

INUS Neuro-Urology News

The Periodical of the International Neuro-Urology Society

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Message from the President

Helmut Madersbacher, MD, PhD
INUS President

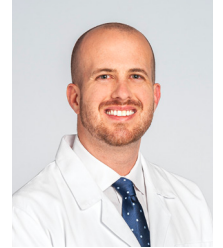
“Neuro-Urology News” is a new digital brochure dedicated to the information of INUS members to increase their awareness on recently published articles, events which have taken place or are coming up news within the society and awards to our members. It will be published every other month starting in March.

I have the pleasure to inform you that the INUS Board unanimously appointed **Dr. Glenn Werneburg** as Editor of “Neuro-Urology News”. Glenn T. Werneburg, MD, PhD, is a resident physician in the Department of Urology of the Glickman Urology and Kidney Institute at Cleveland Clinic. He will be working under the guidance of INUS Board Member

and Professor and Vice-Chair of Urology at the Cleveland Clinic, **Dr. Howard Goldman**. Glenn Werneburg has been an INUS member since 2019, and is also a member of the American Urological Association and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction. His basic science work has characterized the protein-protein interactions that underlie urologic infection in fine molecular detail. He is also investigating the role of biofilms and the microbiome in urologic pathology, as well as artificial intelligence in clinical decision-making. His clinical interests include neuro-urology, and female pelvic medicine and reconstructive surgery.



Helmut Madersbacher, MD, PhD
INUS President



Glenn Werneburg, MD, PhD
Neuro-Urology News Editor

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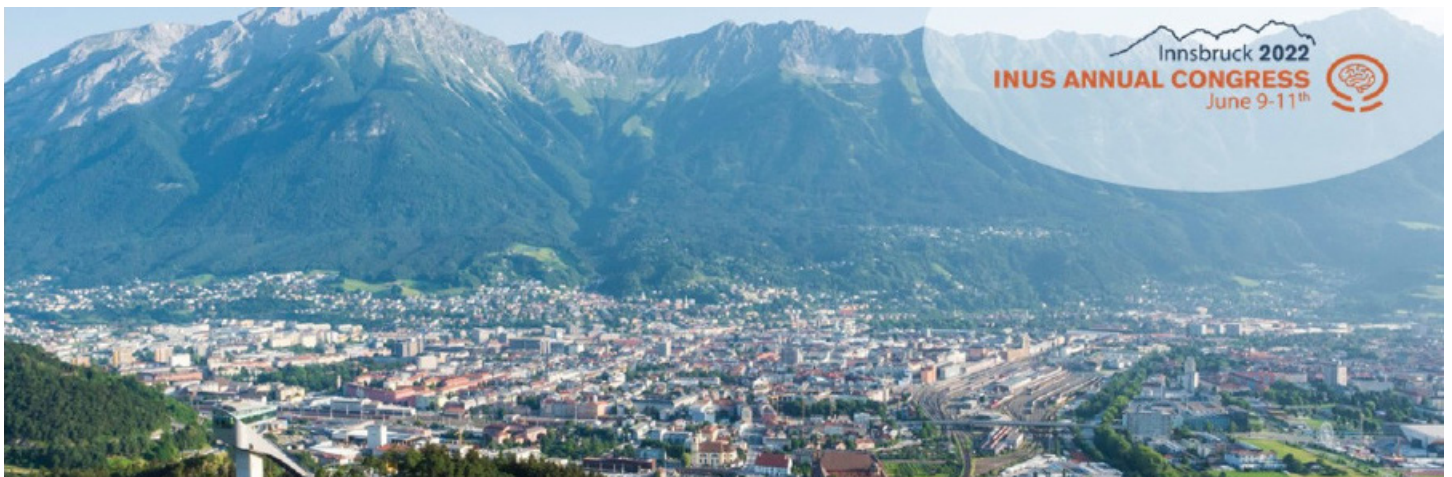
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Interview with the Expert

Bacteriophages in Neuro-Urology

Thomas M. Kessler, MD, FEBU

Professor and Chair, University of Zurich, Switzerland

Glenn Werneburg, MD, PhD, Editor, Neuro-Urology News



Dr. Kessler is Professor and Chair of Neuro-Urology at the University of Zurich and Head of the Department of Neuro-Urology at Balgrist University Hospital, Zurich, Switzerland. He is former vice-president, and current Treasurer of INUS

For the first Neuro-Urology News Interview with the Expert, we will be discussing the recent advances and applications of bacteriophage therapy in Neuro-Urology with **Dr. Thomas M. Kessler**.

