In this issue of Dialogues in Pediatric Urology, we will focus on the management of children with lower urinary tract (LUT) dysfunction. Although surgical genitourinary reconstruction is the driving passion of every pediatric urologist, approximately 20 to 25% of referrals to a pediatric urologist involve the care of a child with LUT dysfunction. The prevalence of LUT dysfunction necessitates that pediatric urologists have a strong understanding of the treatment of LUT dysfunction. Additionally, the significant volume of patients presenting with LUT dysfunction has led pediatric urologists to partner with ancillary care providers, e.g., nurse practitioners, to manage these non-surgical patients. The families and children that present with LUT dysfunction are commonly frustrated and exhibit sincere gratitude after successful therapy. LUT dysfunction is a prevalent problem that demands an efficient and pragmatic approach so that pediatric urologists can integrate the other 75 to 80% of their patients with surgical needs and diagnoses into their office practice.

Given the prevalence of LUT dysfunction, it is imperative that pediatric urologists take the lead in the education and care of these children. We will discuss the nuances and the “tricks-of-the-trade” during the evaluation and treatment of children with LUT dysfunction. Additionally, we will address the child who presents to the office for management of intractable LUT symptoms. I have asked an esteemed group of experts to present their personal views and offer their insights to novel approaches in managing these challenging patients. While many of these approaches are “off-label” or unapproved for refractory LUT dysfunction, they have nevertheless been extensively published as second-line treatments of LUT dysfunction. The panelists I have asked to contribute to this DPU topic include the following with special emphasis on different second-line treatments.

**Panelists:**
- Piet Hoebeke, M.D. (PH) – Pelvic Floor Rehab
- Zoran I. Radojicic, M.D. (ZH) – Botox Therapy
- Israel Franco, M.D. (IF) – CNS Agents
- Kenneth I. Glassberg, M.D. (KG) – Alpha Blockers
- Yves Homsy, M.D., FRCSC, FAAP (YH) - Bowel Management

We have come a long way from advocating anticholinergic therapy for every child who has wetting. I remember this in my practice many years ago. It is so different now. In this issue Paul Austin has put together an outstanding team of experts in lower urinary tract dysfunction in children. Interestingly, each of these experts has a specific treatment modality in which they have significant amount of experience that seems to work best for them. To bring all of these treatment modalities together is outstanding, as we have the opportunity to understand the rational as well as the successes and failures of each modality. It is unprecedented to see our armamentarium for treating these common problems in children grow so significantly over recent years. This issue tells us how best to utilize each of these modalities.

My thanks and congratulations to Paul Austin and his group of contributing experts!
Q1: What is the typical time spent with a family during an initial office visit for LUT dysfunction? Do you use any educational materials in your treatment?

PH: Typical time at initial visit is around 30 minutes, including history taking, clinical examination, uroflow and ultrasound. We then explain the voiding and drinking diary. The educational material at this stage is limited to a booklet on voiding and drinking advice and on how to keep a voiding and drinking diary.

ZR: At the initial contact it is important to differentiate patients with true LUT dysfunction from those with variants of normal or delayed maturation of LUT function. The pediatrician will inform the parents that their child has a “thickened urinary bladder wall”, a “neurogenically-changed bladder”, and that the kidneys are at risk. This is usually confirmed by ultrasound findings, urine culture showing the presence of bacteria, and uroflowmetric findings, which are rarely normal in small children. This will make the parents feel confused and scared.

It is not always an easy task to explain to the parents (and to the child) the manner of LUT functioning, i.e., to adopt the story to their level of education. It is necessary to reassure a great number of patients and parents that the child is not ill, but that this is only a transitional phase of a slowed-down maturation of LUT function. I believe that many patients do not require treatment (except for counseling). This statement may seem unacceptable (even sound heretical) to urologists dealing with LUT dysfunction.

In addition, it is necessary to explain that in some patients the problem may relapse later in life. It has not been proven by any scientific study that the problem will not relapse despite treatment initiated “on time” or early enough. All these are only assumptions. But, under such pretext many patients are unnecessarily treated by drugs or other methods.

All this information may be given to the parents in a written form. However, the explanation is best given through personal contact, which is full of empathy communicated by a person of authority and trust and adapted to the circumstances and patients. This requires time and patience. The time spent at first contact varies from patient to patient, and also depends on circumstances. This makes it difficult for me to define precisely the amount of time which I spend during the first contact with such patients.

