Second Gothenburg Conference on Vesicoureteral reflux

June 11-12, 2015
Quality Hotel 11, Göteborg

Program book
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We would like to thank Petter Silfverskiölds Memorial Foundation for their generous contribution.
As the Second Gothenburg Conference on Vesicoureteral Reflux in Children is finally launched we welcome you all to an interesting and challenging program. Focus will be on high grade reflux in infants from both a clinical and scientific point of view. Results from the Swedish Infant High Grade Reflux Trial, just recently completed, will be presented and the related topics will be thoroughly discussed in well renowned panels. We also have the great pleasure to present prominent authorities to deliver state of the art lectures on congenital VUR and renal dysplasia and bladder function. The first day will be closed by a talk on how to optimize VUR treatment in developing countries, complemented by practical experiences from Pakistan.

The second day will be continued with a slightly broader approach. We will be guided through the results of the RIVUR study and the ongoing Predict study will be outlined to us. Both are randomized studies on prophylaxis treatment in infants and children with VUR. Long-term aspects of childhood UTI will be presented and discussed. The conference will end in a very practical and clinically applicable summary of the latest UTI guidelines.

We hope you will remember the conference as rewarding and intriguing, leaving you with new insights and friends and many ideas for future research.

Sofia Sjöström
MD, PhD
Paediatric Urology

Per Brandström
MD, PhD
Paediatric Nephrology

Ulla Sillén
Professor
Paediatric Urology

Sverker Hansson
Associate professor
Paediatric Nephrology
EXHIBITORS

We wish to thank all the exhibitors for their participation and contribution which is an important part for the success of the Conference.

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Bladder Development: Thoughts on Megacystis-Megaureters

Laurence S. Baskin, MD
Frank Hinman, Jr., MD, Distinguished Professorship in Pediatric Urology, UCSF

The function of the adult human bladder is to store and empty urine at socially appropriate times. Despite this seemingly simple function, micturition is a complex anatomic and physiologic function that involves interaction between the urothelium, bladder smooth muscle, afferent and efferent nerves, spinal cord, and higher-level cerebral processing. The urinary bladder is a dynamic organ that is both compliant in order to allow storage of urine and contractile to allow for coordinated emptying. The detrusor, which is the muscle that contracts to expel urine, comprises randomly oriented smooth muscle fibers and, under normal conditions, is under autonomic control. In conjunction with a normally functioning nervous system, the physiologic properties of the bladder are derived from the anatomic properties of the bladder smooth muscle. During filling, the normal adult bladder maintains a low intra vesical pressure (of 10 cm H2O) and has a capacity of 350–500 cm3. At a socially appropriate time, urethral pressure decreases and intravesical pressure increases as the bladder smooth muscle undergoes coordinated contraction, allowing for effective emptying. Concomitant with expelling urine through the urethra, detrusor contraction also closes the muscular tunnel through which the ureters traverse as they join the bladder. This prevents retrograde flow (vesico-ureteral reflux), which protects the kidneys from the pressure generated by detrusor contraction.

Smooth muscle differentiation and patterning is a fundamental process in urinary bladder development that involves a complex array of local environmental factors, epithelial–mesenchymal interactions and signaling pathways. An epithelial signal is necessary to induce smooth muscle differentiation in the adjacent bladder mesenchyme. The bladder epithelium (urothelium) also influences the spatial organization of the bladder wall. Sonic hedgehog (Shh), which is expressed by the urothelium, promotes mesenchymal proliferation and induces differentiation of smooth muscle from embryonic bladder mesenchyme. Shh, whose signal is mediated through various transcription factors including Gli2 and BMP4, is likely also important in the patterning of bladder smooth muscle. However, it is not known to what extent early mediators of mesenchymal migration, other Shh-associated transcription factors, and crosstalk between the Shh signaling cascade and other pathways are i
nvolved in the patterning of bladder smooth muscle. In this presentation I will review the role of epithelial–mesenchymal interactions and Shh signaling in smooth muscle differentiation and patterning in the bladder. I will also discuss emerging signaling molecules, transcription factors, and mesenchyme properties that might be fruitful areas of future research in the process of smooth muscle formation in the bladder. Finally I will try and relate some of the basic science finding to the Megacystis-Megaureters syndrome.