Dr. Thomas M. Kessler comes to us from the University of Zurich, in Switzerland, where he is professor and chair of Neuro-Urology. He is the head of Neuro-Urology at Balgrist University Hospital.

Dr. Kessler studied medicine at the Universities in Fribourg, Lausanne, and Bern. He then trained in surgery in Sursee and Zofingen, and in urology at the University Hospital Bern. He underwent subspecialty training in Neuro-Urology at the University Hospital Innsbruck and University College London. He is chairman of the Swiss Continence Foundation, the past-president of the Swiss Society for Sacral Neuromodulation, former vice-president and current treasurer of the International Neuro-Urology Society. He is a renowned authority with extensive academic contributions to the fields of neuro-urology, functional urology, and urologic infection.

Dr. Kessler has recently been involved in the investigation of bacteriophage therapy for the treatment of urinary tract infection. He and his team have reported the results of a randomized controlled trial wherein bacteriophage therapy was noninferior to standard of care antibiotics in patients with urinary tract infection undergoing transurethral resection of the prostate. The study also further established the safety of the therapy. Subsequent trials have stemmed from this work, including one designed to assess the efficacy of bacteriophage therapy in individuals with catheter-associated urinary tract infection.

Our conversation follows, edited for length and clarity.

GW: What is bacteriophage, or phage, therapy and how does it work?

TK: The term bacteriophage comes from the Greek bakterion, meaning “bacterium”; and phagein, which means “to eat”. Literally, phages are “bacteria eaters”. Phages are viruses that are the natural killers of bacteria. The concept of bacteriophage therapy is not new. In fact, bacteriophages have been used therapeutically for the past 100 years. In 1919, Dr. Félix d’Hérelle used phage therapy to successfully treat infections in children. However, about a decade later, Alexander Fleming discovered the antibiotic penicillin. When penicillin was introduced clinically in the 1940’s, the interest in bacteriophage therapy effectively ceased in Western countries. In parts of the East, especially in post-Soviet countries such as Georgia, Ukraine, and Russia, however, bacteriophage therapy continued and it remains an established treatment today.

GW: Will you describe your recent randomized controlled clinical trial of bacteriophage therapy in those with urinary tract infection?

TK: In the neuro-urology subspecialty, many of our patients have urinary tract infections. The current cornerstone of treatment for urinary tract infection is antibiotics. However, we know that there are also adverse effects associated with antibiotics including the killing of good bacteria in the intestine. This can lead to conditions such as pseudomembranous colitis. We are also now in a world of significant antibiotic resistance. These factors really pressed us to consider what could be done as an alternative to antibiotics, and bring this point forward in a randomized controlled trial.

Much like the movie, we looked Back to the Future. We were not interested in reinventing the wheel, so we researched what

was already being done in the East. In Georgia, bacteriophages are commercially available, and one can go to the pharmacy in Tbilisi and purchase them. We used one such bacteriophage cocktail, “Pyophage”. The study, funded by the Swiss Continence Foundation and the Swiss National Science Foundation, was a partnership with a great group of specialists at the Alexander Tsulukidze National Center of Urology and at the Eliava Institute of Bacteriophage, Microbiology, and Virology in Tbilisi, Georgia.

The study was a three-armed randomized controlled clinical trial. Patients with urinary tract infection who were to undergo transurethral resection of the prostate were identified, and their urine was tested in the microbiology lab. If the organism isolated in their urine was sensitive to the bacteriophage cocktail, they were offered enrollment. The first arm of the study was bacteriophage treatment. The second arm was placebo treatment with bladder irrigation. The third arm was standard of care antibiotics according to susceptibility patterns.