IF: The initial visit for me for a patient with LUT dysfunction can last from 30 min to 45 min depending on the child and the family. Obviously if the patient is coming from out of town to see me this is typically a more complex case and requires a more detailed history and exam. At times I will show certain patients slides on neuroanatomy and functional MRIs to explain what is going on at the time their child has the urgency or wets and doesn’t know that they wet.

KG: The typical first visit with a child who has LUT dysfunction varies depending on which office (satellite vs. hospital) they are seen. In my satellite office, children with significant symptoms will have a formal kidney and bladder ultrasound during their office visit with pre- and post void images. At that visit, 15 to 20 minutes are spent with the family and child. Prior to being seen, the parent and/or patient fills out a general questionnaire regarding review of systems and a few specific questions regarding presence of LUT symptomatology, constipation and encopresis. Before leaving, they will be given a voiding dysfunction specific questionnaire, detailed instructions on how to prepare for a uroflow-EMG study, and a voiding diary with a male or female urinal to measure consecutive urine volumes and record symptoms for at least 48 hours. While treatment is generally deferred until the workup is complete, if the child has significant constipation I will treat that aspect immediately. A subsequent appointment will be made to see one of our nurse practitioners or the physician assistant for a noninvasive uroflow-EMG along with pre- and post void bladder ultrasound images.

On the other hand, when patients are initially seen at my office at the Children’s Hospital, they usually will have a uroflow-EMG and formal ultrasound on the same day. At these visits only 10 or 15 minutes will be spent with me and an additional 30 to 60 minutes with the NP or PA. The staff will explain the plan of care in detail and provide the family with educational materials as well.

YH: The typical time spent with a family at the initial encounter varies between 30 and 45 minutes (which includes 15 minutes of physician face time). The educational materials I use include a voiding diary, a stooling diary, a diagrammatic representation of the Bristol Stool Form Scale (see diagram), a handout on the importance of a high-fiber diet with recommended foods listing their fiber content and a handout on pelvic floor rehabilitation. These materials are handed out based upon the patient’s individual requirements. The parents fill a questionnaire relating to the patient’s reason for the visit, with emphasis on urinary tract symptoms when they register.

Q2: Do you use any ancillary health care providers? If so, what is their role in caring for children with LUT dysfunction?

PH: We have dedicated urotherapists who in our setting are physiotherapists specialized in pelvic floor rehabilitation, and who will see the children after the first screening and start a non-interventional treatment also called urotherapy. After 6 weeks of urotherapy children are re-evaluated and if necessary interventional treatment is prescribed (neuromodulation, pharmacotherapy, alarms). We also have child psychologists who are involved with patients with major psychological problems at start of therapy or for children with motivational problems during therapy. If child abuse is suspected they are the first and only to take care of the patients.

ZR: Simple advice on the normal position during voiding, the frequency of voiding, the quantity of fluid intake, the treatment of constipation – sometimes seem superfluous and monotonous to be repeated over and over. Often, only the watchful eye of the urotherapist (or ancillary healthcare provider) can recognize a mistake in these habits. Also, it is necessary to constantly remind and correct them until the proper habits are adopted. A caring urotherapist (or ancillary healthcare provider), who has patience, without too great egocentricity; often seen in surgeons, will often do this job much better than we can.

IF: We were one of the first to use nurse practitioners to care for patients with LUT dysfunction. We started back in 1997 with the NP’s and nurses doing biofeedback and expanded their role to complete care (continued on next page)
of the patients. One of my NPs has pediatricians that speak just to her and don’t even need to speak to us. Patients refer their friends to her and bypass the doctors. We would be overwhelmed if not for the NP’s in our practice. We have 2 nurses that do biofeedback and uroflow/EMG’s aside from the NPs. Some NPs do their own biofeedback while others prefer to see patients and let the nurses do the biofeedback.

