

INUS Neuro-Urology News

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From the Editor: Year in Review



Glenn Werneburg, MD, PhD (USA)
Editor, Neuro-Urology News

 @gwerneburg

This issue concludes the first year of Neuro-Urology News. It has been my great pleasure to serve as Editor for this publication. The publication has been distributed to more than 500 individuals in 32+ nations (see map, below). In the five issues of 2022 we have highlighted some of the most important updates in the field of Neuro-Urology. We have interviewed **Dr. Thomas Kessler** on the use of bacteriophages for urinary tract infection treatment, **Dr. Rose Khavari** on transcranial neuromodulation in voiding dysfunction, **Dr. J. Todd Purves** and **Dr. Monty Hughes** on NLRP3 in bladder dysfunction, **Dr. Evgeniy Kreydin** on transcutaneous electrical spinal cord neuromodulation, and this month, Dr. Limin Liao on intravesical electrical stimulation in underactive bladder. We have highlighted several of our board members. This year at the INUS Congress, a new contingent of executive board members has been elected: INUS President

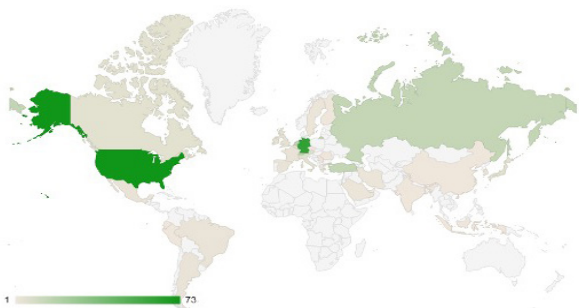
Dr. Thomas Kessler, Vice-President
Dr. Blayne Welk, Treasurer
Dr. Márcio Averbeck, and Secretary
Dr. Stefania Musco. This month, we continue to introduce board members starting with Interdisciplinary Officer **Dr. Jalesh Panicker**, Professor of Neurology and Uro-Neurology at University College London. The publication has been well-received, with many positive comments from readers globally. While we are happy to reach hundreds of individuals with each issue, we believe that there are many others who would benefit from receiving this publication. We ask our readers to share this publication with their colleagues and encourage their subscription to Neuro-Urology News, which will remain available free of charge. As we approach the start of 2023, we look forward to continuing to provide the latest news in Neuro-Urology for INUS members and all those around the world with neurourological interest.

INUS Calendar

**Society for Urodynamics,
Female Pelvic Medicine
and Urogenital Recon-
struction Annual Meeting**
Nashville, United States
March 7-11, 2023

**INUS Annual Congress
2023**
Athens, Greece
June 8-10, 2023

ICS 2023
Toronto, Canada
September 27-29, 2023



Map of the Neuro-Urology News readership. The predominant nations of readership in 2022 were United States, Germany, Switzerland, The Netherlands, and Turkey.

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Meet the Board Member

Jalesh Panicker, MBBS, MD, DM, MRCP (UK)

Professor of Neurology and Uro-Neurology at University College London

Jalesh N. Panicker is a neurologist specialising in Uro-Neurology, and is Professor of Neurology and Uro-Neurology at University College London (UCL) and Clinical Lead in the Department of Uro-Neurology at The National Hospital for Neurology and Neurosurgery, Queen Square, under University College London Hospitals NHS Foundation Trust.

Dr. Panicker developed a clinical and academic interest in Uro-Neurology after recognizing the limited opportunities that neurological patients have for the assessment and treatment of their neurogenic urinary, sexual and bowel problems. His clinical interest spans voiding dysfunction in young women, characterisation of pelvic somatic and visceral dysfunction in neuroinflammatory, neurodegenerative and neurogenetic disorders, and developing non-invasive therapeutic options for managing neurogenic urinary incontinence. He has developed multidisciplinary care pathways among Urology, Neurology and Gastroenterology that also involve Pelvic Floor Physiotherapy and Psychology. Despite the challenges of being a full-time clinician on the NHS, Dr. Panicker has established a robust research program with external funding, exploring multimodal techniques to evaluate the lower spinal cord and its role in the control of pelvic functions. He leads a multi-site collaborative project to establish novel non-invasive neurophysiology techniques for the evaluation of pelvic sensory and motor innervation. His team has been phenotyping pelvic visceral and somatic dysfunction in patients presenting with unexplained urogenital symptoms. Dr. Panicker has been involved in developing an MRI sequence imaging the lumbosacral spinal cord to understand spinal correlates to urogenital dysfunction and applications in neurolog-