In terms of urinary tract infection cure, the results were similar across the three arms. On one hand, this was interesting because we would expect antibiotics to do better than placebo, and placebo to do the worst. In practice, at least in our department, we commonly use bladder washing to avoid recurrent antibiotic treatment. Thus, this may have had a therapeutic effect in the placebo group. Further, although our sample size was reasonable, with over 100 patients randomized, the number needed to treat to detect a real difference may have been higher.

The trial gives us reason to be optimistic. First, it establishes the safety of bacteriophage administration via the intravesical route. Second, given the similar efficacy between the antibiotic and bacteriophage groups, phage therapy could avoid a relevant amount of antibiotics, thus sparing side effects and selection for resistance. In the current world of antibiotic resistance, this is an important point to consider.

GW: Are phages less likely than traditional antibiotics to promote antibiotic resistance?

TK: The Western standard of evidence-based medicine is not yet established with bacteriophages. This is why in the West, there is not a single bacteriophage product recognized as a standard treatment for human pathology. Similarly, resistance to phages has not been well-characterized, but we suspect the mechanisms of resistance may be different in phages relative to traditional antibiotics. Phages naturally develop mutations, as do the bacteria they target. Thus, there is an action-interaction dynamic between phage and bacterium. Perhaps the most relevant issue is the lack of understanding of how antimicrobial treatment may promote growth of another strain of bacteria, or why it selects for resistance. It is very clear that bacteriophages are extremely specific for a particular bacterium. Thus, phage therapy can be personalized in its targeting, at least in theory.

GW: Do you suspect this specificity may pose unique challenges in patients with neurogenic lower urinary tract dysfunction, who frequently harbor polymicrobial and atypical flora?

TK: Absolutely. The other challenge is with biofilm. In biofilms, bacteria, often polymicrobial, adhere to one another and a catheter in such a way that they can evade antibiotics. Many patients with neurogenic lower urinary tract dysfunction require artificial bladder drainage assistance through intermittent catheterization or indwelling catheters. These individuals are at risk for biofilm formation and thus catheter-associated urinary tract infection.

Another consideration is the environment surrounding the infection. For example,

some individuals perform intermittent catheterization in a sterile or near-sterile way, and still suffer from recurrent infections. Others who perform intermittent catheterization in the “clean” way, even reusing catheters, may never have a urinary tract infection. Thus, it is not only about killing the bacteria, but also about the interaction with the environment. The immune system must also be considered. We do not yet fully understand the mechanisms that underlie the bacteriophage-immunity interactions.

GW: Will you describe your upcoming clinical trial?

TK: Our upcoming randomized controlled clinical trial will be in patients with catheter-associated urinary tract infection, CAUTI. In selecting this population, we thought about the best group for the application of bacteriophages. Those with CAUTI are unique in that, by definition, they already have urinary catheters. Thus, the route of intravesical instillation for bacteriophages is already defined. We can therefore avoid intravenous administration, wherein we would have to also consider systemic side effects. Theoretically, CAUTI is an easy problem to address, in that after instilling the bacteriophages, all of the bacteria are gone. However, as we know from the Georgian trial, this is not the case, and in the population with CAUTI, the biofilm problem must also be addressed.

Currently, we are looking into these aspects of the study in detail, and we are in the pre-clinical testing phase. We are partnering with our engineering colleagues at ETH Zürich. Our goal is to be able to genetically engineer bacteriophages patient by patient, in a very targeted way. We hope to start enrolling the first participants in the trial by the end of this year.

GW: In the long term, do you foresee phage therapy working alongside antibiotics, or as an alternative to antibiotics?

TK: Currently, we are planning our studies to assess bacteriophage efficacy as an alternative to antibiotics. This randomized controlled trial will allow us to clearly determine the effect of phages versus the effect of standard of care antibiotics. However, it may ultimately be the case

that phage therapy works in conjunction with antibiotics. For example, perhaps a bacteriophage treatment could kill most of the dangerous bacteria, but then other strains could overgrow, and these could be targeted with traditional antibiotics.