**KG:** Our Physician Assistant, Andrew Combs and Nurse Practitioners, Agnes Bayer and Daisy Medina-Kreppein, will do the uroflow-EMG studies or other urodynamic studies as indicated, review the bowel and bladder diaries with the parents and child, and institute a plan of care. This may include pelvic floor biofeedback for dysfunctional voiders, management of constipation and encopresis, behavior modification and anticholinergic or alpha blocker therapy as indicated. These clinicians also provide follow-up for urinary tract infections. Often patients are scheduled for a follow-up uroflow-EMG six to eight weeks after the initiation of therapy in order to monitor response and make additional adjustments in treatment. As therapy progresses the intervals between visits and any follow-up uroflow studies lengthens. Ideally, brief phone conversations between clinicians and parents occur between visits helping to keep patients on track, uncover potential problems early and contain costs for the parents by reducing visits.

**YH:** My nurse who is an R.N., takes a history regarding allergies, medications the patient may be taking, inquires into a review of systems and whether pediatric subspecialists are following the child. She notes any history of UTI and whether these were febrile or afebrile and if there was any recurrence. She goes into specifics about symptoms of voiding dysfunction (frequency, urgency, dysuria, hesitancy, straining, diurnal and/or nocturnal incontinence). A history of constipation is taken regarding frequency and consistency of bowel movements using a pictoral of the Bristol Stool Form Scale. She will ask the child to point to the type of stool on the scale that most closely resembles his/her usual bowel movements as well as their frequency. A score of 4 or below is suspicious of some degree of constipation. A urinalysis is then performed.

**Q3:** For those who use an ancillary care provider, how does the pediatric urologist integrate in the care of these children?

**PH:** We evaluate the children every 2 months together with the urotherapists. We together evaluate and decide on more invasive investigation or treatment.

**ZR:** The treatment of LUT patients is a team activity in which each participant of the team bears equal responsibility, both the one who performs the routine part of the work (rather unrewarding), as much as the one whose responsibility is to perform the non-routine part (creative work). Uroflowmetry is the procedure which requires patience and the repetition. This is also the most opportune moment when the patients can be instructed about the normal act of voiding. In my opinion, at this stage of the evaluation and treatment the urotherapist can be extremely beneficial to most patients.

On the other hand, in patients with incontinence not responding to classical forms of treatment, cystometry provides good insight to guide treatment. The physician may or may not need to be present for the cystometry depending on the need for specific questions or concerns during the cystometry. However, to catch the moment when the child is not anxious, to record this moment and interpret it is only possible if an attentive physician is present during the examination. If looking at the paper-work only, we shall often finish with the treatment of paper instead of the patient.

**IF:** When a patient does not show signs of progressing on the prescribed treatment plan this will usually make the NP consult with me. We may agree or change the treatment plan. In cases that surgical intervention has been recommended such as botox injections or cystoscopy and deflux injections, I will see the patient simultaneously with the NP and discuss the surgery with the family. In New York some patients don’t think that they are getting their dimes worth unless they are seen by the MD and they will migrate to me.

**KG:** It is important that physician contact is made just before or after our initial uroflow/EMG studies. The need to clarify issues and a family’s expectations for physician involvement will determine the frequency of visits with me or the need for a telephone call from me to review a study or progress. Fortunately for me, most of the care, follow-up and therapy are performed by our physician assistant or the nurse practitioners in the pediatric urodynamic center.

**YH:** After my nurse performs the above tasks, I will review them prior to my encounter with the family. I will focus on the significant portions of her assessment and will check the accuracy of the answers to some of the questions and confirm the nurse’s findings to my satisfaction. I will then dwell somewhat longer on the child’s bowel function history, which often requires further questioning of the parents as well as the child (because if you don’t ask, they won’t tell!). After I feel that the child has acquired some degree of comfort with my presence I will proceed to the physical examination. The spine is examined for deformities, sacral dimples and hair tufts. The costovertebral angles are assessed and the external genitalia evaluated. Palpation of the abdomen is done very carefully after ensuring total relaxation of the abdominal wall by gently asking the child to breathe in and exhale slowly. All four quadrants are examined with particular attention to the left lower quadrant. The presence of a distended sigmoid is a pathognomonic finding in constipation as it indicates that stool is being accumulated in the sigmoid. Physiologically, healthy bowel motility calls for stool to transit through the sigmoid and be stored in the rectum prior to evacuation. Storage of stool in the sigmoid colon is a sure indication of a disturbance in bowel transit.

**Q4:** What is your typical approach for an initial visit for symptoms of LUT dysfunction and are there “key” aspects that trigger different approaches?