VUR treatment in developing countries

**Lars Hagander, MD MPH PhD**
Pediatric Surgeon, Lund, Sweden
Director, Global Pediatrics, Lund University
Co-chair of the Lancet Commission on Global Surgery

Through a decision analysis, we have assessed how VUR is best treated in low- and middle-income countries, and which factors that determine optimal treatment strategy. We reviewed evidence on the effectiveness of preventive and therapeutic interventions for VUR-associated pyelonephritis, and in a Markov model we compared lifetime outcomes for seven competing care delivery strategies worldwide, accounting for patient heterogeneity and differences in health systems. VUR-related urinary tract infections caused considerable mortality and morbidity, particularly in areas where access to effective pyelonephritis treatment was limited. The preventive role of surgical management was striking, and non-operative strategies for VUR were more beneficial only in centers with very high perioperative mortality, and in settings with excellent access to inpatient acute pyelonephritis care. Mortality data and QALY thresholds are presented. We identified pivotal factors that influence clinical decisions. We conclude that state-of-the-art management algorithms from high-income countries can be suboptimal when applied to the health care systems of low- and middle-income countries.
Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) Trial

Tej K. Mattoo, MD, DCH, FRCP (UK)
Wayne State University School of Medicine
Children’s Hospital of Michigan
Detroit, MI

In the last decade many prospective studies have been done to evaluate the role of antimicrobial prophylaxis in the prevention of recurrent urinary tract infection (UTI) and renal scarring in children with vesicoureteral reflux (VUR). This includes the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) Trial, which was the largest, randomized, placebo-controlled, double blind, multicenter study in young children 2-72 months old with grade I-IV VUR and first or second febrile/symptomatic UTI. The primary outcome of the study was UTI recurrence and the secondary outcomes included renal scarring, antibiotic resistance, and treatment failure. Pilot studies for dimercaptosuccinic acid (DMSA) renal scans and voiding cystourethrograms (VCUG) were done before the study; images were read independently by 4 blinded central radiologists, two each for DMSA scans and VCUG/renal ultrasounds. Altogether 607 children were randomized from 19 centers with very diverse clinical settings; 302 received trimethoprim/sulfamethoxazole (TMP/SMZ) prophylaxis and 305 received exactly matching placebo.

The median age of the children in the RIVUR Trial was 12 months, 92% were females, 91% were randomized after a first UTI, 86% had a febrile index UTI, and 71 of 126 toilet-trained children had bladder bowel dysfunction. Recurrent UTI occurred in 39/302 children on prophylaxis compared with 72/305 children who received placebo (relative risk, 0.55; 95% confidence interval [CI], 0.38 to 0.78). Prophylaxis reduced the risk of UTI recurrences by 50% (hazard ratio, 0.50; 95% CI, 0.34 to 0.74). No significant difference was seen in stool Escherichia coli resistance, but the first symptomatic UTI recurrence with resistant E. coli was significantly more likely to occur among those on prophylaxis (63%) compared with those on placebo (19%), (absolute risk difference (95% CI) -44.0 (-64.1 to -24.0 (p = <0.001). 58 (10%) of 599 children and 63 (5%) of 1197 renal units were found to have renal scarring at the end of the study. Children with scarring were significantly older with a median age of 26 months vs. 11 months (p=0.006), had second UTI prior to enrolment (p=0.003), and had higher grades of VUR (p=0.001). The proportion of renal scars in renal units with grade IV VUR was significantly higher than units with no VUR (p=0.0001).
In view of the RIVUR Trial and other studies that showed similar results, albeit in selected groups of pediatric patients, the deliberations on antimicrobial prophylaxis in VUR should be on “selective prophylaxis” in those who are likely to benefit the most. This would also mean a review of the current guidelines by the American Academy of Pediatrics and others on the management of UTI in young children.