ical disorders. He has led numerous projects evaluating innovative treatments for managing LUTS in neurological disorders including transcutaneous and percutaneous tibial nerve stimulation, melatonin for treating nocturia in Parkinson's disease, transperineal botulinum toxin injections for treating voiding dysfunction in women and D-mannose for preventing urinary tract infections in patients with multiple sclerosis. He has published over 200 articles and book chapters, has been editor of two textbooks. He has been a panellist for a number of committees focused on validating LUTS questionnaires, establishing best Uro-Neurology practice, and developing national and international guidelines for managing neurogenic urogenital dysfunction. He has been involved with setting up a Uro-Neurology platform in his native India.

Dr. Panicker is involved in teaching and training including academic supervision of PhD and MSc students and direct Uro-Neurology training of fellows across Neurology, Urology, Gynaecology and Physical medicine and Rehabilitation in the UK and abroad. He is a module convenor for the MSc Clinical Neuroscience program at University College London which includes Uro-Neurology in its curriculum. He has taken on a mentoring role for neurologists interested in careers in Uro-Neurology and Pelvic neurology. Dr. Panicker's prominent international reputation has led to invitations to several invited lectures. He has served on the Neurourology Promotion Committee of the International Continence Society and has been involved with all the International Consultations on Incontinence since 2012. He serves on the editorial board of several continence related journals.

Dr. Panicker has been serving as the interdisciplinary officer of INUS since its inception and has been involved in setting up collaborative links between stakeholder organisations interested in the management of urogenital dysfunction and neurological patients. A highlight has been the official collaboration among INUS, the European Academy of Neurology (EAN), and the European Federation of Autonomic Societies (EFAS), which has resulted in lively multidisciplinary neuroscience workshops at annual INUS congresses. The collaboration has also led to the NEUROGED project, which aims to establish guidelines for the management of urinary and sexual symptoms in patients with neurological disease intended specifically for practising neurologists. The project has received funding from the 3 societies and the task force includes specialists and key opinion leaders across Neurology, Urology and Physical Medicine and Rehabilitation. Once the project is completed in 2023, Dr Panicker hopes that the NEUROGED guidelines will serve as a benchmark for neurologists across the world in the assessment and management of urogenital symptoms reported by their patients.

Outside of the world of Uro-Neurology, Dr. Panicker enjoys playing the violin and gardening. He is married to a computer science teacher and has two teenagers.



Interview with the Expert

Intravesical Electrical Stimulation in Underactive Bladder

Limin Liao, MD, PhD (China)

Professor, Capital Medical University, Beijing
Chairman, Department of Urology, China Rehabilitation Research Center, Beijing, China



Glenn Werneburg, MD, PhD (USA)

Editor, Neuro-Urology News

Dr. Limin Liao M.D. PhD is the officer of the INUS Board Committee for Regional Chapters. Dr. Liao is a Professor of Urology in Capital Medical University (CMU) in Beijing, China. He is the vice-director of the China Rehabilitation Research Center (CRRRC) and Chairman of the Department of Urology and Chairman of the Department of Neurourology of CRRRC in Beijing, and Director of the Ph.D. training program on Neurourology and Urodynamics in the Rehabilitation School of CMU and the Cheeloo College of Medicine of Shandong University. His group recently published the manuscript entitled “**Randomized controlled trial of intravesical electrical stimulation for underactive bladder**” (Liao et al, BJUI 2022). In this month’s Interview with the Expert, we discuss this study, its rationale, and its implications. The below is our correspondence, edited for length and clarity.

Glenn Werneburg: What is underactive bladder, what are its clinical manifestations, and why did you choose this condition for your study?

Limin Liao: Underactive bladder (UAB) is a symptomatic syndrome that includes detrusor underactivity observed in urodynamics. The latest symptomatic definition is: “UAB is characterized by a slow urinary stream, hesitancy and straining to void, with or without a feeling of incomplete bladder emptying and dribbling, often with storage symptoms”. However, the International Continence Society (ICS) has

not yet provided a unified definition of UAB.