**PH:** Initial approach is urotherapy. Only if an ultrasound shows abnormalities such as dilatation of upper tracts or if the uroflow is obviously obstructive then we will do videourodyamics first. Those children with dysfunctional voiding on their first flow will come back for half a day of uroflowmetry. If consistent dysfunctional voiding is observed pelvic floor rehabilitation will be introduced at start of therapy.

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ZR: At the first step it is necessary to define whether the child has a true LUT dysfunction or whether it is a variant of normal maturation – establishment of normal LUT function. Is the treatment of such patients necessary at all? The protection of children from exaggerated therapy (primarily from pharmacotherapy) is significant, particularly at the time of “medical marketing” and perpetual search for patients.

In everyday practice, the diagnosis of LUT dysfunction is based on different criteria. Some authors base the diagnosis only on symptoms; others on the results of noninvasive functional diagnostic procedures (uroflowmetry and ultrasound examination), as well as urohydagnostographic examination findings. Rarely, the diagnosis is made on cystometry.

Dysfunctional voiding symptom score (DVSS) is currently used in the diagnosis and grading of LUT dysfunction. However, there are patients with symptoms of LUT dysfunction, although without confirmation of urodynamic findings, and vice versa. In patients with negative voiding history, the possibility of having LUT dysfunction is not excluded. This suggests that the diagnosis of LUT dysfunction based only on symptoms or a symptom scoring system is doubtful and other diagnostic tools would be necessary.

If the child undoubtedly suffers from LUT dysfunction, the next step is to define whether the child has pyelonephritis and kidney damage (UTI with fever, ultrasound, DMSA); also, whether the problem is at the LUT level only.

Next, we stratify patients on the subtypes of LUT dysfunction: 1) overactive bladder, 2) detrusor-sphincter dysfunction (internal or external), 3) patients with the former or latter subtype, or 4) underactive bladder. Illness history, voiding diary, ultrasounds, uroflowmetry/EMG with PVR (post-voiding residuum) measurement, possibly VCUG, can help us in the classification of such patients.

Patients with clearly described constipation make a special group, because it requires the primary treatment of this problem. Patients with VUR also require a different follow-up and treatment.

After routinely applied behavior therapy, at the next level different treatment modalities are used. The success of such modalities has mostly remained unconfirmed. Unfortunately, as common in studies, we have similar results in groups of patients on active drugs and placebo groups. Patients with overactive bladder are treated with anticholinergics, those with detrusor sphincter dysfunction with alpha-blockers, and patients with combined subtypes with both drugs. We also treat the underactive bladder with a high PVR with alpha-blockers. If the therapy is without effect, the next alternative is biofeedback. However, availability of biofeedback equipment is a major problems. This also requires skillful staff and considerable finances, so that in many undeveloped and transitional countries such therapies are performed sporadically and unsystematically. Treatment of dysfunctional voiding can be frustrating and bothersome both for the unmotivated patient and therapist, while at the same time requiring permanent cooperation.

This classification and approach is too rough and simplified, but it can be of help in everyday practice and serves as a main orientation.

IF: My initial approach to LUT dysfunction is first get a detailed history from the child and parents. I cautiously rely on what the parents tell me about the child’s bowel habits. A good exam is essential and one needs to feel the abdomen for stool. There is no reason to ever do a rectal exam on a child with LUT dysfunction unless you are worried that they have a rhabdomyosarcoma. It is critical to watch the interaction of the child with the parent and how they interact with you. The child that is difficult to engage is more likely to be the one that is going to be the difficult one, while the one that engages well and interacts normally will typically respond readily to a simple timed voiding and bowel program protocol. A routine bladder ultrasound is done to determine if the child has a post void residual and to measure rectal diameter. The amount of stool will dictate how aggressive I need to be with cathartics. Everyone gets a bowel program regardless of the fact that I can or cannot feel stool in the abdomen. I have found that Miralax by itself does not do the job in many cases and it is essential to use senna based laxatives regardless of what the gastroenterologist tell you. We prefer to use the Iowa criteria for the definition of constipation to the Rome criteria.

Boys with dysuria all get an uroflow/EMG to evaluate for external or internal sphincter dyssynergia. If they have it, then we have them sit to void, as well as doing timed voiding and a bowel program. After they come back in 4-6 weeks if there is no improvement and they have done a thorough job with the bowel regime and sitting then we will offer directed therapy.

