	First generation: surgeon console, two robotic arms and one camera holder, robot cart	FDA-approved 2000
First upgrade of da Vinci	Three operating arms, one camera holder, identical to initial system	FDA-approved 2003
da Vinci S	HD vision, TilePro, multi-image display features	FDA-approved 2006
da Vinci Si	Better handling, increased range of motion of arms (allowing bigger surgical field), HD system, dual console	FDA-approved 2009
<b>Current versions of da Vinci robots (2010–2020)</b>		
da Vinci Xi	Articulating instrument, sharper 3D HD, arms are smaller and thinner, dual console, single-port option	Released 2014
Fourth generation da Vinci X	Uses voice and laser guidance to set up, lightweight, integrated endoscopy, simplified drape design	Released 2017
da Vinci SP surgical system	Camera and instruments emerge through the same port and triangulate to avoid collisions at surgical field, three multi-joint wristed instruments, first fully wristed da Vinci system, 3D HD camera	Released 2018

AESOP: Automated Endoscopic System for Optimal Positioning; FDA: U.S. Food and Drug Administration; HD: high definition; PAKY: percutaneous access to the kidney; PUMA: Programmable Universal Machine for Assembly; RCM: remote centre of motion.

platform, which helped surgeons position a laparoscopic camera by voice control. Further modifications resulted in the system being re-launched as the ZEUS operating system.<sup>7</sup>

Concurrently, Intuitive Surgical, Inc., (Sunnyvale, California, USA) released the Green Telepresence system, which became the early version of the current da Vinci system.

The two rival systems, ZEUS and da Vinci, pushed the frontiers of minimally invasive surgery. The da Vinci platform was first used on a human patient for a cholecystectomy, which was conducted by Jacques Himpens in 1997.<sup>8</sup>

The first laparoscopic radical prostatectomy with a remote-controlled robot (da Vinci) was performed by Abbou et al.<sup>9</sup> in 2000. The ZEUS and da Vinci system finally unified when Computer Motion, Inc., and Intuitive Surgical, Inc., merged in 2003. As a result, Intuitive Surgical, Inc., became the sole proprietor. Since then, the da Vinci system has dominated the world of robotic surgery for almost two decades. Newer technologies with improved versions of robots have emerged and are rapidly evolving the field (Table 1).

### **Robots in the Post-millennium Era (2001–2010) and Current Version (2010–2020)**

The da Vinci platform produced various models for a decade. The first series of 50 robot-assisted radical prostatectomies was published by Menon et al.<sup>10</sup> in 2002, using the first-generation of the robot. Subsequently, upgraded versions of the da Vinci system entered the market with improved technology (Table 1).

Over the past 30 years, more than 21,000 peer-reviewed articles have confirmed the safety, efficacy, and benefits of the da Vinci system (Intuitive Annual Report, 7 Feb 2020). Despite the high capital investment and high costs for disposables, updated versions of the da Vinci robot are introduced into the market continuously (Table 1).

The total number of robotic platforms installed as of 31<sup>st</sup> December 2019 was 5,582. In addition, robotic procedures of various types in hospitals throughout the world numbered 1,229,000 (data on file; da Vinci Annual

Report, 7<sup>th</sup> Feb 2020), an annual increase of approximately 20%. Most surgical procedures performed robotically in the USA were in general surgery, followed by gynaecology and then urology. Conversely, outside the USA, most of the procedures were in urology.

### **Training Platform to Improve Skills and Performances**

Approximately 400,000 deaths occur every year in the USA as a result of medical errors, making it the third-leading cause of death in the country.<sup>11,12</sup> Surgical errors are common but potentially preventable.<sup>13</sup> Adequate surgical skills and techniques have been directly related to patient outcomes.<sup>13,14</sup>

Robot-assisted surgery in urology is growing. The development of structured and validated training programmes is important in order to gain adequate skills and prevent poor surgical outcomes and medico-legal issues.

### **Technical and non-technical skills**

The da Vinci robotic platform is complex and expensive. Therefore, users should be properly trained and certified. A recent paper calculated that 100–180 robotic operations are required to obtain better, or at least equivalent, results compared with open surgery.<sup>15</sup> Another article quoted a learning curve of 8–150 procedures.<sup>16</sup> However, surgeons experienced in both open radical prostatectomy and laparoscopic radical prostatectomy can make smooth and quicker transitions to robotics.<sup>17</sup>

Robotic platforms require both console training and patient side training. Patient side training involves patient positioning, establishing pneumoperitoneum, port placement, robot docking, and basic laparoscopic skills. Console training requires dry and wet lab simulations and supervised operating. To improve skills and performance, a variety of structured curriculums have been developed to shorten the learning curve.<sup>18,19</sup>

Non-technical skills (e.g., teamwork, leadership, and decision-making skills) are an integral part of surgical training and should be developed in parallel with the development of technical skills. One study showed that 86% of adverse surgical events were due to system



errors rather than technical skills.<sup>20</sup> Furthermore, 40% of intraoperative errors were related to failures in communication.<sup>20</sup>

Intuitive Surgical, Inc., provide integrated training with virtual simulation, data-driven optimisation, and customised solutions. Over the last 20 years, a robust training programme has therefore been built-up. This time-tested, comprehensive training programme can help develop the skills essential to using da Vinci technology.

### **A pathway to gain technical and clinical skills: two steps and four phases**

Initially, optimisation of proficiency by developing knowledge and skills to use da Vinci technology. Second, progress with a surgeon-led series of procedures focused on clinical application, advanced techniques, and procedure refinement.

Firstly, training is centred on the core system and advanced technology. This consists of two phases: introduction to da Vinci technology (familiarisation with the system through 'test drives', videos, and live case observations) and da Vinci technology training (the development of technical skills via online learning, simulation, and hands-on training).

The second step is focused on progressive peer-to-peer clinical skill advancement and again consists of two phases: an initial case series plan (the integration of da Vinci technology into practice with support from experienced proctors) and continuing development (the expansion of skills through mentoring, surgeon-led programmes, and simulation).

However, a variety of new robotic systems from numerous countries are coming onto the stage. Several console-based robots for laparoscopic multi- and single-port surgery with various modifications of robotic arms, instruments, haptic feedback, eye tracking, and video technology will soon emerge. These developments with new robotic platforms would require precise, operation-specific teaching and training that could potentially be different from the current da Vinci training curriculum. In the future, the range of simulation platforms is likely to increase, with a variety of robotic training programmes and robotic simulated tasks.

## **Types and Levels of Robots with New Platforms**

There are three main types of robotic systems currently in use in surgery: active, semi-active, and master-slave systems (Table 2).

Active systems essentially work autonomously (while remaining under the control of the operative surgeon) and undertake pre-programmed tasks. The PROBOT and ROBODOC platforms are two examples.

Semi-active systems allow for a surgeon-driven element to complement the pre-programmed element of the robot system.

Master-slave systems (the da Vinci and ZEUS platforms) do not have any pre-programmed or autonomous elements.

Currently, available robots are completely dependent on human control. Attempts are being made to program the robot to operate, at least for parts of the procedure, independently (Table 2).

In future, robots may be equipped with artificial intelligence to independently perform procedures, or parts of it, by autonomous robot-assisted surgery to overcome operator-dependent variations and improve patient care. However, use of autonomous technology will come at the cost of sacrificing meaningful human control and at the expense of uro-surgical jobs. Robot-assisted surgery systems with various levels of autonomy have already been developed (Table 2).

## **Evidence Supporting Robot-Assisted Surgery in Urological Procedures**

The majority of robotic procedures are radical prostatectomy, radical cystectomy, partial nephrectomy, and pyeloplasty. Below, the authors explore the implementation of robot-assisted surgery.

### **Robot-assisted radical prostatectomy**

The first robot-assisted radical prostatectomy (RARP) was performed in 2000. The first series of 50 RARPs was published in 2002.<sup>10</sup> Subsequently, numerous articles have been published. Several meta-analyses demonstrated a significant advantage in terms of potency, continence, and

**Table 2: Types and different levels of robotic systems.**

Types of surgical robot	Action	Example	Criteria
Master-slave system	First (stereotaxis) and second (endoscopic) generation	da Vinci system ZEUS system	Entirely dependent on surgeon's activity
Semi-active system	Surgeon-driven	Acrobot and Rio (orthopaedic)	Partially autonomous, haptic feedback
Active system	Robot-driven under control of surgeon	PROBOT ROBODOC	(Surgeon-controlled) autonomous Non-haptic
<b>Classification of robotic system with various level of autonomy</b>			
Level 0	No autonomy	Teleoperated robot: AESOP and ZEUS systems	Follow command (operator performs all tasks)
Level 1 (direct control)	Passive assistance during a task	da Vinci Trauma Pod	Robot provides some assistance during a task but remains under full human control
Level 2 (shared control)	Autonomy for part of the task	AquaBeam ablation (BPH) Acrobot	Robot performs a task but is monitored by surgeon
Level 3 (conditional autonomy)	Different autonomous task strategies (autonomy for specific tasks)	Flexible endoscopic robot Autonomous bowel anastomosis	Appropriate task/surgical plan is approved or selected by surgeon. Robot performs tasks without close oversight
Level 4 (supervised autonomy; high autonomy)	Robot is able to perform entire procedure ('robotic resident')	Radiosurgery ROBODOC (total knee arthroplasty) PROBOT (TURP)	Robot is able to make decisions under supervision
Level 5 (full autonomy)	Robot performs entire surgery, no human/surgeon is needed.  Independent robotic surgeon	NA	Still surgical fiction No surgeon needs to be in the loop

Acrobot: Active Constraint Robot; AESOP: Automated Endoscopic System for Optimal Positioning; BPH: benign prostate hyperplasia; RIO: Robotic-Arm Interactive Orthopedic System; TURP: transurethral resection of the prostate.

blood transfusion for RARP compared with open and laparoscopic approaches.<sup>21,22</sup>

Robotic surgery has revived the perineal approach for radical prostatectomy and Kaouk et al.<sup>23</sup> presented an overview of the recent advances based on their experience with RARP.

Robotic surgery is also implemented for the surgical treatment of benign prostatic hyperplasia<sup>24</sup> and low-risk cancer

with lower urinary tract symptoms due to prostate enlargement.<sup>25</sup>

## Robot-assisted radical cystectomy

Radical cystectomy with pelvic lymphadenectomy and urinary diversion is the standard of care for treating organ-confined muscle-invasive bladder cancer and refractory non-invasive disease. Despite high morbidity and the risk of perioperative mortality, open

radical cystectomy remains the gold standard.<sup>26</sup> Minimally invasive techniques are gaining momentum and popularity because they provide similar oncological outcomes with lower morbidity. The first series of robot-assisted radical cystectomies (RARC) was reported by Menon et al.<sup>27</sup> in 2003. Since then, there has been a dramatic increase in utilisation of RARC, from under 1% of all cystectomies performed in the USA in 2004 to approximately 23% in 2014.<sup>28</sup>

The two most recent meta-analyses found no differences regarding oncological outcomes between RARC and open radical cystectomy, but a lower 90-day complication rate, a lower transfusion rate, a shorter time to flatus, and a greater lymph node yield in patients who underwent RARC.<sup>29,30</sup>

As part of RARC, many centres are still conducting an extracorporeal urinary diversion through an abdominal mini-incision. Complete intracorporeal urinary diversion seems to fully unlock the potential of RARC. Yet, despite already being performed in some expert centres worldwide, this approach is still considered as experimental by the European Association of Urology (EAU).<sup>31</sup> Brasseti et al.<sup>32</sup> reported one of the largest series with long-term data about RARC with totally intracorporeal urinary diversion.

### **Robot-assisted radical nephrectomy**

Laparoscopic radical nephrectomy is the gold standard and recommended by the EAU for patients with  $\geq T2$  renal tumours.<sup>33</sup> No significant differences in post-operative complications have been observed between robotic-assisted radical nephrectomy (RARN) and laparoscopic radical nephrectomy;<sup>34</sup> however, robotic surgery is associated with a prolonged operating time and higher hospital costs. Despite this, the use of robot-associated nephrectomy in the USA increased from 1.5% in 2003 to 27.0% in 2015.<sup>34</sup>

Over the last decade, robots have been used to operate on patients with advanced renal cell carcinoma with inferior vena cava thrombus. RARN with inferior vena cava thrombectomy is a complex procedure that requires a multimodal approach involving urological, cardiothoracic, and hepatobiliary surgeons. Patients are traditionally treated with open surgery with large abdominal or thoraco-abdominal incisions. RARN with inferior vena

cava thrombectomy was first reported by Abaza et al.<sup>35</sup> Recently, Gill et al.<sup>36</sup> presented a series of 16 patients with Level II and III inferior vena cava thrombus with good outcomes.

### **Robot-assisted partial nephrectomy**

Robot-assisted partial nephrectomy is considered the gold standard for most small renal tumours. A meta-analysis of 4,919 patients from 25 studies showed decreased complications, less conversions to open surgery, reduced positive surgical margin rates, and a shorter warm ischaemia time in the robotic group relative to their laparoscopic counterparts.<sup>37</sup> Complex tumours of  $>4$  cm with high nephrometry scores are increasingly being managed using the robotic approach, with good oncological outcomes.<sup>38</sup> Robot-assisted partial nephrectomy has proven feasible and superior to conventional laparoscopy even in solitary kidneys, multifocal renal masses, and for new or recurrent tumours in a kidney previously treated with partial nephrectomy.<sup>39</sup>

### **Robot-assisted nephroureterectomy**

Nephroureterectomy is almost the ideal procedure to demonstrate the advantages of minimally invasive surgery in terms of cosmetics and post-operative use of analgesics.

A recently published review, despite showing some perioperative advantages for minimally invasive access, found no statistically significant differences between the laparoscopic and the robotic approach, and consequently called for larger, better designed randomised controlled trials.<sup>40</sup>

Veccia et al.<sup>41</sup> reported a systematic review and meta-analysis of comparative outcomes of robotic versus other established nephroureterectomy techniques.

### **Robot-assisted retroperitoneal lymphadenectomy**

Open retroperitoneal lymphadenectomy (RPLND) is still the gold standard based on oncologic outcomes and long-term follow-up data. However, complications and morbidity from open RPLND incision affect 3.7–10.0% of patients. Therefore, the demand for minimally invasive surgery for cosmetic reasons is

increasing. The first case of laparoscopic RPLND was described in 1992 and that of robotic RPLND in 2006. Thirteen studies subsequently suggested that functional outcomes and in-field recurrence rates may be comparable to open approaches.<sup>42</sup> A large case series of 47 patients with low-risk non-seminomatous germ cell tumours showed a 9% perioperative complication rate, preservation of ejaculation in 100% of patients, and a recurrence-free rate of 97% at 16 months.<sup>43</sup> Another study showed no retroperitoneal recurrences at 22 months and a minor complication rate (Clavien-Dindo Grade II) of 17%.<sup>44</sup> Rocco et al.<sup>45</sup> reported the largest series of primary robot-assisted RPLND for non-seminomatous germ cell tumours.