GW: Just under 50% of International Neuro-Urology Society members are under age 36. Will you share any thoughts or advice for early career urologists who aspire to become clinician-investigators in Neuro-Urology?

TK: From my perspective, it is very clear. You must first find a great mentor. You will have this opportunity within INUS. There are many key opinion leaders here who will support young talents. My suggestion is to look for a mentor – the mentor will be the door opener, and then the ball is with you. Here in Neuro-Urology, you will be an integral member of a functional- or Neuro-Urology team. You will have opportunities to make discoveries and bring the field forward. It is a bit of a different story from other urological subspecialties such as onco-urology. On the functional side, we try to work together, and we try to avoid working against each other – together we are strong!

Further reading

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Leitner, L., Kessler, T. M., & Klumpp, J. (2020). Bacteriophages: a panacea in neuro-urology?. *European Urology Focus*, 6(3), 518-521.

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Ujmajuridze, A., Chanishvili, N., Goderdzishvili, M., Leitner, L., Mehnert, U., Chkhotua, A., ... & Sybesma, W. (2018). Adapted bacteriophages for treating urinary tract infections. *Frontiers in microbiology*, 1832.

Leitner, L., Sybesma, W., Chanishvili, N., Goderdzishvili, M., Chkhotua, A., Ujmajuridze, A., ... & Kessler, T. M. (2017). Bacteriophages for treating urinary tract infections in patients undergoing transurethral resection of the prostate: a randomized, placebo-controlled, double-blind clinical trial. *BMC urology*, 17(1), 1-6.



Meet the Board Member

Limin Liao, MD, PhD

Professor, Capital Medical University, Beijing

Chairman, Department of Urology, China Rehabilitation Research Center, Beijing, China

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 (CRRC) and Chairman of the Department of Urology and Chairman of the Department of Neurourology of CRRC 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.

He graduated and received the Degree of Medical Bachelor from the 3rd Military Medical University in Chongqing, China (1986). He completed his urological training and postgraduate education in the General Hospital of PLA in Beijing and received his M.D. (1994). In 1998, he joined the Department of Urology of Medical School of Aachen Technical University (RWTH) in Germany, where he earned his Ph.D. in Urodynamics.

Dr. Liao is the president of Chinese Continence Society (CCS) and vice-chairman of the China Neuromodulation Society (CNS). He is member of editorial board of 8 Chinese Journals including the Journal of Chinese Urology. He became an expert with special state allowance in China (2004), and in 2007 received the Dayu Prize, the highest Chinese achievement award in Urodynamics and Incontinence. He is the first member of the International Continence Society (ICS) in China (1997). He is also a member of the Urodynamic and Neurourology subcommittees of the ICS. He is an associate editor of Neurourology and Urodynamics. In 2008, Dr. Liao was elected as a trustee of the ICS and the chairman of the 42nd ICS annual meeting in Beijing in 2012.

Dr. Liao's main clinical interests are: neurourology, urodynamics, voiding dysfunction, incontinence, pelvic floor dysfunction, and BPH. He has published over 300 papers and book chapters in Chinese and English, and had over 100 presentations

on these topics. He has received extensive research funding including from the national key technology R&D program. Dr. Liao specializes in urodynamic quality control, urinary tract reconstruction, neuromodulation and neurostimulation for the treatment of neurogenic lower urinary tract dysfunction and bowel dysfunction.

His current research includes augmentation uretero-enterocystoplasty for refractory urinary tract dysfunction, functional MRI study on central control of storage and central pathogenesis of overactive bladder (OAB) and the central mechanism of action of sacral neuromodulation. Most recently he co-edited the book Neurourology: Theory and Practice with **Professor Helmut Madersbacher**, a book of 80 chapters, which will serve as a useful resource for physicians, nurses and students in the neurourological fields. All the topics are written by internationally recognized specialists.