The same goes for girls with recurrent UTIs and wetting, we use the same treatment paradigm and if there is no improvement they move on to directed therapy, be it biofeedback or alpha-blockers.

The child that tells me that they don’t feel when they wet is usually going to end up on imipramine after we have exhausted all avenues. These kids probably have a central processing problem and using anticholinergics generally is fruitless. The same goes for the ones that have encopresis and tell you they don’t know when they had the accident.

Post void dribblers all go to biofeedback or alpha-blockers after they have had little or no response to other therapies.

KG: Minimal symptomatology, particularly in younger children, is treated with timed voiding and when indicated with bowel management. Patients with recurrent urinary tract infections or a history of one febrile urinary tract infection are managed more proactively. Patients with recurring UTIs are maintained on antibiotic prophylaxis until we are satisfied that they are responding well to their bladder and voiding regimen. Once LUT symptomatology has disappeared and voiding has normalized, then consideration is given to discontinuing prophylactic antibiotics. Any patient with LUT symptoms who has an indication for a VCUG, (especially a history of one febrile UTI, a significantly thickened bladder wall or dilated lower ureters on ultrasound, or a suspicion of anatomic urethral obstruction) will have a video urodynamic study (VUDS), i.e., a VCUG with simultaneous urodynamics. Patients who have failed treatment based on history and uroflow-EMG findings will also be considered for VUDS.

The screening uroflow-EMG serves to direct therapy according to the voiding disorder that we are treating: 1) dysfunctional voiding; 2) idiopathic detrusor overactivity with a quiet pelvic floor (or idiopathic detrusor overactivity disorder, i.e. IDOD); 3) underutilized bladder (includes infrequent voiding with enlarged bladder capacity and the rarely seen decompensated bladder); and 4) primary bladder neck dysfunction (PBND). We almost never obtain a uroflow alone without simultaneous EMG unless we are strongly suspicious of a urethral stricture or following the patient post-dilatation or urethroplasty. In our experience treating patients solely on the basis of symptomatology and a simple uroflow is prone to making an incorrect diagnosis and mismanagement because of the overlap in LUTS amongst disorders and alternative reasons for flow pattern appearance. Symptomatology, particu-
lary amongst dysfunctional voiders and patients with IDOD, often overlaps. For example, both often have urgency, frequency and incontinence. Patients with IDOD by definition have detrusor overactivity and of those with dysfunctional voiding, more than 90% have detrusor overactivity as well. An uroflow with EMG is extremely useful in differentiating between these and other disorders. Staccato voiding on a simple uroflow can have a quiet EMG if the cause is straining because of obstruction or detrusor hypocontractility. Conversely, patients with an active pelvic floor EMG during voiding often have staccato voiding because of it, but patients with a tense pelvic floor throughout voiding may have a normal flow pattern despite being dysfunctional voiders as well. Patients with an underutilized bladder or volitional infrequent voiding tend to have a larger than normal bladder capacity, sometimes provoke bladder overactivity during late filling but almost always relax their pelvic floor muscles when voiding.

We look carefully at the uroflow-EMG when diagnosing a voiding disorder, and pay particular attention to the EMG lag time, i.e. the time interval between the cessation of pelvic floor EMG activity and the start of urine flow (normal is 2-6 seconds). An active pelvic floor during voiding by definition is dysfunctional voiding whether with or without detrusor overactivity. A short or negative EMG lag time, i.e., < 2 seconds, especially with the symptoms of urgency and a quiet pelvic floor EMG on voiding, suggests the diagnosis of IDOD and the possible need for anticholinergic therapy. However, while greater than 90% of IDOD patients will have a short lag time (particularly if allowed to have an age appropriately full bladder for the uroflow-EMG) those without a shortened lag time but with severe urgency and a quiet pelvic floor during voiding also are likely to have IDOD, but were just not experiencing it at the time the flow study was performed. Both groups benefit from timed voiding and depending on the severity of the overactivity and impairment of compliance (as evidenced by diminished functional capacity and a thickened bladder wall on ultrasound), will likely require anticholinergic therapy as well. Voided volumes much smaller than expected for age on the voiding diary also support the diagnoses of IDOD or dysfunctional voiding, but cannot differentiate between the two. However, once a diagnosis is established and therapy is initiated (biofeedback, anticholinergic medication or both) the parents can be taught to use the volume measurements as a tool to monitor recovery.