### **Robot-assisted pyeloplasty**

The published data regarding robot-assisted pyeloplasty show excellent results and success rates (of 94–100%), as well as very good results in redo operations after failed primary procedures (with success rates of 78–94%). A meta-analysis of nine published studies on 277 robotic cases and 196 laparoscopic cases showed no differences between the two techniques apart from a shorter operative time for the robotic operation.<sup>46</sup>

### **Robot-assisted laparoscopic ureteric re-implantation**

Over the past decade, there has been an increasing shift toward robot-assisted laparoscopic distal ureteric reimplantation. The first reported robot-assisted laparoscopic ureteric re-implantation was performed by Yohannes et al.<sup>47</sup> in 2003. A recent review by Asghar et al.<sup>48</sup> in 2020 showed advantages in terms of blood loss, length of hospital stays, and post-operative pain for the robotic compared with the open approach.

### **Under scrutiny: recent expansion of other robotic uro-surgery procedures**

Robotic surgery is being explored for adrenal surgery. Heger et al.<sup>49</sup> recently published a meta-analysis of 1,710 patients who underwent either a minimally invasive (robotic or laparoscopic) or an open adrenalectomy. Blood loss was lowest in the robotic group. A significant reduction in the length of stay compared with

conventional laparoscopy was also recorded. Ye et al.<sup>50</sup> described a novel robotic adrenal enucleation technique.

Two randomised trials comparing laparoscopic and robot-assisted sacrocolpopexy showed higher costs, a longer operative time, and more post-operative pain in the robotic group.<sup>51</sup>

Robotic platforms have allowed lymph node dissection for several genitourinary cancers.<sup>52</sup> In children, the success rate of robotic-assisted surgery for the treatment of vesicoureteral reflux was below 90% whereas the success rate of open extravesical ureteric re-implantation was approximately 98%.<sup>53</sup>

## **The Future of Robotic Surgery**

Despite the high cost of robots, there is a continuing expansion of robotic surgical procedures. Although adoption of robots for surgery was introduced in the 1990s, only 15.1% of all common operations in the USA are performed robotically (increased from 1.8% in 2012 to 15.0% in 2018).<sup>54</sup> Robotic-assisted laparoscopic prostatectomy increased from 0.7% in 2003 to 42.0% in 2010<sup>55</sup> and by 2014, RARP accounted for up to 90% across the USA.<sup>56</sup> However, this figure is likely to be much lower outside America.

The global market for surgical robots keeps growing. The initial capital investment for a da Vinci system is 1.2–1.5 million USD, with an annual maintenance cost of 100,000 USD and an average disposable instrument cost of 1,400–1,700 USD per case. Bolenz et al.<sup>57</sup> compared costs for a RARP with laparoscopic and open procedures. They calculated the costs of RARP, laparoscopic RP, and open RP as 9,450 USD, 5,687 USD, and 4,437 USD per operation, respectively.

As there are no competitors, da Vinci do not yet have to compromise on the cost because of their monopoly. A centre needs to perform 100–150 cases of robot-assisted surgeries per year to be cost-effective.<sup>58</sup> The fastest growing Asian and other developers are coming to the market with low-cost surgical robots that will soon challenge the expensive da Vinci monopoly while also providing the same or better surgical outcomes (Table 3).

Western countries have possibly already reached, or will soon reach, the peak and plateau



**Table 3: Recent and future emerging robotics in urology.**

Company	Target technology	Configuration	Current status
<b>USA</b>			
da Vinci Xi (Intuitive Surgical, Inc., Sunnyvale, California, USA)	MIS, multi-port	Master console, four arms, and patient cart	FDA-approved 2014
da Vinci X (Intuitive Surgical, Inc., Sunnyvale, California, USA)	MIS, multi-port	Master console, four arms, and patient cart	FDA-approved 2017
da Vinci SP (Intuitive Surgical, Inc., Sunnyvale, California, USA)	MIS, single-port	Master console, one arm, and patient cart	FDA-approved 2018
Senhance (TransEnterix, Inc., Morrisville, North Carolina, USA)	MIS, multi-port	Master console and separated arms	FDA-approved 2017
Monarch Platform (Auris Health, Inc., Redwood City, California, USA)	NOTES	Master console, one arm, and patient cart	Clinical trial
<b>Europe</b>			
Verisus (CMR Surgical, Cambridge, UK)	MIS, multi-port	Master console, four arms, and patient cart	Under development
Roboflex Avicenna (Elmed Medical Systems, Inc., Ankara, Turkey)	Remote ureteroscopy	Master console, robot manipulates conventional ureteroscope	Approved for ureterorenoscopy 2014
DLR MicroSurge (German Aerospace Center [DLR], Cologne, Germany)	MIS	Master-slave telemanipulation, two haptic input device, three arms, 3D camera, visual and force feedback	Clinical Trial
Surgenius (Surgica Robotica, Trieste, Italy)	MIS	Master-slave telemanipulation, haptic feedback	Under development
<b>ASIA</b>			
Revo-I (Meere Company, Hwaseong-Si, Gyeonggi, South Korea)	MIS, multi-port	Master console, four arms, and patient cart	Currently, clinical use in South Korea only
RIVERFIELD Inc., (Shinjuku City, Tokyo, Japan)	MIS, multi-port	Master console, four arms, and patient cart	Under development
EndoMaster (EndoMaster Pte Ltd., Singapore)	NOTES	Master console, one arm, and patient cart	Clinical trial
Micro Hand S robot system (Tianjin University, China)	MIS, multi-port	NA	Under development
<b>CANADA</b>			
SPORT surgical system, (Titan Medical Inc., Toronto, Canada)	MIS, multi-port/LESS	Master console, one arm and patient cart, two articulated instruments, haptic system, 3D HD flexible camera	Under development

FDA: U.S. Food and Drug Administration; LESS: laparoendoscopic single-port surgery; MIS: minimally invasive surgery; NA: not applicable; NOTES: natural orifice transluminal endoscopic surgery; SPORT: Single Port Orifice Robotic Technology.

level for the installation of new robots. The Asia-Pacific and South American markets are the target of future robot installations and expected to grow very fast. Currently, differences in surgical robot density are marked.

In Brazil, there is one robot per 5.1 million people, in Europe there is one robot per 998,000 people, and in the USA there is one robot per 112,000 people.<sup>59</sup> Moreover, in emerging countries, most robotic platforms are usually concentrated in affluent cities and at private healthcare institutions. Only affluent patients pay out of their pocket because insurance, if it even exists, does not cover the cost of robotic operations.

However, the ongoing COVID-19 crisis will likely be followed by a global recession in the near future. The costs of robotic surgery have become the prominent factor driving treatment and investment decisions. The COVID-19 pandemic led to a 40% reduction in its shares on the stock market in late March 2020. Globally, procedures performed using the da Vinci surgical system decreased by 19% worldwide in Quarter 2 of 2020 compared with 2019 because elective procedures were either cancelled or postponed. Quarter 3 revenue was 1.1 billion USD, down 4% from last year. During Quarter 3, Intuitive Surgical, Inc., shipped 195 new da Vinci surgical systems, a 29%

decline from the same quarter in 2019. The global robotic surgery market is expected to decline from 5.04 billion USD in 2019 to 4.84 billion USD in 2020, which is a decrease of 3.91% from 2019, as a consequence of the COVID-19 crisis. The market will eventually stabilise and is expected to reach 7.71 billion USD in 2023.<sup>60</sup>

A future ideal robotic system should be cost-effective, easy to use, easy to set up, and portable so that it can be used in different locations and settings.

The main limitation of this article is that it is a non-systematic literature review; therefore, there is a possibility of subjective bias.

## CONCLUSION

Over the past decade, minimally invasive approaches have revolutionised surgery, and robotic surgery has accelerated these changes. Without doubt, robotic urologic surgery is here to stay and will expand further in all surgical disciplines. Utilisation of robotics should be coupled with a reduction in costs to healthcare systems and improved clinical outcomes for the general population rather than a privileged few. Therefore, making this expensive technology more affordable must be part of the equation.

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# Office-Based, Point-of-Care, Low-Field MRI System to Guide Prostate Interventions: Recent Developments

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## Abstract

Prostate cancer (PCa) is the second most frequently diagnosed cancer in males; early-stage PCa is asymptomatic, and PCa has an indolent course. The current standard of care of systematic transrectal biopsy (SBx) is preferred by urologists because of its ease of use and portability, despite its shortcomings in cancer detection rate. The advent of multi-parametric MRI (mpMRI)-enabled PIRADS protocol for lesion diagnosis and characterisation has helped minimise unnecessary biopsies, supporting the active surveillance protocol of patients with low-risk PCa. The use of annotated pre-procedure MRI fused with real-time ultrasound (US) to guide biopsies has been gaining traction in clinical use, but the challenges in registration of two different modalities, gland deformation due to the probe, and significant learning curve associated with fusion have resulted in slower than expected adoption in routine clinical practice. Moreover, the fusion biopsy has only marginally improved cancer detection rate, with a complex workflow. Higher infection rate with transrectal prostate interventions has resulted in an increased use of the transperineal approach to guide biopsies and therapies. There has been significant progress made in the development of point-of-care, portable MRI systems for specific use. In this report, the authors discuss the recent developments in office-based prostate interventions that have occurred with the arrival of low-field MRI systems. The smaller footprint of the low-field system avoids the high costs associated with the installation and management of regular



MRI. Additionally, the availability of transperineal MRI visible grid makes the targeting and guidance processes relatively easier with a less-steep learning curve. Since the system uses pre-plan high-field MRI acquired in the same transverse orientation as the low-field MRI, registration errors are smaller than the MRI-US registration. The use of MRI to target lesions has reduced the number of cores sampled, benefiting the patient with early clinical study showing significantly higher cancer detection rate than SBx.

## INTRODUCTION

Prostate cancer (PCa) is the second most prevalent cancer among males in the USA, with >180,000 new cases diagnosed in 2016.<sup>1</sup> The 5-year survival rate for patients initially diagnosed with local or regional prostate cancer is almost 100% but falls to 31% for those with an initial diagnosis of PCa that has metastasised.<sup>1</sup>

The current diagnostic pathway of PCa requires males with elevated prostate-specific antigen and/or an abnormal digital rectal examination to undergo a transrectal ultrasound (TRUS)-guided biopsy.<sup>2-6</sup> As a blind systematic biopsy (SBx), which randomly samples prostate tissue, it can lead to missing or under-diagnosing clinically significant cancer and over-diagnosing clinically insignificant disease.<sup>4-5,7</sup> Moreover, TRUS biopsy is associated with morbidity and can also sometimes cause life-threatening sepsis.<sup>2,7</sup>

An alternative to the transrectal approach is the transperineal approach (TPUS), which allows for easier access to all parts of the prostate and avoids contamination by the rectum, therefore resulting in greater accuracy and lower infection rates.<sup>8</sup> Recently, the European Association of Urology (EAU) published a position paper<sup>9</sup> recommending TPUS as a first choice due to its least-contaminating approach, reducing the rate of infection complications.

In recent years, multi-parametric MRI (mpMRI) has been reported as an efficient tool to guide prostate biopsy decision-making.<sup>2,10</sup> Indeed, EAU guidelines recommend performing mpMRI before prostate biopsy in biopsy-naïve patients, as well as patients with prior negative biopsy with a clinical suspicion PCa.<sup>11</sup> Moreover, techniques such as MRI-ultrasound (US) fusion biopsy have emerged as a way to target lesions more precisely, compared to the traditional systematic transrectal and transperineal US biopsy techniques. These targeted MRI-based approaches have been

reported to show improvement in rates of cancer detection compared to a SBx<sup>12-14</sup> but do have shortcomings.

Most common MRI systems, 1.5 Tesla (T) or 3T scanners, are very expensive to purchase and maintain, as well as time consuming and uncomfortable for patients<sup>15,16</sup> for image-guided interventions. This has led to the development of portable, less expensive, and office-based low-field MRI systems.<sup>17,18</sup>

In this review, the authors describe the recent developments of a U.S. Food and Drug Administration (FDA)-cleared, first of its kind, single-sided, low-field, open, point-of-care MRI system and its role in office-based prostate interventions.

## CURRENT DIAGNOSTIC PATHWAY

### Systematic Transrectal Biopsy

TRUS SBx is the most common approach for the initial diagnosis and grading of prostate cancer. It consists of 10-12 core biopsies,<sup>19</sup> and is usually performed in the urologist's office under local anaesthesia. It is easy to perform, widely available, and well tolerated by patients.<sup>20</sup> SBx provides a non-targeted, blinded sampling of the prostate (usually the periphery of the prostate), and is associated with missing or under-diagnosing clinically significant cancer and over-diagnosing clinically insignificant disease.<sup>2</sup> One consequence is over-treatment of patients with clinically insignificant disease, which even if left untreated, have little to no clinical impact on an individual's remaining life.<sup>21</sup> Moreover, over-treatment often leads to side effects like erectile dysfunction and urinary incontinence.<sup>21</sup>

Another consequence is incorrect risk stratification due to under-sampling or false negative biopsies. It occurs in up to 30% of cases in some series,<sup>22</sup> with the PROMIS trial reporting 52% false negative rates,<sup>2</sup> which leads to under-

grading and missing clinically significant disease on initial biopsy. Interestingly, increasing the number of cores has a marginal increase in overall detection rate, while it appears to increase the rate of insignificant PCa detection.<sup>23</sup>

Furthermore, SBx is associated with morbidity, mainly in the form of haematuria, haemospermia, pain, and urinary retention.<sup>2,7</sup> In addition, as long as the biopsy needle passes through the rectum, it can lead to urinary infection and even life-threatening sepsis. Higher rates of infection from TRUS has led to the use of TPUS biopsy, but the increased burden of resource utilisation combined with the lack of Level-1 evidence has limited wider adoption.<sup>24</sup>

## MRI-Ultrasound Fusion Biopsy

In recent years, mpMRI appears to be a complementary screening and diagnosis tool in the PCa diagnostic pathway. Its ability to detect PCa has been extensively validated in several previous studies.<sup>6,25,26</sup> A recent meta-analysis looking at the ability of mpMRI to detect PCa showed that mpMRI had high specificity 0.88 (95% confidence interval: 0.82–0.92) and sensitivity of 0.74 (95% confidence interval: 0.66–0.81), with negative predictive value having broader range of 0.65–0.94.<sup>27</sup>

Moreover, MRI-targeted biopsy (MRI-TB) has emerged as a way to more precisely target lesions under ultrasound guidance seen on a prior mpMRI scan. These targeted MRI-based approaches have been reported to show improvement in rates of cancer detection, decrease the number of unnecessary biopsies, and reduce the treatment of clinically insignificant disease.<sup>12–14,26,28</sup>

Three clinical trials have demonstrated this approach in biopsy-naïve males. In the MRI-FIRST trial, Rouviere et al.<sup>10</sup> conducted a prospective, multi-centre study comparing MRI-TB to SBx within the same patient. They found that detection of clinically significant PCa was not different in one of the two techniques (32% versus 30%;  $p=0.38$ ), but the detection was improved by combining both techniques. The 4M trial<sup>29</sup> was also a prospective, multi-centre study comparing MRI-TB to SBx within the same patient. The results showed a similar detection rate of clinically significant PCa (25% versus 23%;  $p=0.17$ ). However, MRI-TB detected a lower proportion of clinically insignificant disease (14%

versus 25%;  $p<0.001$ ). Lastly, the PRECISION trial<sup>30</sup> was a multi-centre, randomised, non-inferiority trial where patients were randomised to either traditional systematic TRUS-biopsy or MRI-TB. Unlike the other trials, MRI-TB detected more clinically significant PCa than SBx (38% versus 26%;  $p=0.005$ ). Furthermore, MRI-TB detected less clinically insignificant PCa (9% versus 22%;  $p<0.001$ ). These findings have been confirmed by systematic reviews,<sup>31–34</sup> both in biopsy-naïve patients and those with prior negative biopsy, and in the active surveillance population.