The PREDICT study

Prof Giovanni Montini
Consultant Pediatric Nephrologist
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Congenital anomalies of the kidney and urinary tract (CAKUT) are among the most common human congenital anomalies. Nowadays, thanks to efficient prenatal screening, CAKUT is typically detected from birth and this population is known to be at increased risk of both urinary tract infections (UTIs) and progressive renal failure, leading to the need for renal replacement therapy. However, the causative role of UTI in the progression of kidney damage in children with CAKUT is unknown and unpredictable. Traditionally, antibiotic prophylaxis is used for the management of children with high grade reflux, despite conflicting evidence regarding its long term effectiveness and safety and also in view of spreading bacterial resistance to antibiotics. The PREDICT trial (Antibiotic Prophylaxis and REnal Damage in Congenital Abnormalities of the Kidney and Urinary Tract) has been designed in order to improve the evidence base in this field by means of a network of clinicians with long-standing expertise in collaborative clinical research and outstanding experts in the fields of microbiomics, genetics and biomarker research. The trial will be conducted in more than 60 clinical centres belonging to the ESCAPE consortium in 14 European countries and will involve 436 children aged 1 to 4 months. The study will evaluate the usefulness and safety (especially related to the risk of early life antibiotic exposure) of primary antibiotic prophylaxis in preventing UTI and chronic kidney damage in children with high grade reflux. Eligible subjects will be randomized into 2 groups: no antimicrobial prophylaxis (surveillance group) versus antimicrobial prophylaxis for 24 months. A subsequent period of 36 months will allow for the evaluation of kidney damage progression. The primary end point is the onset of symptomatic UTI during the 24-month observation period. A diagnosis of UTI is given when all the following criteria are present: acute symptoms, positive urinalysis and positive urine culture. Biospecimens (DNA, plasma, urine, stool) collected during the trial will be made available to the partner laboratories in order to study the impact of antibiotic prophylaxis on the gut microbiome and resistome and to identify genetic and biochemical risk
factors for developing UTI and/or progressive kidney damage. The PREDICT trial will help us to understand if antibiotic prophylaxis will postpone the first UTI and then reduce its recurrence rate. This result will allow for the correct utilization of long term antibiotic prophylaxis, helping clinicians and pediatricians to reduce both the rate of UTIs and the major public health problem of emerging bacterial resistance and other possible long-term effects secondary to the continuous use of low dose antibiotics.

Review of UTI guidelines

Kjell Tullus MD, PhD, FRCPCH
Great Ormond Street Hospital for Children
London

I will compare guidelines from four different countries: UK, USA, Italy and Sweden. They share many similarities in reducing the number of investigations recommended for children with one uncomplicated UTI. There are however also some differences. All guidelines recognise the difficulties in making a correct diagnosis and in particular in collecting urine samples that are not contaminated with bacteria. The US and Swedish guidance recommend a suprapubic bladder puncture or a bladder catheterisation while the UK and Italy finds that too difficult in practice and thus recommends a clean voided sample. The US guidelines are the only that discuss the difficult question on which number of bacteria that is “significant”. And they do also recommend a lower threshold of $5 \times 10^4$ bacteria /ml.

None of the guidelines discuss modern data suggesting that the VUR occurs in 30-40% of all small children regardless of if they have had a UTI.

The US, UK and Italian guidance has gone furthest in reducing imaging recommending only an ultrasound in most uncomplicated cases.

Sweden recommends two different models relying much more on the use of DMSA. The US does not recommend prophylactic antibiotics in any case and the UK not routinely. Italy and Sweden feels that it should be used in children with high grade VUR or after several recurrent febrile infections.
Developmental Changes in the Physiology of Micturition

**Stephen A. Zderic, M.D., Professor of Urology**  
The Perelman School of Medicine at the University of Pennsylvania  
The John W. Duckett Endowed Chair in Urology  
The Children’s Hospital of Philadelphia

The literature on vesicoureteral reflux expanded in the 1950s as various surgical procedures to correct the problem began to appear. Although early investigators focused on reflux as an anatomic malformation which resulted in the observed clinical phenotype, Hinman reported on a series of patients undergoing cineradiographic studies in 1962 and proposed a classification scheme based upon the passive resting pressure and the volume at which reflux began. Several investigators explored the relationship between voiding dysfunction, UTIs, and reflux in the 60s and thus began to emphasize the role of bladder physiology in the pathology vesicoureteral reflux. These early series tended to focus on older female patients; but this changed as pediatricians began to routinely search for urinary tract infections as the source of fever in neonates and infants. Studies done here in Gothenburg in the late 1980s by Sillen and her colleagues were instrumental in describing the high voiding pressures that are observed in neonates with vesicoureteral reflux. Their key observations were that voiding pressures were elevated in neonatal reflux, and this was especially pronounced in males with high grade reflux. Furthermore the voiding pressures dropped with age and this also correlated with an increase in bladder capacity. Subsequently these findings were confirmed in another large series of videourodynamic studies. In this presentation we shall review the clinical and experimental literature devoted to the ontogeny of bladder function within the first years of life. What might be the origin of such high voiding pressures? Do these increased voiding pressures simply reflect the Law of LaPlace, or might there also be changes in smooth muscle contractility, innervation, extracellular matrix, and might the bladder outlet be a sexually dimorphic structure? Evidence in the literature will be presented in support of these possible explanations. While there are challenges in comparing the clinical and experimental studies due to patient age ranges, and species differences, there are some common themes. In Vitro whole organ experiments showed neonatal bladders were capable of generating significantly higher pressures. There is also experimental evidence of a developmental shift in the growth of the sarcoplasmic reticulum and the mechanism of excitation contraction coupling. Experimental and clinical studies have also suggested that the bladder neck is sexually dimorphic, and this can help explain why the voiding pressures are so much higher in neonatal boys.
The Swedish Infant High Grade Reflux Trial