**YH:** I will then perform a pelvic ultrasound to rule out post-void residual and the diameter of the rectal crescent is measured as described by Joensson et al. A value superior to 29.4 mm ± 2 S.D. represents fecal impaction and has been referred to by Koff as FABBY (Fecal Accumulation Behind the Bladder in Youths). After determining the presence and type of voiding dysfunction present and the presence or absence of constipation, I usually focus on management of constipation for a period of 6-8 weeks before addressing any therapy specifically directed to the urinary tract. In the presence of daytime associated with nighttime wetting, I inform the parents that these issues will be addressed sequentially focusing on the daytime wetting first.

**Q5:** Each of you has expertise on modes of treatment that can be applied to children with refractory response to LUT dysfunction. Please describe and explain your application of these treatments.

**P. Hoebeke: Pelvic Floor Rehabilitation**

Since Kegel first described his experience with physiologic therapy for stress urinary incontinence in women, pelvic floor rehabilitation (PFR) has long been the most common form of conservative treatment for stress urinary incontinence in women. The use of PFR for stress urinary incontinence is based on 2 functions of the pelvic floor: support of the pelvic organs and contribution to the sphincteric closure mechanism of the urethra. In recent years, PFR has increasingly become part of the treatment of overactive bladder (OAB) in adults. The rationale for its use in OAB is less clear, however, a reflex inhibition of detrusor contraction on contraction of pelvic floor muscles has been demonstrated. A recent Cochrane review concludes PFR can be recommended to be included in the first-line conservative management program for women with stress, urge or mixed, urinary incontinence. In children stress urinary incontinence is rare, however, overactive bladder and dysfunctional voiding are rather common. In dysfunctional voiding children habitually contract the urethral sphincter during voiding. Normalizing pelvic floor activity in children with dysfunctional voiding is one of the new specialized therapies based on the rationale that the pelvic floor contributes to the sphincteric closure mechanism. In contrast with the therapy in adults which aims at reinforcement of the pelvic floor muscle activity, in children with dysfunctional voiding pelvic floor relaxation is the primary aim of therapy. In OAB the contraction of the pelvic floor inhibiting the overactive detrusor contraction is the aim of therapy. As many children have simultaneous overactive bladder during filling and dysfunctional voiding during emptying they should learn both to relax and to contract the pelvic floor. Kjolseth et al were the first to report on the use of PFR in children for dysfunctional voiding and for overactive bladder.

A dedicated urotherapist (nurse, physiotherapist...) is the most important part of this treatment. There are different ways to teach children the exact way to relax their pelvic floor. In our centre EMG and uroflow biofeedback are most frequently used. We have been reporting immediate success in 92% of children and long-term effect in 82% in different patient groups. Others have published equal outcomes with different treatment modalities. Use of videogames, group sessions and short courses have been described. However the evidence is still low and we need further comparative studies to proof the benefit.

We recently conducted a prospective controlled study in which 38 children with non-neurogenic LUT conditions, resistant to outpatient urotherapy, were included to evaluate the effect of a clinical or in patient voiding re-education program or voiding school (VS). Sixteen children on the waiting list for the same program were included as controls having no treatment while on the waiting list. The clinical voiding re-education program consisted in instructions on voiding and drinking, individualized voiding diaries, PFR, uroflowmetry, cognitive therapy and psychological support. Data on voiding, drinking, pelvic floor control, voided volume, uroflow, incontinence and stool habits were gathered before the program, during the program and 6 months later. In the control group the same data were gathered when they were put on the waiting list and 6 months later. In the study group
a positive effect of the VS was observed in 92% of children, with 42% became completely dry, 24% changed from incontinence during day and night to incontinence day or night only, while in 26% incontinence remained. However, in all patients the number of incontinence periods and the amount decreased. In the control group no differences were observed between the point of intake and 6 months later. The study group did significantly better with improved voided volume and incontinence compared to the control group. This is the first prospective controlled study on the effects of urotherapy including PFR. (Unpublished data).

Further prospective controlled studies are needed, but evidence from treatment in adults and the preliminary evidence from our study support our idea that pelvic floor rehabilitation is part of treatment for LUT conditions in children.