## Limitations of Fusion Biopsy

Despite all the advantages of MRI-TB, the rate of adoption in routine clinical practice has been slower due to certain issues. The MR image used to guide biopsies are a composite of mpMRI comprising T2-weighted imaging (T2W), diffusion-weighted, and dynamic contrast-enhanced images.<sup>35</sup> Though there are automated tools available to create the composite image, it still adds overhead to the workflow. Registration of mpMRI to US poses problems since there exists different techniques of registration such as cognitive registration, MRI-US fusion registration, and in-bore MRI-targeted registration,<sup>36</sup> resulting in errors in lesion targeting and resulting in significant impact on clinical outcomes. The median target registration error between MRI and 3D US is 3.8–5.6 mm, and 2D US is 2.5–3.6 mm, dependent on operator experience.<sup>37</sup> In different trials, none have shown a superiority in detecting clinically significant PCa, but the detection rate was higher when MRI-TB and SBx approaches were combined.<sup>38–40</sup>

There has been evidence that MRI's ability to identify PCa varies with factors like reader expertise, grade and disease volume, MRI sequences, etc.<sup>27,28</sup> Despite the existence of Prostate Imaging Reporting and Data System (PI-RADS) guidelines that offer a standard to radiologists for reporting prostate MRI,<sup>41</sup> a multi-centre study including six prostate radiologists found a moderate reproducibility and a high inter-centre and -reader variation of mpMRI.<sup>42</sup> Moreover, in a Cochrane systematic review,<sup>43</sup> a negative mpMRI falsely predicted the absence of clinically significant prostate cancer in 9% of males.

As there is a learning curve for the interpretation of prostate mpMRI, there is also one for all techniques of MRI-TB. A retrospective study of a prospective cohort of 1,813 males with prostate biopsy demonstrated a 26% increase in clinically significant PCa detection rate in a 4-year period.<sup>44</sup>

In spite of the benefits, in-bore MRI interventions are limited as they are time-consuming, create higher demand on resources, and require MR safe instrumentation. Additionally, the economics associated in the purchase and maintenance of MRI systems are prohibitive for specialised use such as image-guided biopsies and require strong-magnetic-field-specific facility upgrades for housing the system. Highly specialised expertise, increase in MR safety training, and hazardous material protocols needed for appropriate cryogen use are other significant drawbacks. The size of the MR bore imposes restrictions on patient selection in addition to the inability to accommodate claustrophobic patients. Moreover, the demand for routine diagnostic use prohibits the use of in-bore interventions except for select academic and research centres.

## LOW-FIELD MRI SYSTEM

### Low-Field MRI-Guided Biopsy

Recently, with the development of better magnet design, radiofrequency, and gradient technologies, there is an increased interest towards low-field MRI for targeted applications. The very first studies in this field were published in the early 80s and 90s, in particular for neurology imaging and interventional applications.<sup>45-47</sup>

The Promaxo MRI System (Promaxo Inc., Oakland, California, USA) is the first of its kind: a single-sided, office-based, low-field MRI system with an open design to accommodate patients of all sizes and types, including those with claustrophobia. It is cleared by the U.S. FDA and is intended to be used for targeting prostate lesions under MR guidance in alignment with the current standard of care. Having a smaller footprint, with a field strength of 65 mT and pre-programmed pulse sequences for optimal workflow, requiring neither significant facility upgrades nor operating costs, makes it suitable for office-based biopsies. A smaller footprint (Figure 1), with low energy utilisation



**Figure 1: Promaxo MRI system.**

The system comprises two main components: the electronic panel (left) and the magnet cart (right). A patient wearable receive coil is not shown in the image.



**Figure 2: A subject in a lithotomy position for a pelvic scan.**

**A)** The yellow arrow points to the surface coil and the orange arrow points to the MRI visible biopsy grid. **B)** A lateral view of the patient positioned with the pelvis against the Promaxo MR scanner (behind the surgical drape) for the procedure.

and the absence of any hazardous materials such as cryogenics, makes it ideal for office-based procedures without requiring any significant facility upgrades.

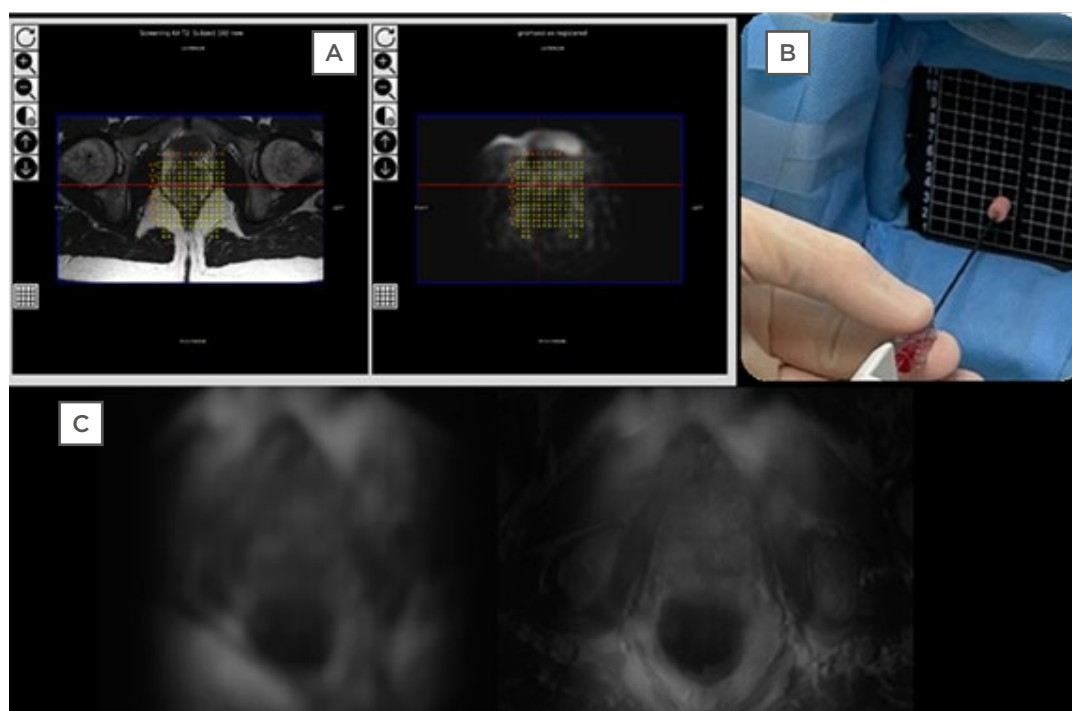
## MRI-Targeted Biopsy Clinical Workflow

The clinical workflow consists of regions of interest identified and annotated on commercial whole-body 3T T2W images obtained in advance by a board-certified radiologist using the Promaxo DICOM Viewer. The annotated images are uploaded to the Promaxo MRI System prior to the procedure date. For the MRI-TB procedure, patients are placed in a high lithotomy position (Figure 2) with their perineum close to the centre of the single-sided MRI field of view (120 mm) magnet, such that the entire prostate gland would be visible in the resulting scan. A 5-channel surface coil containing an MR-visible biopsy grid (Figure 1) for transperineal access encloses the pelvic region, and an additional 1-channel fiducial and back coils are placed on the pelvis and lower back region, respectively.

The Promaxo MRI protocol starts with a 4-minute localiser scan to locate the prostate (repetition time/echo time: 1,200/45.93 ms; sequence [spin echo]: RARE; image type: cartesian; percent sampling: 50%; echo train length: 8). Once positioning is confirmed, a T2W MRI scan (repetition time/echo time: 1,500/15.3 ms; radial sampling; echo train length: 7) is acquired. Forty slices of T2W images in the axial plane are obtained with a 120x120 mm field-of-view, and are reconstructed to a field-of-view of 180x180 mm, with 2.8 mm slice thickness, resulting in an approximate voxel size of 9 cc. On the day of the procedure, patients undergo sedation as preferred by the practice.

A board-certified urologist uses the Promaxo graphical user interface to manually co-register the annotated 3T T2W images with the acquired Promaxo MRI T2W scans (Figure 3), and identifies the lesion targets based on the physical template co-ordinates and depth displayed on the registered images. Following registration and target planning, the needle(s) are inserted





**Figure 3: Example of the Promaxo in use with prostate images.**

**A)** 3T T2W images on the left (with the annotation) is co-registered with T2W Promaxo MR image on the right (shown here in Promaxo viewer). The red circle shows the target, once identified by the urologist. **B)** The appropriate needle is inserted, and samples are taken as shown. **C)** Left: axial T2W slice; right: T2W axial Promaxo MR fused with high-field (1.5T) MR.

3T: 3 Tesla; MR: magnetic resonance; T2W: T2-weighted.

transperineally through the designated co-ordinate location and tissue samples are extracted. The grid is designed to accommodate an MR-safe 20 cm biopsy gun with an 18 G biopsy needle and either a 14 G or 17 G cannula.

## Clinical Experience

The system currently is in use at Mississippi Urology, a community-based practice in Jackson, Mississippi, USA. Using an institutional review board-approved research protocol (WIRB #20203968), 16 males (average age:  $67 \pm 8$  years) referred for SBx to a community urology practice were consented for MRI-TB with the Promaxo MRI for biopsy guidance. Cancer was found in six of 16 patients by both SBx and MRI-TB, while MRI-TB found cancers in six more patients resulting in a 37% higher cancer detection rate with MRI-TB. Initial results from this ongoing study demonstrate in-office prostate MRI-TB biopsy with a low-field MRI system is feasible, and confirm the benefits of co-registering high-

field with low-field MRI for improved guidance to target lesions.

## Future Possibilities

The use of artificial intelligence (AI) in healthcare is ubiquitous from automated segmentation of mpMRI,<sup>48</sup> de-noising of medical images,<sup>49</sup> and treatment.<sup>50</sup> AI technology enables health professionals to deliver better care for their patients and increase productivity, while improving patients' experiences and outcomes. Deep-learning-based U-Net architecture<sup>51</sup> is used in Promaxo MR to reduce noise from the system and remove artefacts due to the inhomogeneous B0 field, non-linear gradients, under-sampling of k-space, and image reconstruction to enhance low-field MR.

The growing interest for the case of simpler and cheaper prostate MRI,<sup>52</sup> followed by the recent recommendation by the UK's National Institute for Health and Care Excellence (NICE),<sup>53</sup> for the use of mpMRI, the authors predict low-field

open systems such as Promaxo MRI will play a significant role. As an office-based system, board-certified urologists would be able to readily screen all males >50 years old with pre-programmed prostate-specific sequences and the help of AI to enhance signal and contrast to noise along with tissue characterisation.

The open design of the MRI and the ability to use it in an outpatient centre or ambulatory surgical centres enables a suitable environment for targeted robotic procedures with greater precision. Moreover, this platform could be used as a treatment tool under live MRI such as focal therapy, radiation treatment, and surgery.

## CONCLUSION

The limitations imposed by high-field MRI systems for prostate interventions in an outpatient centre or ambulatory surgical

centre have enabled the development of better magnet design, radiofrequency, and gradient technologies for low-field MRI. The Promaxo MRI System is the first single-sided, low-field, and open MRI system developed and cleared by the U.S. FDA for prostate biopsies of target lesions under MRI guidance. The smaller footprint of the system is suitable for office-based procedures and allows board-certified urologists to perform prostate interventions in outpatient settings. With relatively straightforward navigation and registration techniques, Promaxo MRI reduces registration errors and improves target rates for therapies. The authors believe that it will improve the rate of clinically significant cancer detection and results for targeting therapies of PCa. This review provides important advances of the low-field MRI system for prostate interventions and its future possibilities in term of interventional applications.

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# Non-papillary Percutaneous Puncture: A Safe Approach to Consider

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## Abstract

Percutaneous nephrolithotomy (PCNL) is the 'gold standard' treatment modality for renal stones larger than 2 cm. It can be also applied to manage smaller renal stones and large, impacted stones located in the proximal ureter. Nevertheless, even in experienced hands, the PCNL procedure is associated with the development of several complications. Despite the existing extensive research in this field, studies evaluating the effect of puncture site on perioperative bleeding are very few. In part, this can be explained by the dogma that the safest way to perform kidney puncture is through the renal papilla. In this paper, the authors summarise their experience of non-papillary PCNL and demonstrate this puncture technique for PCNL tract establishment.

## INTRODUCTION

Percutaneous nephrolithotomy (PCNL) is the 'gold standard' treatment modality for renal stones larger than 2 cm. It can be also applied to manage smaller renal stones and large, impacted stones located in the proximal ureter. Nevertheless, even in experienced hands, the PCNL procedure is associated with the development of several complications. Perioperative bleeding represents one of the serious complications and accounts for 7.8% of cases, of which significant bleeding requiring blood transfusion occurs in 5.7%.<sup>1</sup> Due to this complication, many specialists still fear practising PCNL. To address the latter issue and reduce the rate of perioperative bleeding, technical refinements of surgical instruments

and surgical approaches have been proposed.<sup>2</sup> Despite the existing extensive research in this field, studies evaluating the effect of puncture site on perioperative bleeding are very few. In part, this can be explained by the dogma that the safest way to perform kidney puncture is through the renal papilla. In this paper, the authors summarise their experience of non-papillary PCNL and demonstrate this puncture technique for PCNL tract establishment.