The clinical manifestations of UAB include hesitancy, straining, dysuria, slow stream, intermittency, spraying, prolonged bladder emptying, and/or incomplete emptying of the bladder induced by different causes.

We chose UAB patients as our research subjects for three reasons: 1) The prevalence of UAB is very high. Jeong et al. reported that 40% of the men (254/632) and 13% of the women (73/547) included in a retrospective study were classified as having detrusor underactivity. Another study also showed that, in patients with lower urinary tract dysfunction (LUTD), the incidence of UAB was 38% (1726/4538, 73% of whom were men and 27% were women). According to Abarbanel et al., 48% of elderly men and 12% of elderly women may experience detrusor underactivity; 2) UAB is harmful to the quality of life of patients. UAB may lead to repeated urinary tract infection, vesicoureteral reflux, hydronephrosis, renal insufficiency, and even renal failure; 3) Treatment options for UAB are very limited. Therefore, UAB patients urgently need a safe and effective treatment, which is also a reason why we chose the population of patients with UAB for our study.

GW: What are the treatment options for underactive bladder, and what was the clinical impetus for this investigation?

LL: There are very limited treatment options for UAB. Intermittent catheterization and indwelling catheterization can promote bladder emptying and delay disease progression, but they are not curative, and may lead to urethral injury and urinary tract infection and other complications, thus limiting the patient’s tolerance to treatment. The effectiveness and safety of drug therapy, such as M receptor agonists and acetylcholinesterase inhibitors, are controversial. Surgical treatment, such as detrusor latissimus dorsi plasty and transurethral incision of bladder neck, are traumatic and have many complications, such as bleeding, vesicovaginal fistula, stress urinary incontinence, urethral stricture and retrograde ejaculation.

In previous decades, a number of studies in China and abroad have confirmed the effectiveness of intravesical electrical stimulation (IVES) in UAB patients. However, China still does not have a set of domestic specialized IVES devices (e.g., stimulators, stimulation electrodes). We completed a pilot study on IVES, but the therapeutic apparatus used was derived from other stimulators, and the electrodes were homemade metal wires. We therefore conducted this multicenter, prospective, single-blind, randomized, controlled clinical trial to evaluate the efficacy and safety of IVES performed using a novel device for the treatment of UAB in China.

GW: What is intravesical electrical stimulation (IVES)? What is known about its efficacy in underactive bladder. How does the device and technology used in the current study differ from other IVES modalities?

LL: Intravesical electrical stimulation (IVES) involves insertion of a urinary catheter with stimulating electrodes into the bladder, using normal saline as a medium to stimulate the detrusor, stimulating the surviving afferent nerve connection between the detrusor and the center to induce urinary urgency in the bladder, increasing the output of nerve impulses and promoting urination or improving the ability to control urination. At present, IVES is an effective and safe conservative treatment for UAB. The IVES technique involves a stimulation electrode that is inserted into the catheter and together with the catheter is introduced into the bladder through the urethra. The other end of the electrode is connected to the stimulator. Normal saline (0.9%) is used as a conduction medium in the bladder. The reference electrode is attached to another area of the skin, usually on the lower abdomen.

In 1878, the Danish surgeon Saxtorph described IVES for the “atonic bladder” by inserting a transurethral catheter using a metal stylet and a neutral electrode on the lower abdomen. In 1899 the Viennese investigators Frankl-Hochwart and Zuckerkandl stated that intravesical electrotherapy was more effective on inducing detrusor contractions than external faradization [therapeutic application of induced electrical current]. In 1975, Katona introduced and popularized this method for the treatment of neurogenic bladder dysfunction.

In UAB, IVES generates or enhances bladder sensation, promotes bladder emptying, reduces residual urine volume, and improves urination efficiency.

The IVES treatment technology used in this study is the same as other IVES technology, but this is a new special IVES device in China. This device has multiple functions depending on the different electrodes.

GW: Describe the design of the current study.