References

Z. Radojicic: Botox Therapy

About ten percent of patients do not react to the above described therapy. In my opinion, most pediatric urologists recognize such patients as a urological-surgical problem only. However, this group of patients is also heterogeneous. Now we classify them (rightly or wrongly?) into the following groups: patients with a small overactive bladder and incontinence, patients with detrusor sphincter dysfunction (in males with evident voiding difficulties and with valvular posterior urethra-like symptoms (without anatomical posterior urethral valves), and patients with underactive large bladder, with difficulties in voiding, a large residual and incontinence.

Botulinum toxin A (BTX-A) certainly has a place in the treatment of such patients. To call a person an expert in BTX-A treatment is rather difficult. The mechanism of BTX-A effect in patients with a strong overactive bladder is logical and clear. Still, in the case of BTX-A usage in detrusor-sphincter dysfunction, the story is not so simple. Does it act on the floor of the pelvis, sphincter, and the complete region or is it again the question of placebo effect? There are urologists believing that it is only the case of a “cosmetic” preparation? The effect of botulinum is transitory; however, it can break the vicious circle of detrusor-sphincter dysfunction and the period when it is sustained can be used for retraining the patient in normal voiding. We treat such patients with BTX-A under general anesthesia. The toxin is injected in dosages of 50-100 units (50 IU/< 40 kg and 100 IU/> 40 kg). 100 IU of BTX-A, diluted in a 4 ml of saline (25 units per ml) and injected by a transperineal 21 or 23 gauge needle in the pelvic floor, which includes the external sphincter (muscle complex around the urethra). In boys the level of external urethral sphincter is localized by endoscopy just under the colliculi seminales (we visualize the light on the perineum), and after palpation of the urerogenital membrane we inject the toxin at this level at 3, 6 and 9 o’clock positions at a depth of 1.5 - 2 cm. Under cystoscopy we also exclude anatomical obstruction. In girls BTX-A is injected approximately 1.5 - 2 cm deep around the urethral meatus at 3, 6, 9 and 12-o’clock positions. We are of the opinion that our variation is especially appropriate in less cooperative patients.

Most difficult to treat is an “underactive” bladder, a large dilated bladder, with difficult voiding and a large PVR resistant to medical and others conservative treatment. I find it most difficult to advise such patients to undergo CIC catheterization with or without a Mitrofanoff stoma. The assessment of risk/usefulness relationship (on one hand kidney damage and on the other disturbed life quality due to catheterization stoma) is an extremely difficult and responsible task. It is very frequent that the decision and judgment on the destiny of such patients is left to the authority. Any treatment modality which is less aggressive and not life-time is justified to be applied; thus, the use of BTX-A has also its place in such patients.

I. Franco: CNS Agents

In children who have persistent issues with overactivity symptoms we have found that the use of tricyclic antidepressants has made a remarkable difference. We obtain a thorough history from the families and in many cases it will become evident that the mother, father, aunt or brother or sister has some type of neuropsychiatric problem. In some cases the family member is on medication for the problem, in others they will tell you that the person definitely has a problem but they are not taking medicine but probably should be. It is these kids that are the ones that are most likely to respond to imipramine or in some cases we will use Cymbalta or Lexapro. In a series of 55 patients that we treated with low dose imipramine we had an 80% complete or partial response and a 65% complete response rate. These were kids who were refractory to alpha-blockers and anticholinergics that responded to tricyclics. There are going to be those who will say that biofeedback works for these kids. I would argue that it does not and I have not seen it be useful in OAB without EDSD. In our refractory patients we took some of our patients off imipramine and tried tiibial nerve stimulation and found that it did not work as well as the medication, aside from the fact that it was more costly and time consuming for the families.

The most difficult kids to treat are the patients with ADD/ADHD as we do not like to use tricyclics in this group because of tachycardia issues. In this case we will consult with the psychiatrist and use SSRIs or SNRIs if indicated or increase the ADD medication dose. In other cases we will use high dose non-selective alpha-blockers to help with the overactivity.

Getting a good behavioral history and seeing how the patient in (continued on next page)
teracts in the office is critical. Also school performance is important as there are numerous kids that we see who have LUT dysfunction and if the parents are pushed they will say that the teachers have suggested that the child be tested for ADD and the parents refuse. In these cases I tell them that they should not bother coming back until they are tested and on medication if they test positive, since many will get better with appropriate treatment of their neuropsychiatric issues.