## DISCUSSION

Successful kidney puncture and PCNL tract establishment are the initial and key steps of the procedure. Until recently, it was believed that papillary puncture through the papilla of the

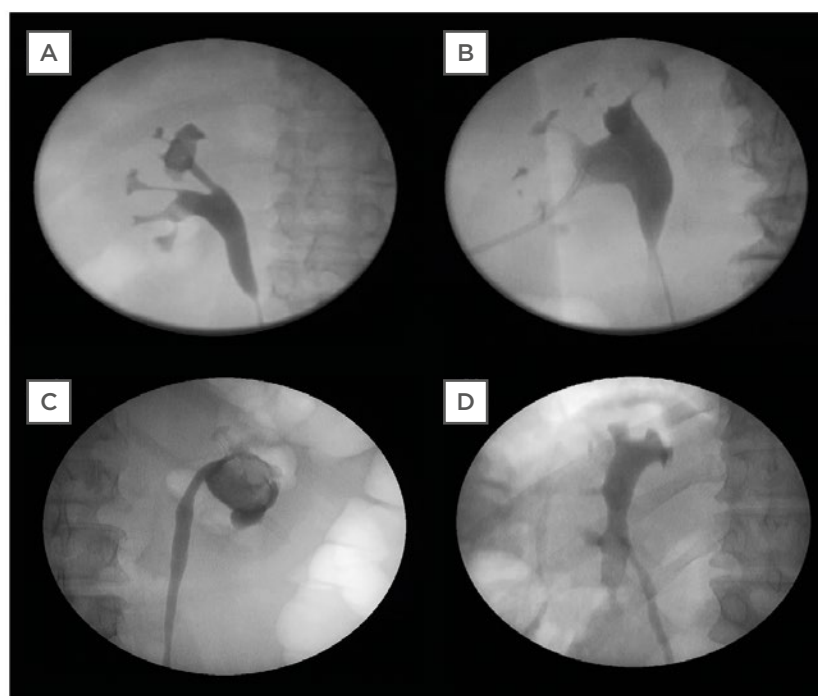


calyceal fornix is the only right and acceptable way to perform the puncture. The background for these beliefs were the anatomical studies by Sampaio et al.<sup>3</sup> performed in the early 1990s. The authors demonstrated that fornical punctures were associated with a significantly lower rate of vascular injury. The punctures to the renal papilla, regardless of the punctured calyx, carried a 7–8% probability of vessel injury, whereas punctures to the upper, middle, or lower infundibulum were associated with 67.6%, 61.5%, and 68.2% vessel injuries, respectively.<sup>3</sup>

At first glance, those studies were ideal and did not leave any room for further research. In fact, until 2016–17 there was no literature discussing any alternative approach to papillary puncture, as this method was considered the safest and a must for practising specialists. However, those studies were associated with several limitations. All the punctures were performed on healthy cadaveric kidneys in an artificial environment. In the clinical setting, before puncturing the kidney, the needle passes through the skin subcutaneous tissue, muscles, and aponeurosis, and even best experimental settings could not replicate

the accurate orientation of these structures. Urologists deal with patients with affected kidneys (urolithiasis, chronic pyelonephritis, dilated system). As such, the effect of those conditions was not evaluated. Moreover, puncture and tract dilation are two separate interventions, and one cannot conclude about tract dilation outcomes considering only findings of puncture studies.

In real life, the patients' anatomy may differ from the ideal, and performing a papillary puncture may not be feasible in all cases (Figure 1). The authors' initial experience for treating these patients showed that there was no increased risk of perioperative bleeding, while the performance of non-papillary puncture shortened and made the kidney puncture and subsequent tract establishment easier compared to standard papillary approach. With an increasing number of patients, the authors performed a retrospective observation of their results to objectively evaluate the outcomes. Out of the studied 137 patients, serious bleeding requiring blood transfusion occurred in only four patients (2.9%), all of them treated conservatively.<sup>4</sup>



**Figure 1: When performing a papillary puncture might not be feasible in patients.**

**A)** Stone in the upper calyx with small papilla. **B)** Stone in the pelvis with narrow renal infundibula. **C)** Stone occupying the entire collecting system (calyces are not visualised). **D)** Stone located in the pelvis and lower calyx of the malrotated kidney.

**Table 1: The outcomes of studies performed on non-papillary percutaneous nephrolithotomy.**

Author	Year	Study population	Access size (Fr)	Stone size (mm <sup>2</sup> )	SFR (%)	Overall complications (%)	Bleeding requiring transfusion or intervention (%)
Kyriazis et al. <sup>4</sup>	2017	137 pts (NP)	30	210±199	84.6	10.20	3.6
Kallidonis et al. <sup>5</sup>	2017	27 pts (P)	30	14.3±5.8	ND	7.40	7.4
		28 pts (NP)	30	14.9±6.6	ND	7.14	0.0
Kallidonis et al. <sup>7</sup>	2021	32 pts (NP)	22	23.5±6.6	93.8	9.40	0.0
Kallidonis et al. <sup>8</sup>	2020	53 pts (NP with staghorn stones)	30	60.1±16.1	81.1	20.70	3.2
Tahra et al. <sup>6</sup>	2020	207 pts (P)	30	2.46±4.6	86.4	7.10	3.8
		69 pts (NP)	30	2.38±5.1	85.5	7.20	1.4

ND: no data; NP: non-papillary; P: papillary; pts: patients; SFR: stone-free rate.

The authors further investigated their hypothesis in a randomised controlled trial comparing papillary and non-papillary PCNL.<sup>5</sup> They did not find any statistical difference in the level of haemoglobin drop, transfusion, and bleeding rates, as well as hospitalisation time between the two groups. In contrast, the operative time was significantly shorter in the non-papillary arm.<sup>5</sup> Similar to their results, no statistically significant differences were reported in a retrospective matched-pair case-control study by Tahra et al.<sup>6</sup> Out of 69 patients with non-papillary puncture, a blood transfusion was only required in one patient. No significant differences were reported for overall complications.

The feasibility and safety of the non-papillary approach were also investigated for mini-PCNL using 18 Fr nephroscope with a maximal outer sheath diameter of 22 Fr.<sup>7</sup> The mean haemoglobin drop in the cohort was 1.23±0.88 gr/dL and none of their patients developed severe bleeding requiring transfusion and additional intervention. The authors reported similar beneficial findings for patients harbouring staghorn stones having a mean stone size of 60.1±16.1 mm.<sup>8</sup> With a 1.2 mean number of PCNL access tracts, a primary stone-free rate of 81.1% was documented. The mean haemoglobin loss was 1.6±1.86 gr/dL and one patient required a blood transfusion.

**Table 1** summarises the outcomes of all studies performed on non-papillary PCNL.

In general, PCNL punctures are mostly accomplished under ultrasound, fluoroscopic, and endoscopic guidance. Fluoroscopic approaches are the most utilised techniques, and interpretation of the 3D renal anatomy on 2D images can sometimes require great effort.<sup>9</sup> The latter can be more challenging for novice specialists following the papillary approach due to the reduced area suitable for puncture. The authors believe that their proposed technique of non-papillary approach eases the orientation, as the puncture is directed toward the stone at the most convenient site for stone lithotripsy.

In the authors' hands, the non-papillary approach was associated with additional benefits. Having straight access to the renal pelvis allows uncomplicated passage of the guide-wire down the ureter, increasing the safety of subsequent tract dilation. Moreover, over-passing the calyces opens room for better manipulation and increases the efficiency of lithotripsy from a single PCNL tract. In such a way, stones located in the pelvis and different renal calyces can be treated simultaneously. The straight access to the renal pelvis also eases the manipulation and successful extraction of stones from the proximal

ureter. Although the pelvis is aimed for with the non-papillary approach, the rate of post-operative urine leakage and issues of tract healing are not observed. The authors' radiological studies demonstrated that the punctures to the infundibula and renal pelvises had a similar area of approach compared to the punctures to mid-calyceal fornices.<sup>10</sup>

The authors acknowledge the criticism that the non-papillary approach is not the standard technique and more research in this field is required. Nevertheless, considering the reported results and aforementioned benefits of non-

papillary puncture, the authors can propose it as a safe and effective approach for PCNL tract establishment.

## CONCLUSION

Kidney puncture and access tract establishment are detrimental steps of the PCNL procedure. The papillary puncture was historically considered a safe approach. In recent years, a non-papillary puncture approach was introduced and evaluated. The initial studies prove its feasibility and effectiveness for the treatment of renal stones with standard and mini-PCNL techniques.

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# The Microbiota and Kidney Transplantation: Influence on the Graft

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## Abstract

The gut microbial community may be associated with complications after kidney transplantation. The indigenous microbiota has a significant and protective function that influences the transplant recipient response. Genetic or environmental factors may modify the indigenous microbiota and pathobionts appear.

In this condition, several disturbances of the kidney graft may be observed. These include acute rejection, infection, diarrhoea, disturbance in the induction of tolerance, and modification of immunosuppressive drug metabolism.

Recently, the use of prebiotics, probiotics, and synbiotics has been demonstrated to be effective in normalising these conditions and in restoring the generation of the normal indigenous microbiota.

An improved understanding of the function and composition of the indigenous microbiota may help in finding further solutions to stabilise the microbiota after kidney transplantation.

## INTRODUCTION

The microbiota encompasses all of the microorganisms that live in specific niches of the body, including gut, skin, lungs, kidneys, bladder, and other organs. The term microbiota refers to bacteria, viruses, fungi, and archaea. This review principally discusses the bacteria living in the gastrointestinal tract, which have been more extensively studied and, in healthy conditions, live in the human body without damaging it. In particular, the authors examine how modifications to the microbiota that are known to be related

to several diseases, including renal diseases, may influence the outcomes of kidney transplantation.

## DEFINITIONS

The terms microbiota and microbiome are often mutually used with the same meaning, but they have different significance.

Microbiota refers to all the microorganisms living in the human body. Recently, the total number of bacteria in the human body has been approximately evaluated to be  $3.8 \times 10^{13}$ .<sup>1</sup> In healthy



conditions, the resident microbiota is also called the indigenous microbiota. The composition and activity of the indigenous microbiota may be modified by genetic or environmental causes, leading to several diseases. In such conditions the indigenous microbiota are called pathobionts and the new condition is called dysbiosis.

Pathobionts are indigenous microbiota that are modified in their composition or activity and should be distinguished from pathogens, which are acquired infectious agents.<sup>2</sup>

The term microbiome refers to all the microbiota genes.<sup>3</sup> In normal conditions, the microbiome exerts important functions for the body, such as metabolic, structural, and protective functions.

## MICROBIOTA FUNCTIONS

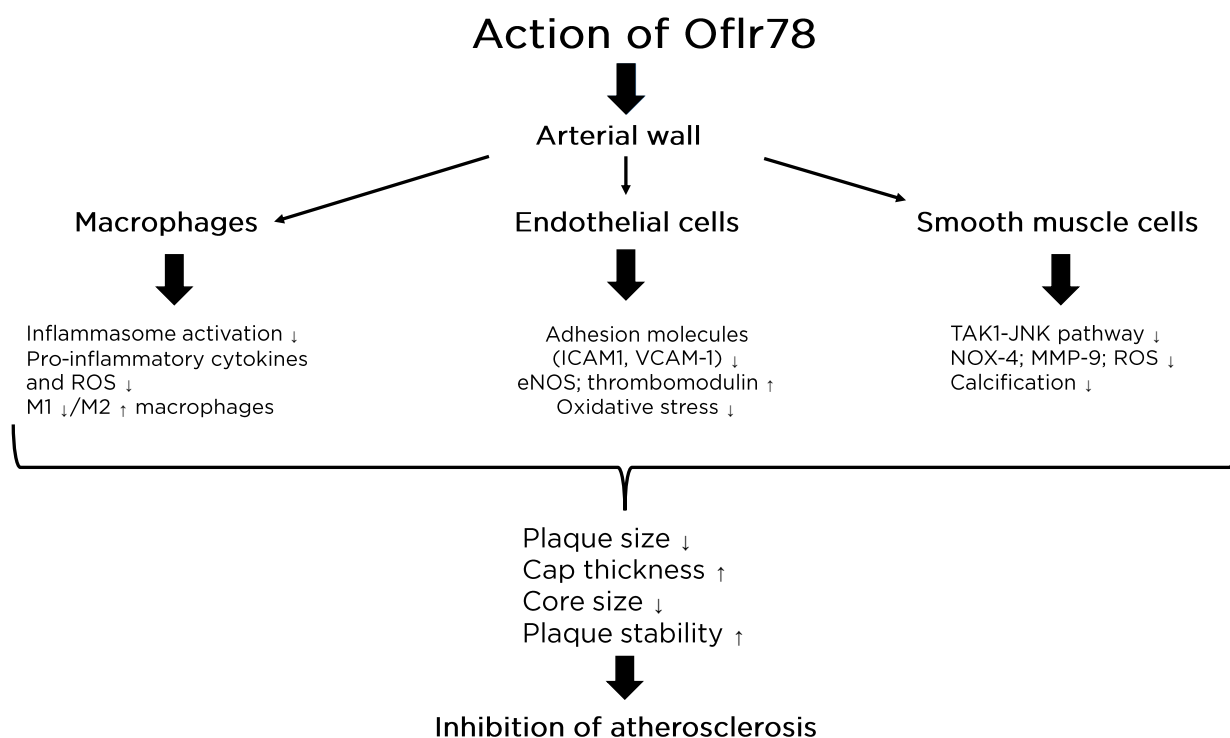
The principal functions exerted by the microbiome are metabolic, structural, and protective.

### Metabolic Function

The metabolic function principally consists of vitamin and amino acid biosynthesis, bile

acid biotransformation, and dietary fibre fermentation.<sup>4-6</sup> The most important metabolic function is the production of short-chain fatty acids (SCFA).<sup>7</sup>

SCFA activate G protein-coupled receptors (GPR) including GPR41, GPR43, and GPR109A. The binding of SCFA to their receptors, which are broadly expressed in a variety of human cells and tissues such as colonic epithelial cells, immune cells, adipocytes, hepatocytes, cardiomyocytes, and renal epithelial cells, regulates metabolic syndromes such as obesity and Type 2 diabetes<sup>8</sup> and regulates energy homeostasis, stimulating glucagon-like peptide 1 secretion and inhibiting atherosclerosis progression.<sup>9</sup> In addition, the binding to olfactory receptor 78 (Olfr78) has beneficial effects on arteriole blood pressure (Figure 1).<sup>10,11</sup> Moreover, SCFA through regulation of the immune system and cytokine production<sup>12</sup> regulate the balance between T regulatory cells (Treg) and Th17, inducing an anti-inflammatory effect. In the case of pathobiont prevalence, dysbiosis is produced and such beneficial effects on the immune system are interrupted, resulting in conditions that favour inflammatory disease.



**Figure 1: Action of Olfr78 on the vascular system.**

eNOS: endothelial nitric oxide synthase; ICAM1: intercellular adhesion molecule-1; NOX 4: NADPH oxidase; Olfr78: olfactory receptor 78; ROS: reactive oxygen substances; VCAM-1: vascular cell adhesion molecule-1.

## Structural Function

The indigenous microbiota regulates the mucus layer property of the gut, normal crypt and villi development, villi vascularisation, and tight junction regulation.

This is essential to down-regulate the back diffusion of cytokines produced in the gut. When pathobionts or pathogens such as *Escherichia coli*, *Clostridium difficile*, and *C. perfringens* prevail, a condition of dysbiosis occurs and the back diffusion of cytokines such as IL-4, IL-1 $\beta$ , TNF- $\alpha$ , and IFN- $\gamma$  is increased.<sup>13</sup>

## Protective Function

The protective function is composed of a three-layered system: a barrier fortification exerted by mucin glycoproteins that form a layer of the gut epithelia that prevents bacterial adhesion; antimicrobial peptides (AMP) secreted in normal conditions by the epithelial cells, as  $\alpha$  and  $\beta$  defensins and other substances;<sup>14,15</sup> and the possibility of activating innate and adaptive immunity. This fact is principally due to dendritic cells that take up bacteria and induce B cells to differentiate into IgA plasma cells that secrete IgA.<sup>16</sup>

In addition, the indigenous microbiota induces CD4<sup>+</sup> cells to differentiate into four main subtypes: Th1, Th2, Th17, and Treg, and contributes to normalising the ratio of these subtypes. An important role is exerted by segmental filamentous bacteria, which induce the growth and differentiation of Th17 and Th1 cells.<sup>17</sup> *Clostridia* also promote the accumulation of Tregs and the production of IL-10, which exerts anti-inflammatory effects. IL-10 and Tregs are also induced by *Bacteriodes fragilis*.<sup>18</sup>

When the indigenous microbiota is altered by any condition, pathobionts appear and dysbiosis occurs, altering the relationship between the microbiota and the immune system, leading to several diseases.