LL: In this trial, a multicenter, prospective, single blind, randomized controlled design method was adopted. Qualified UAB patients were selected in seven research centers according to the corresponding inclusion and exclusion criteria, and the patients were randomly divided into test group and control group; The researcher collected the data related to the effectiveness and safety evaluation of the patients during the treatment process. The change of residual urine volume at the fourth week of treatment was the primary outcome. The incidence of adverse events at the fourth week of treatment was the safety evaluation indicator. Comparison of the differences between the two groups was performed to verify the effectiveness and safety of the Chinese IVES device.

GW: What were the main findings of the current study? What are its implications?

LL: After 4 weeks of treatment, the residual urine volume of the test group was significantly lower than that of the control group. The maximum urinary flow rate and urination efficiency of the test group were significantly higher than those of the control group. In the safety analysis, there were only 6 cases of adverse events possibly related to the device, all of which were urinary tract infections, and there were no other serious adverse events.

The above results indicate that the new IVES device is safe and effective for the treatment of UAB patients.

GW: What were the limitations of the study? What are the next steps?

LL: First, the study focused only on the efficacy of IVES in UAB patients, excluding patients with other indications, so the efficacy of IVES in patients with other indications needs further research. Second, the trial treated patients for 4 weeks, leaving open the following questions. How long will this benefit last after 4 weeks of treatment? Will the symptoms worsen after stopping treatment? Would long-term treatment have further benefited patients? In the follow-up study design, we will be able to choose a longer treatment time, as well as perform long-term efficacy observation after treatment, aiming at more diversified indicators and incorporating patients' expectations. Third, the mechanism of action of IVES needs to be further explored to help optimize inclusion criteria, rationally formulate treatment plans, and prolong clinical efficacy.

GW: What do you suspect is the underlying mechanism of the efficacy found with IVES in this study?

LL: The underlying mechanism of IVES may be to increase the afferent impulse by exciting the low threshold mechanical A δ afferent nerve terminal receptors on the bladder wall. When the impulses reach the primary voiding reflex center of the sacral cord, on the one hand, they continue to upload to the brain stem and the senior voiding reflex center of the cerebral cortex, generating the desire to urinate. On the other hand, the impulses flow out along the pelvic nerve, causing the contraction of the detrusor, relaxation of the internal sphincter of the urethra, and excretion of urine. Or, it induces micturition reflex by enhancing excitatory transmitter of central and/or peripheral micturition reflex pathway.

GW: The IVES efficacy appeared to improve over time in the current study. For example, at 2 weeks there was a reduction on PVR of 64 cc, and at 4 weeks 97 cc reduction. Do you think a longer duration of IVES might improve results? Do you suspect the benefits would persist after the cessation of therapy?

LL: Repeated artificial stimulation of bladder mechanoreceptors to increase bladder sensory afferent can improve or restore the effectiveness of synaptic transmission, thus gradually normalizing bladder sensation and urination function. Once restored, normal micturition contractions may be sufficient to drive afferent nerves to maintain synaptic transmission at an appropriate level. Normal urination can be regarded as a daily “self-training” process. This indicates that the treatment effect will be continuously improved by prolonging the treatment time of IVES to a certain extent. It also suggests that for some patients, the efficacy of IVES is long-term and will not disappear with the cessation of treatment. More specifically, whether the efficacy will decline or disappear after the cessation of IVES treatment may be related to the patient’s condition, the degree of nerve injury, the degree of bladder function improvement before the cessation of treatment, and the bladder management after the cessation of treatment.

GW: Do you think the findings of this study might be applicable to other neurourological conditions, such as complete spinal cord injury, which was specifically excluded from the present study? Briefly describe your findings with these conditions.

LL: Van Balken et al. believed that IVES was most suitable for patients with incomplete nerve injury accompanied by bladder sensory loss and detrusor muscle weakness. Madersbacher stated that according to the basic research, only

those with at least some intact afferent fibers from the bladder to the cortex and with incomplete spinal cord lesions and with a presence of pain sensation corresponding to sacral dermatomes S3 and S4 can benefit from IVES. Our previous single center study also found that IVES was ineffective for bladder dysfunction in patients with complete spinal cord injury. Therefore, we believe that IVES is suitable for patients with intact or partially intact neural pathways between detrusor and cerebral cortex, but not for patients with complete spinal cord injury.