Meeting Highlights

The 2022 Society for Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) Annual Meeting took place from February 22-26 in San Diego, CA, USA. This was the first in-person Annual Meeting since 2020, and was led by SUFU President, **Dr. Sandip Vasavada**, Cleveland Clinic, Ohio, USA, and Vice-President, **Dr. David Ginsberg**, University of Southern California, USA. There was a fantastic lineup of speakers, debates, panels, and abstract sessions. There was a strong showing of work in the neuro-urological area. **Dr. Evgeniy Kreydin** and his group from University of Southern California, USA, presented their investigation of outcomes of non-invasive

spinal neuromodulation for treatment of neurogenic bladder symptoms following stroke, including improvement in incontinence symptoms. **Dr. Rose Khavari** and her group from Houston Methodist Hospital, USA, compared the bladder-brain connectivity between healthy individuals and those with multiple sclerosis and voiding dysfunction. The group found specific deficits in brain connectivity associated with bladder function in the multiple sclerosis group. **Dr. Blayne Welk**, Western University, Ontario, Canada, and his group demonstrated that continuous antibiotic prophylaxis may be more effective for individuals with some neurogenic lower urinary tract dysfunction etiologies

over others. It was most protective among those with spinal cord injury, and least protective among those with spina bifida. UTIs were not associated with renal deterioration. Dr. Welk also discussed applications and implementation of big data in urology. **Dr. Anne Cameron**, University of Michigan, ended the conference with a highly-interactive session reviewing the risk stratification in neurogenic lower urinary tract dysfunction based on the new AUA/SUFU guidelines. Many others discussed new and exciting work in the neuro-urological field. Next year's SUFU Annual Meeting will take place March 7-11, 2023 in Nashville, Tennessee, USA.

SUFU Annual Meeting

Glenn T. Werneburg, MD, PhD

Editor, Neuro-Urology News

INUS Annual Congress



Dr. Blayne Welk
INUS Vice-President &
Next Generation Officer



Dr. Jorge Moreno-Palacios
INUS Educational
Officer

Innovations in Neuro-Urology: Past - Present - Future

INNSBRUCK

Innsbruck is located in Austria, in one of the most beautiful Alpine regions. It is accessible via its international airport with daily flights to and from Frankfurt and Vienna. Furthermore, various charter companies connect to Innsbruck including from the UK and Netherlands, but also other European cities. Innsbruck can also be reached via Munich, which is a 2-hour drive away. This can be done by car, charter bus (direct), or by train (1 stopover). Trains also connect Innsbruck to most major cities in Middle Europe. The congress center is surrounded by different hotels within walking distance. Remember to check the Austrian government requirements for entrance to the country. They are updated regularly according to the pandemic situation. If you have any questions please contact the INUS office.

PROGRAM

The INUS Scientific committee has prepared several high-quality conference lectures and workshops (Urodynamics, Neuromodulation, Translational research, Sacral anterior root stimulator, Neurosciences and our traditional Gladiators debate). During the three days you will have the opportunity to exchange experiences with colleagues from around the world. The program

includes panel discussions about Neurourology guidelines from around the world, Hot topics in clinical neurourology, Management of urinary tract infections in the neurologic patient, neuro-urological voiding dysfunction, neural imaging and many more!

Keynote lectures will be given by **Professors Madersbacher, Wyndele and Castro-Diaz**. In addition, several exciting lectures are scheduled through INUS partnerships with different societies (ICS, EAU, EAN, IUA, EAUN, SIU,PACS, TAU), bringing you specially selected speakers from around the world.

ABSTRACT SUBMISSION

The Scientific Board of INUS welcomes the submission of original research and clinical abstracts for presentation at the annual meeting in a special poster session. If you have already submitted your research work, you will have information soon about your status. A record number of submissions were received at the first deadline! A second round of submission will start on April 1st and end on April 30th 2022. There will be three poster-sessions. The best poster of each session will receive a poster prize. You can find the submission instructions on the website.

INUS Calendar

INUS Lectures at the 25th Iranian Urological Association Annual Congress

Tehran, Iran
May 17-20, 2022

INUS Annual Congress 2022

Innsbruck, Austria
June 9-11, 2022

American Urological Association Annual Meeting

New Orleans, United States
May 13-16, 2022

INUS Session at ICS 2022

Vienna, Austria
September 7-10, 2022


Innsbruck 2022
INUS ANNUAL CONGRESS
June 9-11th