## MICROBIOTA AND BIOLOGICAL SYSTEMS

In healthy subjects, the indigenous microbiota provides several benefits to different biological systems. Indeed, the indigenous microbiota

affects the host by the production of metabolites and gut neuropeptides. As a consequence, it exerts control over many important functions such as mood, immune response, digestion, and heart rate. A bidimensional communication between the gut, its microbioma, and the nervous and neuroendocrine systems is established.<sup>19</sup> Changes in the composition of the intestinal bacterial community may result in dysbiosis, which contributes to triggering various diseases in almost all the biological systems. This imbalance of intestinal microbiota homeostasis may alter commensal bacteria and host metabolism, as well as immune function. Dysbiosis also causes an increase in intestinal permeability due to exposure to molecular patterns, leading to a chronic inflammatory process that can result in diseases in all biological systems.<sup>20</sup>

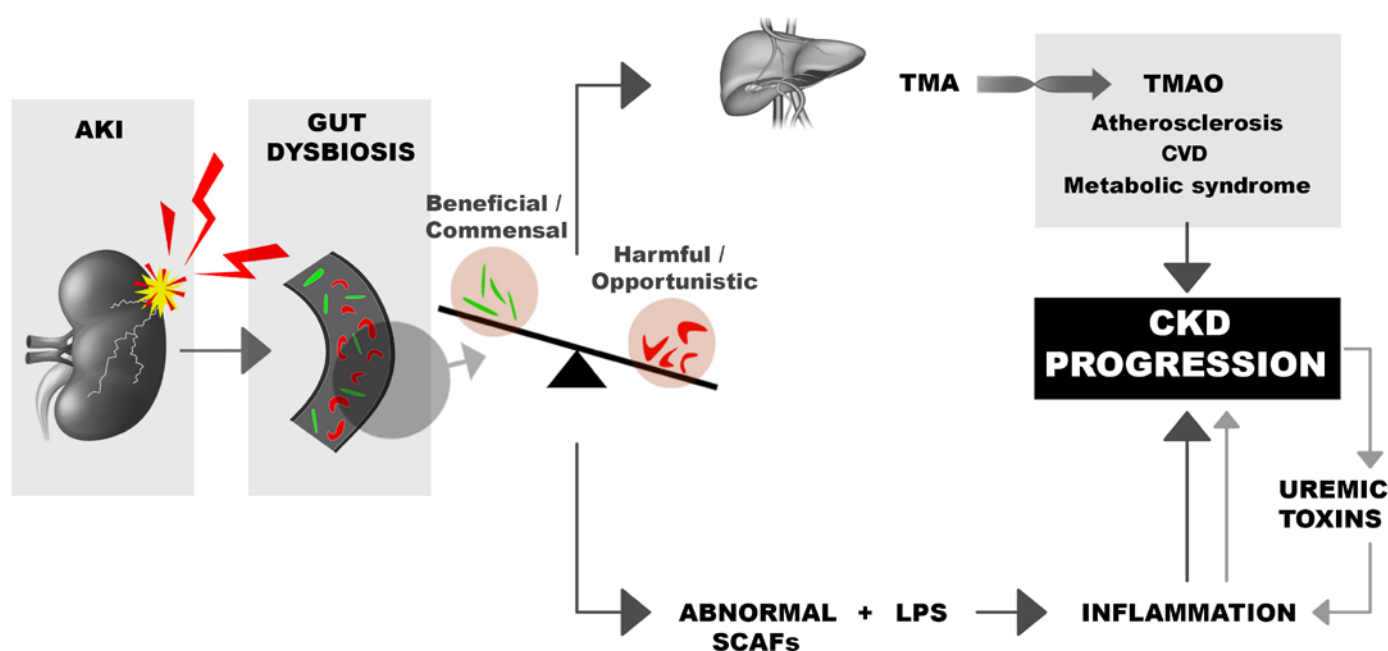
Of particular interest is the relationship between indigenous microbiota, dysbiosis, and the kidney.

## INTESTINAL MICROBIOTA AND THE KIDNEY

An inter-relationship between the gut and the kidney occurs either by the activation of the immune system or by the microbiota-derived metabolites. While the indigenous resident microbiota induces a normal balance between Treg and Th17 cells, pathobionts may activate Th17 cells and favour renal inflammation and injury.<sup>21</sup>

Similarly, microbiota-derived metabolites may affect kidney function. The protective role of SCFA has been already highlighted. In addition, SCFA have beneficial effects by reducing the production of cytokines and chemokines such as IL- $\beta$ , IL-6, TNF $\alpha$ , and monocyte chemoattractant protein.<sup>22</sup>

On the contrary, pathobionts such as *E. coli* have deleterious effects. The phenomenon is bilateral. Indeed, dysbiosis may facilitate acute kidney injury (AKI) by modifying SCFA composition and generating high quantities of toxic indoxylsulfate and trimethylamine N oxide (TMAO). This fact may favour the transition from AKI to chronic kidney disease (CKD). On the other hand, AKI may modify the gut bacterial composition (Figure 2).<sup>23</sup>



**Figure 2: Relationship between acute kidney injury, chronic kidney disease, and toxic substances.**

Dysbiosis may facilitate AKI by modifying the SCFA composition and generating high quantities of toxic indoxylsulfate and TMAO.

AKI: acute kidney injury; CKD: chronic kidney disease; CVD: cardiovascular disease; LPS: lipopolysaccharides; SCFA: short-chain fatty acids; TMA: trimethylamine; TMAO: trimethylamine N oxide.

Overall, the association of AKI and pathobionts may favour atherosclerosis, cardiovascular diseases, inflammation, and CKD progression.

Dysbiosis in patients with end-stage kidney disease (ESKD) has been observed in several studies<sup>24</sup> that found the presence of pathobionts and a huge difference between the gut microbiota composition in healthy subjects and that of patients with ESKD.

## MICROBIOTA AND RENAL TRANSPLANTATION

### Microbiota Composition, Pre-/Post-transplant Dysbiosis, and Effect on the Immune System

After kidney transplantation, gut microbiota composition further modifies, principally in the first period after transplantation. Indeed, in this period, kidney transplant patients are receiving high doses of immunosuppressants to avoid rejection and chemoprophylactic therapy to avoid infection. Both immunosuppressants

and antibiotics modify indigenous microbiota and favour the appearance of pathobionts. Other factors involved in the modification of gut microbiota after kidney transplantation are the use of proton pump inhibitors, the use of mycophenolate mofetil (MMF), and a low estimated glomerular filtration rate (eGFR). In a recent study by Swarte et al.,<sup>25</sup> faecal samples of 139 kidney transplant recipients were compared with 105 healthy controls. The aforementioned factors (immunosuppressant assumption and antibiotics) were significant determinants in the modification of gut microbiota. In a study from Lee et al.<sup>26</sup> using polymerase chain reaction in 26 kidney transplant recipients, an important change in microbiota composition was documented in samples obtained in the pre- and post-transplant period. There was a decrease in Firmicutes and an increase of Actinobacteria and Proteobacteria (Table 1). In a different study of 142 kidney transplant recipients,<sup>27</sup> pathogens such as *C. difficile* and *E. coli* were found in 30% of patients. Major changes in the microbiota composition occur in the first month post-transplant.<sup>28,29</sup>

**Table 1: Alterations in the gut microbiota following kidney transplantation, according to phylum and order.**

Phylum	Pre-transplantation cohort (%)	Post-transplantation cohort (%)
Firmicutes	91.8	87.7
Actinobacteria	2.0	7.6
Proteobacteria	0.9	4.1
Bacteroidetes	2.8	0.6
<b>Order</b>		
Clostridiales	64.8	64.3
Lactobacillales	19.1	12.0
Erysipelotriales	5.6	10.2
Bifidobacteriales	1.6	6.6
Enterobacteriales	0.4	3.9
Bacteroidales	2.8	0.6

**Table 2: Studies of post-transplant interactions between microbiota modifications and different outcomes.**

Author	Year	Patients (n)	Aim of the study	Main findings
Swarte et al. <sup>25</sup>	2020	139 KTR; 105 controls	Characterisation of pre- and post-transplant microbiota	Reduction of Firmicutes
Fricke et al. <sup>29</sup>	2014	60 KTR	Characterisation of pre- and post-transplant microbiota	Dysbiosis occurs in the first month after transplant
Lee et al. <sup>26</sup>	2014	26 KTR	Characterisation of pre- and post-transplant microbiota	Decrease of Firmicutes; Increase in Actinobacteria and Proteobacteria
Westblade et al. <sup>27</sup>	2019	142 KTR	Characterisation of pre- and post-transplant microbiota	Presence of <i>Clostridium difficile</i> and <i>Escherichia coli</i>
Wang et al. <sup>28</sup>	2015	NA	Characterisation of pre- and post-transplant microbiota	Dysbiosis occurs in the first month after transplant
<b>Dysbiosis and acute rejection incidence</b>				
Lee et al. <sup>26</sup>	2014	26 KTR	Incidence of AR	3 patients with AR had different microbiota
Fricke et al. <sup>29</sup>	2014	60 KTR	Incidence of AR	Reduction in Firmicutes in patients with late AR
Carron et al. <sup>35</sup>	2019	146 KTR	Incidence of AR	39% of AR associated with increase of inflammation biomarkers
Wang et al. <sup>36</sup>	2021	24 KTR with AMR; 29 KTR without AMR	Incidence of AMR	AMR associated with Clostridiales



Table 2 continued.

Dysbiosis and infection incidence				
Fricke et al. <sup>29</sup>	2014	60 KTR	Incidence of urinary infections	Higher incidence of UTI when Firmicutes reduced
Lee et al. <sup>26</sup>	2014	26 KTR	Incidence of UTI	Faecal abundance of <i>Enterococcus</i> associated with UTI
Lee et al. <sup>40</sup>	2019	168 KTR	Incidence of viral infection	High butyrate-producing bacteria associated with less viral infection
Dysbiosis and interstitial fibrosis				
Modena et al. <sup>42</sup>	2017	25 KTR with fibrosis; 25 KTR without fibrosis	Dysbiosis of UTI and fibrosis	Presence of pathobionts associated with fibrosis
Dysbiosis and diarrhoea				
Lee et al. <sup>26</sup>	2014	26 KTR	Incidence of diarrhoea	Diarrhoea associated with reduction of <i>Ruminococcus</i> , <i>Dorea</i> , and <i>Coprococcus</i>
Lee et al. <sup>44</sup>	2019	71 KTR	Incidence of diarrhoea	Diarrhoea associated with increase of <i>Lachnospirillum</i> , <i>E. coli</i> , and <i>Enterococcus</i>
Zhang et al. <sup>46</sup>	2021	97 KTR	Incidence of diarrhoea	Diarrhoea associated with higher faecal $\beta$ -glucuronidase activity
SCFA after kidney transplant and tolerance				
Lee et al. <sup>40</sup>	2019	168 KTR	Butyrate-producing bacteria and infection	Higher infection incidence associated with low butyrate levels
Poesen et al. <sup>51</sup>	2016	51 KTR	Uraemic toxins after transplant	Uraemic toxin levels lower after transplant
Colas et al. <sup>50</sup>	2019	113 KTR	Induction of tolerance	Presence of Proteobacteria favours tolerance
Dysbiosis and immunosuppressants				
Lee et al. <sup>53</sup>	2015	19 KTR receiving TAC	Need to increase TAC dosing	Patients with high levels of <i>Faecalibacterium prausnitzii</i> needed higher doses of TAC
Zheng et al. <sup>52</sup>	2019	260 KTR receiving TAC, treated or not with antibiotics	Need to increase TAC dosing	Patients receiving antibiotics had dysbiosis and needed higher TAC doses

**Table 2 continued.**

Gibson et al. <sup>55</sup>	2021	Review of 75 articles	Change in microbiome due to immunosuppressants	70% of the articles indicated changes in quantities of anaerobic bacteria including Ruminococcaceae, Lachnospiraceae, Firmicutes, Bacteroides, and Clostridiales
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AR: Acute rejection; AMR: antibody-mediated rejection; KTR: kidney transplant recipient; NA: not available; SCFA: short-chain fatty acids; TAC: tacrolimus; UTI: urinary tract infection.

The dysbiosis related to the imbalance between indigenous microbiota and pathobionts has relevant metabolic and clinical consequences on different post-transplant outcomes such as acute rejection, acute infection, interstitial fibrosis, post-transplant diarrhoea, reduced production of SCFA, and abnormalities in immunosuppressant levels. **Table 2** shows all the principal studies that have been conducted on post-transplant dysbiosis and its consequences.

The table clarifies the more important studies in these fields, according to the different variables taken into consideration. All the cited studies have been conducted in humans, and it is not surprising that sometimes the same study was conducted to explore different outcomes simultaneously.

## Post-transplant Dysbiosis and the Immune System

Post-transplantation complications are closely associated with the host immune system. There is also an interaction between a person's gut microbiota and immune system. Animal and human studies have shown that gut microbial population and diversity are altered after allogeneic transplantation. Moreover, when complications such as infection or rejection occur, gut microbial populations and diversity present a significant dysbiosis.<sup>28</sup> Different factors, including immunosuppression and antibiotic therapy, lifestyle, and diet may alter the microbiota and lead to dysbiosis in kidney transplant patients.

Dysbiosis disrupts gut epithelial barrier, loses barrier integrity, and leads to overgrowth of pathogens. Leaky gut and increased permeability allow translocation of bacteria and their components into the inner environment.<sup>30</sup> In this dysbiosis situation, the pro-inflammatory response triggers to eliminate pathogens by intestinal epithelial cells and IL-1, IL-6, and IL-18 secretion by dendritic cells (DC) and by macrophages that induce development of the effector CD4<sup>+</sup> T cells Th1 and Th17. The innate immune response leads to a state of systemic and allograft inflammation.<sup>31</sup> Moreover, dysbiosis decreases the regulatory T cells and increases the effector T cells that beside activated innate immunity boost adaptive immunity.<sup>32</sup> These immune responses can preserve the activation of alloreactive T cells by cross-reacting with commensal organisms and molecular mimicry, leading to graft rejection. On the other hand, in the colon and liver dysbiotic gut-derived uraemic toxins (e.g., phenols and indoles) are further metabolised to TMAO, p-cresyl sulfate (PCS), and indoxyl sulfate (IS) and leaked into the systemic circulation. Accumulation of PCS in kidney tubular cells generates reactive oxygen species (ROS) that lead to the production of inflammatory cytokines and profibrotic factors, resulting in cell injury. Moreover, through special receptors localised on the basolateral membrane of renal proximal tubular cells, IS induces inflammation and nephrotoxicity.<sup>33</sup>

The main consequences of dysbiosis in kidney transplant patients are a higher

incidence of acute rejections, acute infections, interstitial fibrosis, post-transplant diarrhoea, reduced production of protective agents such as SCFA by the gut microbiota and reduced tolerance, and modification of immunosuppressant levels in the blood.