Management of high-grade vesicoureteral reflux in infants is challenging due to the high frequency of associated renal abnormalities, recurrent urinary tract infections and bladder dysfunction. Previous research in the field has called for further evidence-based knowledge. This is an open, randomized, controlled, multicenter, one-year follow-up study including infants younger than eight months of age with VUR grade 4-5. The patients were randomized to either prophylaxis alone or endoscopic treatment with prophylaxis until VUR resolution.

The aim of the study was to investigate the following research questions:

• Can high-grade VUR in infants be treated by endoscopic injection of dextranomer/hyaluronic acid polymer?
• Is endoscopic treatment superior to prophylaxis alone in reducing the risk of UTI and new renal damage the first years of life?
• Can early treatment of high-grade VUR prevent the development of bladder dysfunction characterized by high bladder capacity?

The study has been coordinated from the Paediatric Uro-Nephrologic Center at the Queen Silvia Children’s Hospital in Gothenburg and study patients have been recruited from participating pediatric centers from all of Sweden. Seventy-seven (77) infants (22 girls and 55 boys) were included between 2004 and 2014, 39 in the prophylaxis group and 38 in the endoscopic treatment (and prophylaxis till resolution) group. The study protocol included; cystourethrography (VCU), ultrasound, renal scintigraphy, measurements of glomerular filtration rate (GFR), videocystometry and 4-hour free voiding observation (FVO) for bladder function evaluation, at study entry and after one-year follow-up.

The study outcome has been analyzed according to intention to treat. We will present the results of VUR, urinary tract infections, renal damage and bladder function outcome at the Second Gothenburg VUR Conference. We thankfully acknowledge all the participating centers for their valuable contribution to the completion of the trial.

From the study committee of the Swedish Infant High Grade Reflux Trial in Gothenburg.

Josefin Nordenström, Ulla Sillén, Per Brandström, Sverker Hansson, Gundela Holmdahl, Tina Linnér, Göran Läckgren, Eira Stokland, Rune Sixt, Sofia Sjöström
Swedish Reflux Trial – a follow-up

The Swedish reflux trial, a randomized controlled trial, included 203 children from 23 centers, 128 girls and 75 boys, 1-2 years of age with dilating vesicoureteral reflux grade 3-4. The children were randomized to antibiotic prophylaxis, endoscopic injection treatment or surveillance without active treatment and followed for 2 years. VCUG, DMSA-scintigraphy and bladder function assessment were performed before randomization and at study end and every UTI was reported. The results showed that in girls from 1-2 years of age with dilating VUR, antibiotic prophylaxis protects from recurrent UTI and new renal damage, and endoscopic treatment lowers the risk of new renal damage. Boys over the age of one year, however, rarely suffer from UTI or develop new renal damages and we concluded that they generally do not benefit from active treatment. In the study we also found that those with bladder dysfunction at follow-up had more renal abnormalities and lower rate of reflux resolution compared to those with normal bladder function.

This is a high risk group of children with a high prevalence of renal damage, with dilating VUR and proneness to recurrent UTI during their first years of life. Previous studies have shown varying degree of long-term complications in subjects with renal damage after UTI and dilating VUR in childhood. These complications include temporarily impaired growth, slightly increased risk of complications in pregnancy, hypertension and renal failure. By following this unique cohort of high risk children during childhood into adolescence our objectives are to study the long term effects of renal damage and dilating VUR by assessing the risk of recurrent UTI, additional renal damage, decreased renal function, hypertension and growth retardation. We here report on the preliminary results of the first follow up reports in 156 children.

Per Brandström
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Ulla Sillén
Professor, Paediatric Urology, Gothenburg, Sweden
Thursday June 11

08.30 Welcome

08.45-09.15 State of the art Congenital VUR with megaureter, megacystis and renal dysplasia. From embryogenesis to clinical appearance, L. Baskin

09.15-10.00 Panel - The obstructive/non obstructive megaureter in the newborn with gross VUR. A diagnostic dilemma. 
Moderator: S. Tekgul
Panellists: A. Khoury, E. Stokland, A. Piepsz

10.00-10.30 Coffee

10.30-11.45 VUR outcome in the Swedish infant reflux study J. Nordenström

Panel - Treatment of high-grade infant VUR. To inject or not inject, that’s the question?
Moderator: G. Läckgren
Panellists: A Caldamone, G Holmdahl, C Radmayr