GW: What advice do you have for junior INUS members interested in embarking on a career as a surgeon-scientist with a neurourological focus?

LL: The growth of doctors is a process from learning to practice, from perceptual knowledge to rational knowledge, and from learning, practice and thinking to continuous improvement and innovation. For INUS junior members, my suggestions are as follows:

We must have a clear goal for ourselves: to become an excellent surgeon. An excellent surgeon should not only strengthen the study of basic theories and clinical skills, but also be attentive to the improvement of humanistic quality and the cultivation of scientific research ability. Without technology, medicine has no trunk; without humanities, medicine has no soul.

“Surgery is not only a technology, but also an art and a philosophy”. In the decision-making and selection of clinical diagnosis and treatment, philosophy and dialectics should be flexibly applied to the work: (1) Set up a comprehensive diagnosis view, and do not look at problems one-sidedly; (2) For the understanding of disease, we must apply the law of quantitative change to qualitative change in the process of diagnosis and treatment, and aim to see

the essence through the phenomenon; (3) Use theory to guide practice, avoid blind medical activities, and be good at thinking and summarizing.

An outstanding surgeon-scientist with neurourological focus should have noble medical ethics, a high sense of responsibility, a high degree of compassion, rich medical knowledge, superb diagnosis and treatment technology, and excellent service technology on neuro-urology to win the trust of patients and inspire their confidence and morale. At the same time, we should be diligent in learning, good at practice, and brave in exploration and innovation in neuro-urology.

Further Reading:

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Liao, L., Deng, H., Chen, G., Chen, H., Huang, M., Xie, K., ... & Jing, H. (2022). Randomized controlled trial of intravesical electrical stimulation for underactive bladder. *BJU International* (online, ahead of print).

Madersbacher, H., Pauer, W., Reiner, E., Hetzel, H., & Sapanudakis, S. (1982). Rehabilitation of micturition in patients with incomplete spinal cord lesions by transurethral electrostimulation of the bladder. *European Urology*, 8, 111-116.

Van Balken, M. R., Vergunst, H., & Bemelmans, B. L. (2004). The use of electrical devices for the treatment of bladder dysfunction: a review of methods. *The Journal of urology*, 172(3), 846-851.



INUS-SIU Joint Session

Howard B. Goldman, MD (USA)

Professor of Urology, Cleveland Clinic, INUS Promotion Officer

Blayne Welk, MD (Canada)

Associate Professor of Surgery, Western University, INUS Vice-President



INUS was privileged to continue our collaboration with the Société Internationale d'Urologie during their meeting in Montreal, Canada (November 9-12, 2022). The joint INUS-SIU session brought together INUS members Dr. Blayne Welk (co-chair, Canada), Dr. Howard Goldman (co-chair, USA), Dr. Jorge Moreno-Palacios (Mexico), and Dr Reynaldo Gomez (Chile) as lecturers. To start, information about the goals of INUS and about next year's meeting in Athens was provided.

The scientific symposium began with a review of neurophysiology and pathophysiology given by Dr. B. Welk. Following that an overview of the most common neurologic diseases leading to lower urinary tract dysfunction

was given by Dr. J. Moreno. Dr. R. Gomez (SIU President) proceeded to provide a comprehensive review of the use of medications and catheters when treating patients with NLUTD. Finally, Dr. H. Goldman reviewed the latest data on the use of neuromodulation - both chemical (botulinum toxin) and electrical (sacral and tibial neuromodulation) for patients with neurogenic lower urinary tract dysfunction (NLUTD).

After these presentations the audience was treated to a number of interesting case presentations that generated a lot of faculty and attendee discussion. The cases included a patient with spinal cord injury who was using clean intermittent catheterization and had frequent urinary infections,

a patient with multiple sclerosis and mixed storage and voiding symptoms, and a patient with spinal cord injury who had a unique complication of recurrent prostatic abscesses. There was excellent interaction with the attendees concerning both the mode of evaluation of these patients as well as treatment modalities.

In summary, INUS provided an important opportunity for SIU attendees to learn about the latest concepts in evaluation and management of NLUTD. We look forward to a continued mutually beneficial collaboration with the SIU.