## Dysbiosis and Acute Rejection

*In vivo* studies and research in humans have documented that post-transplant dysbiosis is associated with clinically significant complications such as graft rejection.<sup>26,34</sup> Lee et al.<sup>26</sup> performed an excellent study to clarify the alterations of gut microbiota in patients pre- and post-kidney transplant. They used the polymerase chain reaction amplification of the 16S, RNA V4-V5 variable region to analyse the bacterial composition of faecal specimens from 26 kidney transplant recipients during the first 3 months of transplantation. The study documented significant differences between the groups with and without acute rejection (AR), with Bacteroidetes being lower at the phylum level in the AR group compared to the no-AR group, while Lactobacillales, Enterococcus, Anaerofilum, and *C. tertium* were higher in the AR group at the order level.

In a recent study<sup>29</sup> the microbiota was evaluated pre- and post-transplant in 60 renal transplant recipients. Samples were obtained from urine, oral swabs, rectal swabs, and blood for up to 6 months after transplantation.

Carron et al.<sup>35</sup> found in 146 kidney transplant recipients that 39% of those experiencing AR had increased inflammation biomarkers in the blood.

The most relevant changes in the microbiota were principally observed in the first month after transplantation. Rejection episodes were correlated with a significant decrease in *Anaerotruncus*, *Coprobacillus*, and *Coprococcus* (all from phylum Firmicutes) in patients with late acute rejection, while significant changes in *Leptotrichia*, *Neisseria*, and *Actinobacteria* were observed in patients with early rejection. The study also documented that pre-transplant microbiota differences can be correlated with post-transplant events, suggesting that specific pre-transplant features of microbiota can act as diagnostic biomarkers in predicting graft outcomes.

In a very recent study, Wang et al.<sup>36</sup> characterised the gut microbiota possibly associated with antibody-mediated rejection (AMR) in 24 kidney transplant recipients with AMR. The study showed the gut microbial community of kidney transplant recipients with AMR was different from controls and that Clostridiales is a potential marker to distinguish recipients with AMR.

## Dysbiosis and Infection

Recent studies suggested that the urinary tract is characterised by a unique specific urinary microbiota, different from that of the gut. In addition to change<sup>37,38</sup> the microbiota composition may be critical for the development of urinary tract infection and differences have been observed between patients and healthy subjects.<sup>39</sup>

Change in the urinary microbiota may cause urinary infections also in transplant patients. In kidney transplant patients, in addition to change in the urinary microbiota, modifications in the gut microbiota may generate infections. Risk factors to generate dysbiosis in kidney transplant recipients are dietary patterns, changes to colonic and bowel transit time, immunosuppression, antibiotics, and lifestyle. All these factors may induce an increased bacterial translocation, an increased metabolic endotoxaemia, and an increased formation of microbial toxins.<sup>34</sup>

The aforementioned study on acute rejection<sup>29</sup> documented that similar changes in the microbiota were also associated with a higher incidence of urinary tract infections. In particular, the abundance of the genus *Anaerotruncus* (phylum Firmicutes) was markedly decreased in respect to other patients.

A high incidence of urinary and gastrointestinal infections was also reported in the studies by Lee et al.<sup>26</sup> and Chan et al.<sup>34</sup> In a different study, Lee et al.<sup>40</sup> found in 168 kidney transplant recipients that the presence of high butyrate-producing bacteria was associated with a reduced number of viral infections. In a recent study,<sup>41</sup> a transplant patient with recurrent urinary infections recovered after faecal microbiota transplantation (FMT), which induced a marked decrease in the abundance of *E. coli* in the urinary microbiota.

## Dysbiosis and Renal Fibrosis

In a recent study on transplant patients, Modena et al.<sup>42</sup> collected urinary samples from 25 patients after kidney transplantation. All of these patients developed interstitial fibrosis/tubular atrophy (IF/TA) at 6 months after transplantation at kidney biopsy. Patients were compared with 23 kidney transplant recipients who did not develop IF/TA. Patients with IF/TA had a decreased number of Lactobacillus and Streptococcus genera. The authors concluded that modification of the urinary microbiota could develop IF/TA by altering the host immune response.

## Dysbiosis and Diarrhoea

Diarrhoea frequently occurs in kidney transplant patients and its aetiology is often not recognised. With the exception of patients whose diarrhoea may be ascribed to a specific infection and the presence of pathogens, in approximately 85% of transplanted patients with diarrhoea the diagnosis is missing. Diarrhoea has been ascribed to the use of MMF, but the discontinuation of MMF is dangerous for the risk of rejection.

In the already-mentioned study by Lee et al.<sup>26</sup> of 26 kidney transplant patients affected by diarrhoea, a reduction of commensal indigenous microbiota, such as Ruminococcus, Dorea, and Coprococcus, was observed without detecting pathogens such as *C. difficile*. Similar data were found by Xiao et al.<sup>43</sup> In a more recent study in faecal specimens, Lee et al.<sup>44</sup> found a reduction in genera similar to the previous study. In addition, the authors found a significant increase in genera Lachnospirillum, *E. coli*, and Enterococcus. The genera that are reduced in the patients with diarrhoea develop in normal conditions, metabolic functions essential for the healthy condition. As a consequence, these functions are lacking during diarrhoea.<sup>45</sup> A very recent study by Zhang et al.<sup>46</sup> confirmed these data in 97 kidney transplant patients with diarrhoea. In this study, diarrhoea was associated with higher faecal  $\beta$ -glucuronidase.

The conclusion of all these studies is that gut dysbiosis, rather than the presence of pathogens or the use of MMF, represents the principal cause of post-transplant diarrhoea in the majority of patients. In addition, in several studies<sup>47</sup> FMT was effective in controlling post-transplant diarrhoea.

## Short-Chain Fatty Acids in Kidney Transplantation and Tolerance

Several studies in animals have documented the beneficial effects of SCFA produced by gut indigenous microbiota and the damage that occurs in the case of reduction of SCFA, as happens post-transplant.<sup>48,49</sup>

Lee et al.,<sup>40</sup> in a study of 168 kidney transplant recipients, documented the beneficial effects of butyrate-producing bacteria (BPG) and a higher incidence of infection in transplanted patients with low levels of butyrate. In an interesting study conducted in mice after transplantation, Wu et al.<sup>48</sup> documented a donor-specific tolerance related to high levels of Tregs induced by SCFA. In a different study,<sup>50</sup> tolerance was related to a Proteobacteria profile that included Janthinobacterium, Clostridia, and Firmicutes. The authors concluded that microbiota may favour the tolerance state that may be inhibited by the use of immunosuppressants. In another study, Poesen<sup>51</sup> documented that uraemic toxins are lower post-transplant and this could have a favourable effect on tolerance.

## Interactions Between the Microbiota and Immunosuppressive Drugs

Factors such as age, sex, race, and CYP3A5 polymorphisms influence the absorption and metabolism of calcineurin inhibitors (CNI). Recently, the indigenous microbiota or the presence of pathobionts have been documented to exert an important role in CNI metabolism.<sup>52</sup>

Lee et al.<sup>53</sup> examined the role of microbiota on CNI metabolism. In their study, the authors observed 19 patients receiving tacrolimus (TAC) as immunosuppressive treatment. There were two groups of patients: patients needing to receive increasing TAC doses to achieve the optimal blood level, and patients whose TAC levels were stable over time, with no need to adjust the dosage. By examining the microbiota, patients needing higher doses had a high level of *Faecalibacterium prausnitzii* in the gut that was the most significant factor among those influencing TAC metabolism.

In a different study, Guo et al.<sup>54</sup> found *in vitro* that *F. prausnitzii* was able to produce a TAC metabolite with less immunosuppressive activity. In the same study, the same metabolite was



found in the stool of patients treated with TAC and with high gut levels of *F. prausnitzii*. Similarly, Clostridia and Bacteroidales were also found to be able to produce inactive metabolites.

The conclusions of these studies were that different microbiota or pathobionts may influence the TAC exposure in kidney transplant patients. On one hand, the microbiota may alter the metabolism of immunosuppressants; on the other hand, immunosuppressants may alter the gut indigenous microbiota, as documented in a review by Gibson et al.<sup>55</sup> The authors reviewed 75 articles and observed that the major part of the studies indicated that immunosuppressants induce modifications in pathobionts mostly modifying anaerobic bacteria, including Firmicutes and Bacteroides.

## Microbial Therapies in Kidney Transplantation

The treatment of gut dysbiosis can be divided into probiotics, prebiotics, symbiotics, and FMT. Probiotics are defined by the World Health Organization (WHO) as live organisms that, when administered in adequate amounts, confer a health benefit to the host.<sup>56</sup> They have the characteristics to be able to survive the harsh conditions of the digestive tract, to proliferate in the lower gastrointestinal tract, to be stable, and to have a positive healthy effect in human studies.<sup>57</sup> Probiotics compete with pathogens for adhesion to the gastrointestinal epithelium, inhibit the production of bacterial toxins, and produce their own antimicrobial substances.<sup>58</sup> Plain yoghurt, cottage cheese, and vinegar are among the substances containing probiotics. Probiotics such as Lactobacilli and Streptococci have been used principally in liver transplantation,<sup>59-61</sup> documenting significant activity in reducing infection rates.

Prebiotics are defined as a non-viable food component that confers health benefits on the host associated with modulation of the microbiota. Prebiotics must be resistant to the actions of acid in the stomach, bile salts, and other enzymes in the intestines and should not be absorbed by the upper gastrointestinal tract. They act by producing SCFA, mucin, and increasing IgA production. To date, only insulin and trans-galacto-oligosaccharides may be considered probiotics.<sup>62</sup>

Symbiotics are a combination of prebiotics and probiotics. An example is the combination of *Lactobacillus rhamnosus* and insulin.<sup>63</sup>

The principal limitation of the use of these compounds is that many have been studied in animals or in human liver transplantation or in diseases different from transplantation. In addition, the tolerability of prebiotics and probiotics in the transplant population has not been adequately assessed.

FMT is a promising option for a range of disorders including transplant disorders sustained by *C. difficile*.<sup>64</sup> The efficacy of FMT in kidney transplantation is, to date, documented by case reports. Henig et al.<sup>65</sup> recently reported the efficacy of FMT in stem cell transplantation.

## FUTURE PERSPECTIVES

The two main new perspectives are the search for new therapies and an improved knowledge of gut microbiota and pathobionts. Lubiprostone, a synthetic derivative of prostaglandins, produced an improvement in the microbiota profile of a rat model.

Similarly, the trimethylamine inhibitor 3,3-dimethyl-1-1 butanol was shown to inhibit atherosclerotic lesions in mice.<sup>66</sup> An improved understanding of microbiota could be possible by the use of sequencing techniques and the application of metabolomics.

## CONCLUSIONS

In the case of kidney transplantation, microbiota and kidney transplant have a reciprocal 'double-edged sword' action. After transplantation, because of the immunosuppressive drugs and of prophylactic antibiotics, the gut indigenous profile modifies, particularly in the first month after transplantation. This modification may influence the graft outcomes, causing acute rejection, infection, renal fibrosis, and modification of the drug metabolism, immunosuppressants included. It is possible to modify an abnormal microbiota with the use of prebiotics, probiotics, and diet modification. It should be highlighted that there are few studies referring to the microbiota in renal transplantation and they refer to a small number

of patients, often in retrospective studies. In addition, many of these studies have been conducted on animals. Because of this fact, the microbiota in general, and in solid organ transplantation in particular, may be considered a new frontier in medical studies.

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# Pathogenesis and Treatment of Refractory Oedema in Nephrotic Syndrome

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## Abstract

Oedema is a hallmark feature of nephrotic syndrome (NS) and can cause significant patient morbidity. The pathogenesis of oedema formation is complex and results from abnormalities in sodium retention, inter-play of neurohormonal factors, and changes in capillary filtration barrier. Salt retention is often primary ('overfill' theory) because of increased sodium-potassium adenosine triphosphatase activity in the collecting duct cells, increased direct epithelial sodium channel activation (ENaC) by urinary proteases (independent of aldosterone), and an overall increased effective arterial blood volume. However, a subset of patients with NS, especially children, demonstrate decreased effective arterial blood volume ('underfill' theory) and secondary sodium retention as the primary mechanism of oedema formation. Increased capillary permeability and vascular inflammation contributes as well. Loop diuretics with or without salt-poor albumin are the mainstay of therapy in adults, although no large clinical trials exist to guide diuretic choice or dosage. Combination diuretic therapy is recommended to achieve multi-site nephron blockade and overcome diuretic resistance, which is a frequent challenge. Use of direct ENaC inhibitors (amiloride) in combination with loop diuretics may be especially beneficial given the primary role of ENaC in sodium retention. Aquaretics such as vasopressin receptor antagonists may have a role in treatment as well. Well-designed clinical trials are essential to guide therapy of refractory oedema in NS. In this review, the authors discuss the pathogenesis of oedema formation in patients with NS and propose a treatment algorithm for management of resistant oedema based on the limited available evidence.

## INTRODUCTION

Nephrotic syndrome (NS) is characterised by hypoalbuminaemia, heavy proteinuria (>3.5 g/day in adults and urinary protein to creatinine ratio  $\geq 2$  mg/mg in children), hyperlipidaemia, and oedema and indicates glomerular pathology. The cause of NS can be idiopathic or secondary

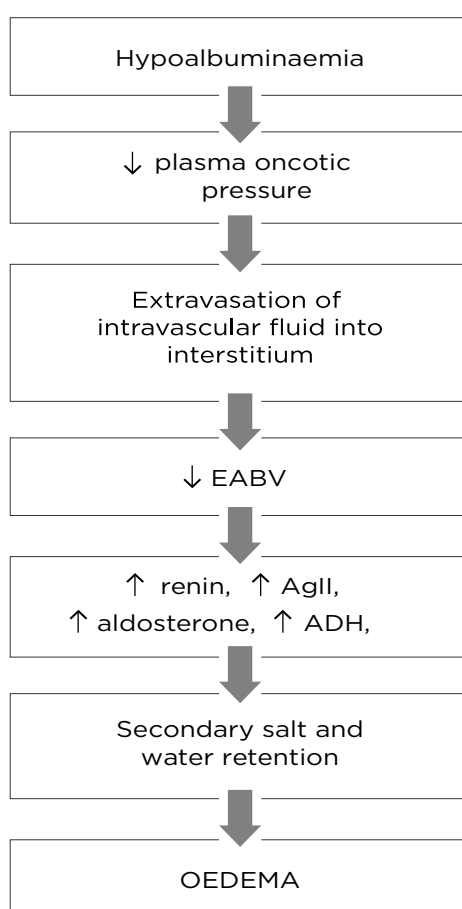
to other disorders, and specific treatment is determined by histopathology and underlying aetiology. Interstitial oedema (and in its severest form, anasarca) is a hallmark feature of NS and results in significant patient morbidity, restricted mobility, discomfort, and increased risk of skin and soft tissue infections. Some patients may accumulate up to 30% of extra body weight.<sup>1</sup> Oedema results from abnormal sodium ( $\text{Na}^+$ )



retention, inter-play of neurohormonal factors, and changes in capillary filtration barrier. Understanding of the pathophysiology of oedema formation in NS has evolved over the years, from the initial ‘underfill’ and subsequent ‘overfill’ theory to recent insights into the role of vascular hyperpermeability and direct epithelial Na channel (ENaC) activation. Treatment of oedema can be challenging because of multiple contributing factors, variability in volume status, and issues with diuretic resistance. Diuretics are frequently necessary for treatment of severe oedema; however, data guiding oedema treatment remains limited and unsupported by large clinical trials. In this review, the authors aim to highlight important theories pertaining to the pathophysiology of oedema formation in patients with NS and treatment strategies for associated refractory oedema.