11.45-13.00 Lunch

13.00-13.30 State of the art Developmental Changes in the Physiology of Micturition , S. Zderic

13.30-14.45 Bladder function outcome in the Swedish infant reflux study, S. Sjöström

Panel - Bladder dysfunction in infants with high-grade VUR. 
Moderator: A. Khoury
Panellists: U. Sillén, C. Radmayr, S. Zderic

14.45-15.15 Coffee

15.15-16.30 Infections and renal damage in the Swedish infant reflux study, P. Brandström
cont’d Thursday June 11

Panel - Infections and renal damage in infants with high-grade reflux.
Moderator: P. Ransley
Panellists: S. Hansson, G. Montini, T. Mattoo

16.30-17.00 VUR treatment in developing countries. L. Hagander

17.00-17.15 Comments and reflections from a Pakistan perspective. P. Ransley

19.00 Conference dinner at River restaurant

Friday June 12

08.30-09.00 Longterm results from the Swedish Reflux Trial
P. Brandström

09.00-09.30 Hypertension and renal function in women with childhood UTI,
C. Gebäck

09.30-10.15 The RIVUR study, T. Mattoo

10.15-10.45 Coffee

10.45-11.15 The PREDICT study, G. Montini

11.15-12.00 UTI review of guidelines, K. Tullus

12.00-12.45 Panel 5 - UTI guidelines
Moderator: K Tullus
Panellists: T. Mattoo, G. Montini, P. Brandström

12.45-13.00 Closing remarks, S. Sjöström, P. Brandström

13:00-13:45 Lunch
Welcome reception

Date: Wednesday June 10
Time: 18.30
Venue: Dicksonska palatset, Parkgatan 2

The Dicksonska palace is a three floor stone building in Florentine Neo-Renaissance style built by Baron Oscar Dickson in 1862.

Conference dinner

Date: Thursday June 11
Time: 19.00
Venue: River Restaurant

The restaurant is situated by the harbour just a few steps from the venue, Quality Hotel 11. You will enjoy the Swedish summer night with a view over the harbour. A three meal course will be served mixed with entertainment.
USEFUL INFORMATION

Tourist information
Tourist information can be found at the following locations:
Main Office: Kungsportsplatsen2, +46 (0) 31 61 25 00
www.gothenburg.com
Branch office: Nordstan Shopping Centre, +46 (0) 31 61 25 00

Language
The official conference language is English.

Audio visual facilities
The plenary hall is equipped with microphones, projectors and computers for PowerPoint presentation.

Internet
The hotel has free internet access and you collect the login from the hotel reception or at the registration desk.

Currency
Sweden’s currency is krona. There are a hundred öre in one krona. Credit cards are accepted almost everywhere. You can use the card on buses, trams, taxi’s and in most stores. The chip and pin is the common method.
Cash machines or ATM (bankomat) are common and takes major credit and debit cards. They can be found in the main shopping centers, at the airport and at the Quality Hotel 11.
If you have bought an item in Sweden worth more than SEK 200, and you are flying out of the EU, you are eligible to a VAT refund. Present the goods (unused and with the price tags attached), your passport and ticket/boarding pass, Global Refund receipt and the shop receipt to customs at the airport. (www.globalrefund.com)

Tipping
Ten per cent of the bill or taxi fare is the usual and appreciated.

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Attractions 09.00 or 10.00 - 17.00 or 18.00
Banks 10.00 - 15.00 Monday - Friday, large city branches 09.30 - 18.00
Shops 10.00 - 18.00 or 19.00 Monday - Friday, 10.00 - 16.00 Saturday; Malls 12.00 - 16.00 Sunday
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Forex is the largest foreign exchange company located at the airport, the Central Station, Nordstan Shopping Centre.

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**Medical services**
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Weekdays 17-22 and weekends 10-16 – Alléjouren, Södra Allégatan 6,
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**Bus or boat to/from City Center to Quality Hotel 11**
Take bus number 16 towards Eketrägatan (from stop Nordstan direction B) and the stop for the hotel is Eriksbergstorget. The travel time is approx. 20 minutes and the price is SEK 25 for one way.

You can also take the boat from stop Lilla Bommen to Eriksbergs Färjeläge which is right outside the venue.

You need to buy the ticket on forehand at a kiosk when travelling with the bus. On-board the boat you can buy the ticket from the staff, please note that you can only pay with credit card.
WELCOME TO GOTHENBURG!