## THE UNDERFILL THEORY OF OEDEMA FORMATION: SECONDARY SALT RETENTION

The ‘underfill’ theory (Figure 1) provides one of the earliest explanations of oedema formation in patients with heavy albuminuria and proposes that, despite the presence of oedema, patients with NS are in fact volume depleted.<sup>2,3</sup> It suggests that decreased plasma oncotic pressure due to hypoalbuminaemia alters capillary Starling forces, resulting in extravasation of intravascular fluid into the interstitial space and a decrease in effective arterial blood volume (EABV).<sup>1</sup> In an attempt to restore EABV, there is compensatory activation of the renin-angiotensin-aldosterone system (RAAS) and other neurohormonal responses (e.g., anti-diuretic hormone [ADH], angiotensin II [AgII]) leading to secondary Na<sup>+</sup> and water retention and oedema formation.



**Figure 1: The pathophysiology of oedema formation according to the ‘underfill’ theory.**

ADH: anti-diuretic hormone; AgII: angiotensin II; EABV: effective arterial blood volume."

There are several studies that support the underfill theory. Adult patients with NS with severe hypoalbuminaemia (<1.7 g/dL) have been shown to have evidence of low EABV (low atrial natriuretic peptide [ANP], elevated AgII, and plasma renin activity [PRA], with increased proximal tubular Na<sup>+</sup> reabsorption) compared to those with serum albumin >1.7 g/dL. This suggests that severity of hypoalbuminaemia correlates with hypovolaemia and upregulation of compensatory Na<sup>+</sup> retaining mechanisms, which is reversed by volume expansion.<sup>4</sup> Elevated serum ADH, high PRA, impaired free water excretion, and hyponatraemia are also noted in patients with NS.<sup>5</sup> Several other studies<sup>6,7</sup> provide evidence that hypovolaemia triggers neurohormonal changes (increased RAAS, ADH, and AgII), resulting in secondary Na<sup>+</sup> and water retention in NS. The specific role of aldosterone in facilitating Na<sup>+</sup> retention in NS was highlighted in a study of 5 patients with NS and 6 controls given a high-salt diet for 8 days. After 4 days of high salt intake, the control group was able to maintain salt balance while the nephrotic group demonstrated positive Na<sup>+</sup> balance. Spironolactone was administered on Day 5. After 72 and 96 hours of spironolactone initiation, patients with NS exhibited a significant increase in natriuresis (205±20 versus 312±13 mEq/day; p<0.005) compared to control subjects, suggesting that aldosterone contributes to salt retention in NS.<sup>8</sup>

## CONTROVERSIES AROUND THE UNDERFILL THEORY

Although the underfill theory provides a plausible conceptual framework for oedema formation in NS and is backed by observational data demonstrating hypovolaemia as an initial precipitant, several other studies have found contrary evidence of expanded EABV and suppressed RAAS in patients with NS, raising concerns about the validity of the underfill theory.<sup>9</sup> The role of hypoalbuminaemia as a trigger has also been questioned.<sup>10</sup>

A key study in paediatric patients described the heterogenous clinical presentation in NS with regards to volume and neurohormonal status.<sup>11</sup> The authors evaluated paediatric patients with a history of steroid-responsive NS, who showed signs of relapse detected by home urine dipstick

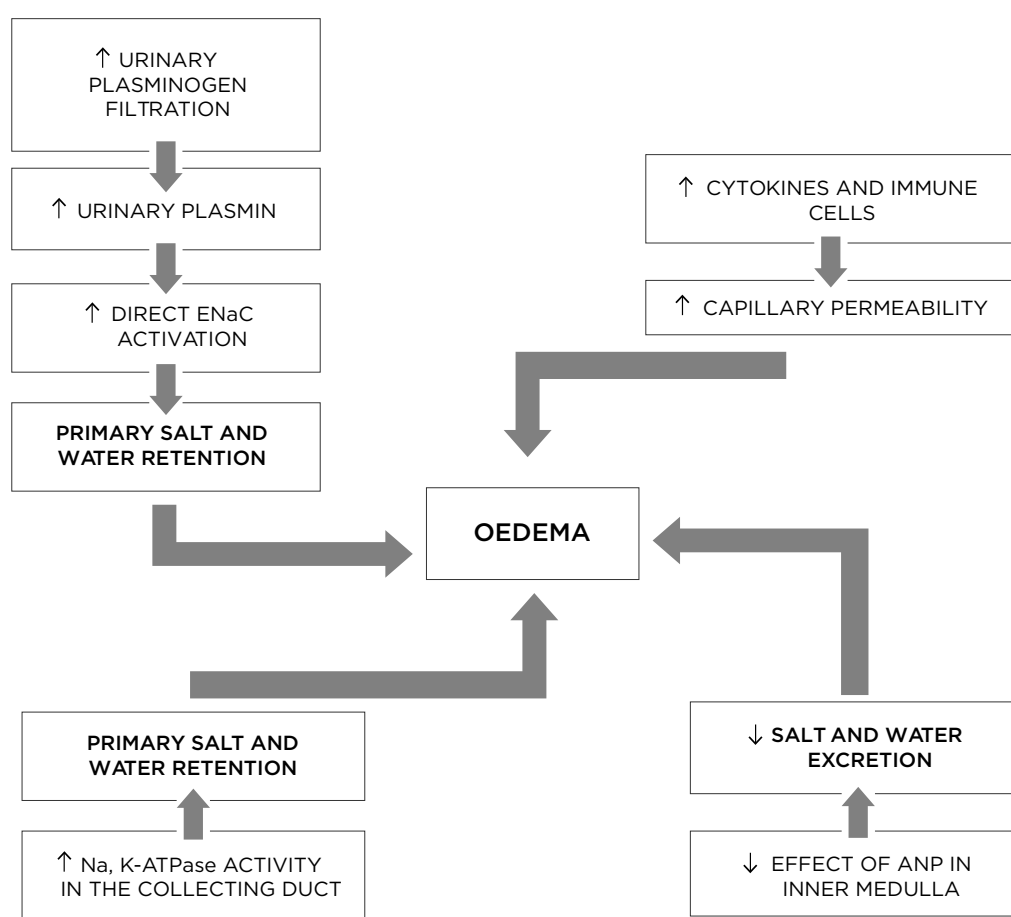
screen, and divided them into three groups based on clinical presentation: proteinuric patients without hypoalbuminaemia; patients with severe hypoalbuminaemia, oedema, and hypovolaemia (high plasma renin, aldosterone, and serum norepinephrine; low ANP and estimated glomerular filtration rate); and patients with severe hypoalbuminaemia and oedema similar to the previous group but without biochemical or clinical evidence of hypovolaemia. Interestingly, the first group demonstrated oedema and slightly increased aldosterone levels despite normal serum protein levels and lack of hypovolaemia. This study not only highlights the variability in clinical features, EABV, and neurohormonal responses in oedematous patients with NS, but was also one of the first studies to suggest that salt retention may precede overt hypoalbuminaemia, questioning the underfill theory. Several studies confirm that a significant number of patients with NS are in fact volume expanded.<sup>12,13</sup> Geers et al.<sup>12</sup> used <sup>131</sup>I-albumin to determine plasma volume and calculated blood volume in 88 adult patients with NS and found that both were either normal or slightly elevated. Another study using <sup>131</sup>I-albumin in adult oedematous patients with NS showed that at least two-thirds had either normal or elevated blood volume compared to healthy controls.<sup>13</sup> Furthermore, studies employing blockade of the RAAS axis using angiotensin-converting enzyme inhibition were unable to demonstrate increased natriuresis in adults with NS, questioning the role of RAAS in oedema formation.<sup>14</sup>

The central role of hypoalbuminaemia in oedema formation has also been questioned.<sup>10</sup> Patients with congenital defects of albumin synthesis do not develop overt oedema despite analbuminaemia.<sup>15</sup> Nagase analbuminaemic rats are able to maintain transcapillary oncotic pressure without signs of abnormal volume regulation.<sup>16</sup> A study looking at 62 patients with NS found no correlation between serum albumin levels and blood volume or PRA.<sup>17</sup> There is evidence that patients with NS are in fact able to regulate their plasma volume fairly well despite hypoproteinaemia. Koomans et al.<sup>18</sup> showed that patients with NS with normal renal function were able to maintain normal intravascular blood volume, even at significantly expanded extracellular fluid volumes. The lack of oedema despite modest hypoalbuminaemia

is explained by the parallel drop in interstitial albumin concentration and thus interstitial oncotic pressure, with slight increase in interstitial hydrostatic pressure, counteracting oedema formation. This occurs due to an increase in lymphatic drainage.<sup>19,20</sup> Furthermore, correction of hypoalbuminaemia via an albumin infusion is insufficient to stimulate natriuresis and correct oedema. Studies in paediatric patients demonstrate diuresis and improvement in oedema with initiation of steroid therapy, even before the resolution of hypoalbuminaemia, suggesting that factors beyond serum albumin levels determine oedema formation in NS.<sup>21</sup>

## THEORY OF PRIMARY SALT RETENTION: THE OVERFILLING THEORY

The ‘overfill’ theory (Figure 2) describes Na<sup>+</sup> retention and expanded EABV as the primary process in oedema formation (and not secondary to hypovolaemia), with onset well before the development of severe proteinuria and hypoalbuminaemia. This model is supported by evidence that a significant subset of patients with NS are volume expanded with suppressed RAAS, as discussed above.



**Figure 2: The pathophysiology of oedema formation according to the ‘overfill’ theory.**

ANP: atrial natriuretic peptide; ENaC: epithelial sodium channel; Na,K-ATPase: sodium-potassium adenosine triphosphatase.

Current understanding of the site and mechanism of Na<sup>+</sup> retention in NS is derived from experimental animal models of disease. The puromycin amino-nucleoside (PAN) rat model of minimal change disease demonstrated that, after a single injection of PAN, these animals developed Na<sup>+</sup> retention and massive proteinuria 2–3 days and 4–5 days later, respectively.<sup>22</sup> Using micro-puncture techniques in a rat model of unilateral PAN NS, the aldosterone-responsive connecting tubule and the cortical collecting duct (CCD) were isolated as the primary sites of Na<sup>+</sup> retention.<sup>23,24</sup> However, the role of aldosterone itself in mediating salt retention in PAN nephrotic animals and NS is questionable. In the unilateral PAN nephrotic model, Na<sup>+</sup> retention was abolished by amiloride but not by aldosterone receptor blockade, indicating that transepithelial Na<sup>+</sup> absorption was independent of aldosterone.<sup>24</sup> In another study, bilateral adrenalectomised PAN nephrotic rats received supplemental infusion of physiologic aldosterone and glucocorticoid.<sup>25</sup> Despite the inability to increase aldosterone production, these animals demonstrated Na<sup>+</sup> retention and volume expansion similar to those with intact adrenals. The primary mechanism was described to be an increase in activity of the basolateral sodium-potassium adenosine triphosphatase (Na<sup>+</sup>,K<sup>+</sup> ATPase) channels in the principal cells of the CCD, due to increased transcriptional induction of the  $\alpha$  and  $\beta$  subunits and insertion of new Na<sup>+</sup>,K<sup>+</sup>-ATPase pumps. Additionally, increased ENaC activity was seen, which was attributed to aldosterone-induced mobilisation of pre-existing pool of sequestered intracellular channels to the apical membrane of the principal cells rather than an increase in transcription. The study concluded that the induction of Na<sup>+</sup>,K<sup>+</sup>-ATPase channels in the CCD is independent of aldosterone and is a robust process that drives ENaC-mediated Na<sup>+</sup> retention in PAN nephrotic rats.<sup>25</sup>

Recent data suggest that proteinuria itself may drive primary salt retention via direct ENaC activation, independent of systemic volume or hormonal triggers. Proteolysis of the ENaC  $\alpha$  and  $\gamma$  subunits via proteases (such as plasmin, trypsin, kallikrein, channel-activating proteases etc.) is an important physiologic mechanism of ENaC activation. Normal urine contains small amounts of proteases; however, there is a substantial increase in their filtered load in nephrotic urine.<sup>25–27</sup>

Inappropriate ENaC activation by proteases can result in pathologic salt retention and oedema in NS.<sup>26</sup> There is reasonable evidence that filtered inactive plasminogen in nephrotic urine is converted to plasmin by tubular urokinase-type plasminogen activator.<sup>26</sup> Activated plasmin further mediates proteolysis of the  $\gamma$ -subunit of ENaC, resulting in its activation. Several studies confirm the role of proteolytic ENaC activation in pathogenesis of salt retention. Urine from nephrotic humans and animals has been found to activate ENaC currents *in vitro*.<sup>27</sup> Pharmacologic inhibition of urinary protease using aprotinin in nephrotic animals prevented volume retention by inhibiting proteolytic ENaC activation.<sup>28</sup> A recent study in 203 adult patients with NS identified urinary plasminogen-plasmin to creatinine ratio as an independent risk factor for oedema formation, and a post-treatment decrease in the ratio as an independent predictor of oedema remission, supporting the role of plasmin-dependent ENaC activation as an important mechanism of salt retention.<sup>29</sup> Amiloride, an ENaC blocker, has been shown to ameliorate salt retention and improve natriuresis in various animal and human studies of NS.<sup>28,30,31</sup> Interestingly, its effectiveness extends beyond just ENaC blockade. In a podocin gene knockout mouse model of NS, intraperitoneal administration of amiloride was associated with a reversible and significant decline in conversion of urinary plasminogen to active plasmin.<sup>30</sup> Amiloride treatment is associated with decreased urine urokinase-type plasminogen activator activity.<sup>30,31</sup> Thus, amiloride may attenuate Na<sup>+</sup> retention in NS by several mechanisms.

Several endocrine and paracrine regulators of Na<sup>+</sup> excretion have been evaluated in NS. ADH,<sup>32</sup> insulin-like growth factor-1,<sup>33,34</sup> TNF- $\alpha$ ,<sup>35</sup> thiazolidinedione agonists of peroxisome proliferator-activated receptor  $\gamma$ ,<sup>36</sup> AgII,<sup>37</sup> and nitric oxide<sup>38</sup> have all been shown to enhance Na<sup>+</sup> retention independent of aldosterone. However, in the PAN nephrotic model, blocking the activity of each of these factors, except AgII, did not show any improvement in natriuresis. Interestingly, increased natriuresis was observed in patients with NS treated with irbesartan for angiotensin-1 receptor blockade but Na<sup>+</sup> excretion was modest and short-lasting.<sup>1</sup> Perhaps the aldosterone-independent effect of AgII is responsible for the ENaC-mediated Na<sup>+</sup> retention only to a limited extent. In addition, patients with



NS may have increased sympathetic activity and elevated ADH and ANP levels but decreased responsiveness to their diuretic and natriuretic effects, respectively.<sup>39,40</sup> In a rat model, renal sympathetic denervation improved excretion of infused normal saline as well as response to ANP infusion.<sup>40</sup> Additionally, Rodríguez-Iturbe B et al. postulated that nephrotic conditions with increased inflammatory infiltrate were more likely to develop Na<sup>+</sup> retention. Conversely, children with minimal change disease and no interstitial infiltrate are less likely to have Na<sup>+</sup> retention and more likely to belong to the cohort of patients with hypovolaemia, suggesting the role of paracrine inflammatory mediators in Na<sup>+</sup> retention.<sup>41</sup>

## INCREASED VASCULAR PERMEABILITY

In addition to primary Na<sup>+</sup> retention, there is reasonable evidence that patients with primary nephrotic glomerulopathies have capillary hyperpermeability, which contributes to the development of interstitial oedema. Rostoker et al.<sup>42</sup> found significantly high capillary permeability (measured using technetium-labelled albumin) in patients with NS and those with idiopathic cyclic oedema (a condition of abnormal vascular permeability) compared to healthy controls. Interestingly, vascular hyperpermeability improved after treatment with steroids in those with minimal change disease. The proposed mechanism of vascular hyperpermeability was the likely presence of a vascular permeability factor released by local immune cells, although this has not been definitively identified yet.

## TREATMENT OF NEPHROTIC OEDEMA

Oedema treatment in NS should be tailored to the individual patient depending on the more dominant underlying pathophysiology (overfill versus underfill). In the overfilled state, diuretics are the mainstay of therapy.<sup>44</sup> Despite the presence of interstitial oedema, patients with underfill pathophysiology and low EABV may require initial volume expansion with salt-poor albumin prior to initiating diuretics to minimise diuretic-induced pre-renal acute kidney injury. Therefore, an important initial step in the management of oedema in NS is a determination of EABV using supportive clinical parameters

such as orthostatic hypotension, pulse rate, haematocrit, PRA, serum aldosterone, capillary refill time, urine output, blood urea nitrogen-creatinine ratio, and urinary electrolytes.<sup>45</sup> In paediatric patients with NS, a fractional excretion (Na<sup>+</sup>) <0.5 and ratio of Urine (K<sup>+</sup>) to the sum of Urine (Na<sup>+</sup>) and Urine (K<sup>+</sup>) >0.6 may suggest hypovolaemia.<sup>46,47</sup> In addition, cardiothoracic index in children (determined by a chest X-ray) or echocardiographic parameters (inferior vena cava index, inferior vena cava collapsibility index, and left atrium diameter) can be helpful.<sup>48</sup> These physical and biochemical parameters are not specific to NS but may provide supportive clues to the underlying volume status.

## GENERAL MEASURES

Dietary salt restriction (<35mg Na<sup>+</sup>/kg/day), use of compression stockings, adequate nutrition, limb elevation, and avoidance of non-steroidal anti-inflammatory drugs are important general measures to treat oedema in NS.

Non-steroidal anti-inflammatory drug-induced intrarenal prostaglandin inhibition leads to Na<sup>+</sup> and water retention and a decrease in afferent arteriolar dilation, leading to worsening hypervolaemia and reduction in glomerular filtration rate, respectively. Patients with NS are particularly sensitive to these deleterious effects.<sup>49</sup> In children with mild, asymptomatic oedema, conservative management with fluid restriction to two-thirds of maintenance and salt restriction is often enough, especially when dealing with steroid-sensitive NS which responds within 4–8 days after initiation of steroids.<sup>50</sup>

## DIURETIC THERAPY

Diuretics are often necessary for treatment of oedema in adults with NS, either alone or with salt-poor albumin. In the paediatric population, diuretic use is reserved for patients with moderate and severe oedema (defined by weight gain of 7–10% or >10%, respectively), those with life-threatening complications such as massive pleural effusions, pulmonary oedema, or cases of steroid-resistant NS with close monitoring for diuretic-induced hypovolaemia.<sup>51</sup> Judicious use of diuretics is recommended after confirmation of volume status as the use of diuretics in the

underfilled cohort raises risk of hypovolaemic shock and thrombotic events.

Unfortunately, there are no established guidelines to help determine optimal diuretic class or dosage in patients with NS and there is significant heterogeneity in management. Based on the limited data available, the authors propose a treatment algorithm (Figure 3).

Loop diuretics are the initial diuretic of choice in NS. They block  $\text{Na}^+\text{-K}^+2\text{Cl}^-$  co-transporter in the thick ascending loop of Henle, where 25% of filtered  $\text{Na}^+$  is absorbed, making them potent diuretics. However, diuretic resistance is not uncommon. Intestinal oedema can decrease oral bioavailability of diuretics. Furosemide has lower oral bioavailability; therefore, bumetanide or torsemide might be preferable.<sup>44</sup> Chronic loop diuretic use results in increased  $\text{Na}^+$  delivery to the distal nephron segments, resulting in significant  $\text{Na}^+$  absorption via ENaC. Distal nephron hypertrophy seen with prolonged diuretic therapy further enhances distal nephron  $\text{Na}^+$  absorption and failure of loop diuretic therapy.<sup>52</sup> It is therefore recommended to attempt nephron blockade using a combination of diuretics acting at multiple nephron sites to maximise natriuresis and aquaresis. For example, a thiazide diuretic (inhibiting  $\text{Na-Cl}$  co-transporter in the distal convoluted tubule), direct ENaC inhibitors (amiloride), or mineralocorticoid antagonists (spironolactone) can be used in combination with a loop diuretic.

Amiloride may be particularly effective in NS due to the primary role of direct ENaC activation in oedema generation, as discussed above. Despite data regarding efficacy of amiloride in mouse models of NS and small human studies, it has not been studied in large clinical trials. In clinical practice, it is not used as a stand-alone diuretic therapy but is promising as an adjunct to loop diuretics.<sup>53,54</sup> Other ENaC blockers such as triamterene have also been used successfully in combination with loop diuretics.<sup>44</sup> Hyperkalaemia may be a limiting factor to the use of amiloride, especially in patients with diabetes and those with a low estimated glomerular filtration rate.

A small study (N=20) of patients with NS and refractory oedema demonstrated the benefit of acetazolamide and hydrochlorothiazide followed by furosemide therapy. This combination of

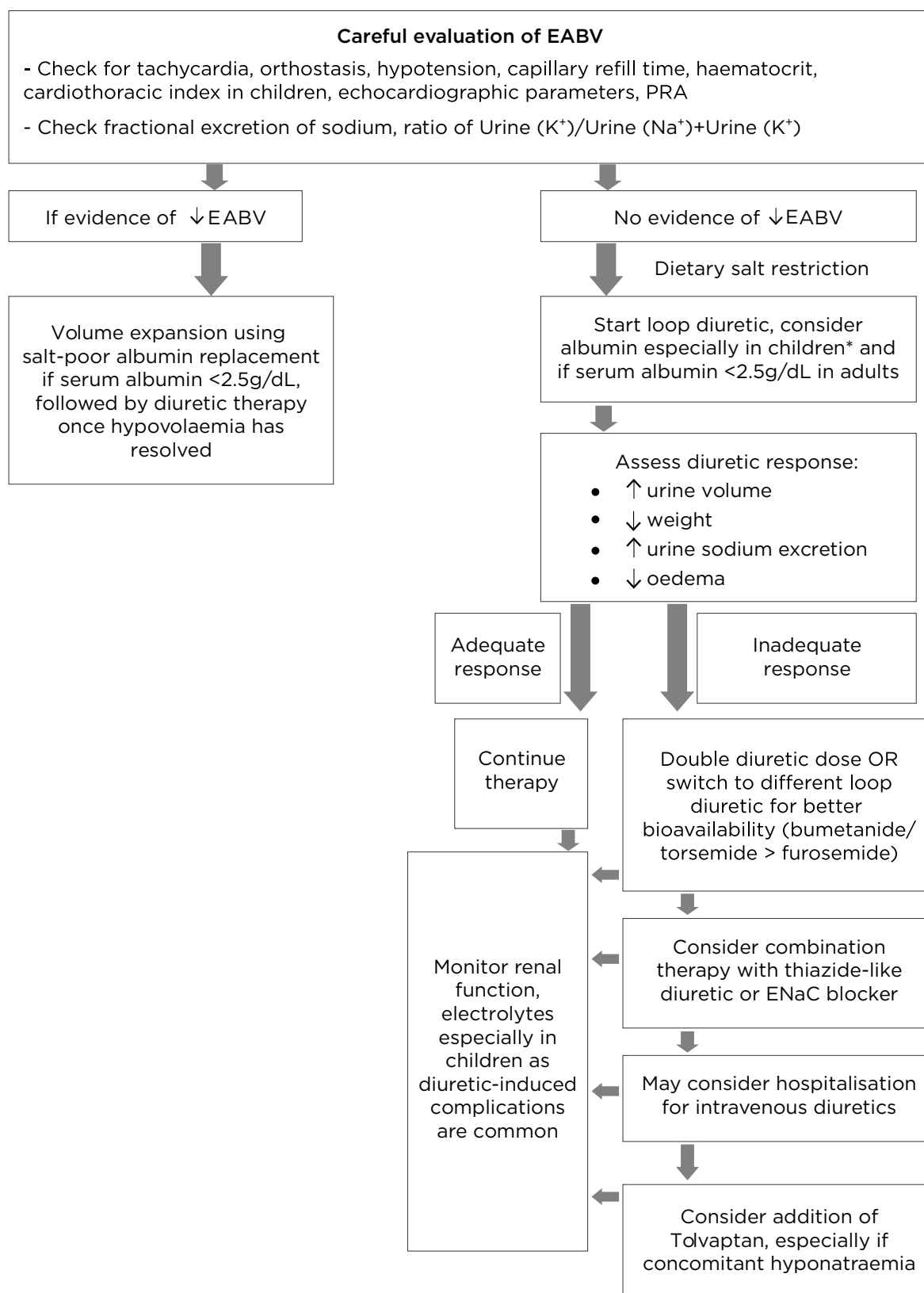
diuretic therapy significantly increased 24-hour urine volume and decreased weight compared to the control group, who received furosemide and hydrochlorothiazide followed by furosemide alone. The study hypothesised that concomitant blockade of pendrin, a  $\text{Cl}^-\text{-HCO}_3^-$  exchanger in the intercalated cell of the collecting duct, by acetazolamide further potentiated the diuretic effects of thiazide and furosemide.<sup>55</sup>

It should be emphasised that diuretic use in NS requires close monitoring for acute kidney injury and electrolyte derangements, especially given variability in EABV, especially in children.

### ALBUMIN COMBINED WITH DIURETIC THERAPY

There are two proposed benefits of using salt-poor albumin infusion with diuretic therapy in NS. Firstly, it may be required in oedematous patients with evidence of low EABV for the purposes of volume expansion prior to diuretic therapy. Secondly, it may be useful in combating diuretic resistance seen with severe hypoalbuminaemia. Loop diuretics are highly protein-bound and hypoalbuminaemia impairs delivery to their site of action, resulting in sub-optimal effectiveness. A small study (N=13) of NS with refractory oedema and diuretic resistance despite high doses of combination furosemide and spironolactone therapy showed that infusion of salt-poor albumin produced a prompt diuresis and weight loss.<sup>56</sup> A cross-over study of 16 paediatric patients with refractory oedema, who were treated with furosemide and albumin versus diuretic alone, demonstrated greater weight loss and urine volume in those receiving albumin and furosemide, although there was no significant difference in  $\text{Na}^+$  excretion.<sup>57</sup> Unfortunately, the data demonstrating benefit of albumin are weak and subsequent data have shown minimal efficacy.<sup>58-60</sup> A recent Cochrane review determined that there was poor quality of published evidence to reach any definitive conclusions regarding the benefit of albumin in NS.<sup>61</sup>

Albumin may have an important role in paediatric NS and is often used in conjunction with diuretics in patients with severe oedema unresponsive to steroids. Excessive use can result in volume overload, and close monitoring for



**Figure 3: Proposed algorithm for the management of severe refractory oedema.**

Fractional excretion of sodium  $<0.5\%$ ; Urine ( $K^+$ )/Urine ( $Na^+$ )+(K $^+$ )  $<0.6$  indicate hypovolaemia.

\*In paediatric NS, diuretics are typically indicated in steroid-resistant nephrotic syndrome or severe symptomatic oedema.

EABV: effective arterial blood volume; ENaC: epithelial sodium channel; NS: nephrotic syndrome; PRA: plasma renin activity.

worsening hypertension and pulmonary oedema is recommended.<sup>51</sup>

## AQUARETICS

Tolvaptan, a vasopressin receptor antagonist, reduces the density of luminal aquaporins in the principal cells of the collecting duct to increase water excretion (aquaresis) but not salt excretion. The use of tolvaptan has been described in patients with congestive heart failure and cirrhosis.<sup>62</sup> More recently, case reports and small case series have shown benefit in combination with loop diuretics (increased urine output and decrease in oedema) in paediatric patients with NS, and may be especially useful in those with hyponatraemia.<sup>63-65</sup> There are no clinical trials to confirm the benefit and there is risk of worsening hypernatraemia with its use. Other aquaretics, such as somatostatin analogues and urea channel inhibitors, may have a theoretical benefit, but are lacking data.<sup>45</sup>

## CONCLUSION

Our understanding of the pathophysiology of oedema in NS has evolved over the last several years with newer insights into the roles of urinary plasmin, aldosterone independent ENaC activation, vascular hyperpermeability, paracrine factors, and interstitial inflammation in primary Na<sup>+</sup> retention. While the underfill theory of hypoalbuminaemia-induced volume depletion and secondary RAAS activation applies to a subset of patients, especially children, the majority of the adult cohort is noted to be volume expanded in the setting of primary renal Na<sup>+</sup> retention due to intra-renal factors. Management of oedema in patients with NS is a major challenge for clinicians due to significant clinical and biochemical heterogeneity, difficulty in assessing EABV, multifactorial aetiology, and issues around diuretic resistance. Well-designed clinical trials are needed to guide treatment, diuretic choice, and drug dosing, as well as to assess the benefit of albumin, direct ENaC blockers, and vasopressin antagonists in the treatment of oedema related to NS.

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