We have used Cymbalta and Lexapro for patients with shy bladder syndrome with good results. I have also used imipramine with great results for giggle incontinence. I have an easier time convincing a mother to give her child imipramine than Adderall or Strattera because of the weight loss and appetite issues associated with those drugs. One thing that we have encountered with our patients is that there is a definite incidence of patients becoming what the parent’s call weepy, crying very easily. In some cases if the child is dry we will lower the dose and that fixes the problem. In other cases we need to stop the medication and find an alternative. Another thing to watch out for when using imipramine is that it can unmask mania. A thorough family history is important since bipolar disease and severe depression run in families. Not being aware of the mania potential can lead to real behavioral issues if not recognized promptly.

Given the data that is now available and some recent interesting studies on brain imaging and neuropsychiatric disorders, it is clear that LUT dysfunction may be a window into future neuropsychiatric problems for some of these children.

K. Glassberg:  Alpha Blockers

Alpha blockers in my practice are prescribed for two different LUT disorders: primary bladder neck dysfunction (PBND) and secondary bladder neck obstruction (BNO). It is important to know which entity is being treated, as expectations for alpha blocker therapy vary for each. Patients with a prolonged EMG lag time, a prolonged flow curve that peaks during the latter half of voiding, and with LUTS, particularly hesitancy, likely have PBND and will require alpha blocker therapy. In PBND, one can expect a doubling of Qmax and Qave within 6 weeks of initiation of alpha blockers; but the patient’s subjective relief of symptoms may take months to occur. It is important to advise families not to be disappointed with the lack of initial symptomatic relief. Instead they should be encouraged by the objective progress that is documented by the normalization of uroflow-EMG parameters.

Secondary BNO is a different phenomenon and can be seen in both dysfunctional voiding and IDOD. We have previously documented that secondary BNO is common in patients with a history of posterior urethral valves. It develops secondary to detrusor hypertrophy in response to more distal obstruction and as the hypertrophied muscle fibers come together at the bladder neck impinging upon the outlet. In patients with dysfunctional voiding, the distal obstruction is the hyperactive external sphincter during voiding. In patients with IDOD, the obstruction is also at the external sphincter occurring with the patient’s attempts to maintain continence during an involuntary detrusor contraction. Either condition leads to a thickened detrusor and bladder neck that does not open as readily as it should. In the absence of videourodynamics, diagnosis of secondary BNO in these patients is not as easy as it is in PBND. It is based on a combination of findings which include an identifiable thickening of the bladder wall on ultrasound, depressed and prolonged uroflow, and frequently elevated post void residuals. Detrusor pressure during voiding would also be elevated if urodynamic studies were performed. Improvement in Qmax and Qave flow rates with alpha blocker therapy tends to be less dramatic then that seen in treating PBND. We reserve alpha blockers only for patients with dysfunctional voiding or IDOD who fail to improve on therapy and who meet the above criteria. This type of BNO represents approximately 10-15% of patients diagnosed with either condition.

Our experience is largely with tamsulosin, which in general is well tolerated in children with minimal incidence of headaches and nasal stuffiness. In general, younger children are started on a regimen whereby the 0.4 mg capsule is opened and half or less of the crystals are added to food or drink. It is important to recognize that this is an off-label use of alpha blockers. We monitor blood pressure before and during therapy; even though documented cases of alpha blocker induced hypotension in our practice have not been seen.

Y. Homsy:  Bowel Management

My nurse will go over our bowel management handout emphasizing the intake of an amount of fiber equal to the child’s age (in years) + 10 (in grams), the normal requirement being age (in years) + 5 (in grams). A recommendation to use a stool softener such as polyethylene glycol powder is also made. Fluid management (one glass of water per year of age per day – with a maximum of 10 – 12 glasses) and a timed voiding regimen is recommended.

The patient is sent home and the parents are requested to maintain a voiding diary for 2 days and stooling diary relying on the Bristol Stool Form Scale for guidance and fill in the number of grams of fiber ingested on a daily basis.

At the next visit the data is reviewed and if there are persistent symptoms the child will either be treated with anticholinergics provided the constipation has improved, while being maintained on a bowel regimen of high fiber and/or stool softeners as anticholinergic therapy alone is likely to make the fecal retention worse.

Persistence of symptoms at the next visit will call for a flow/EMG study to determine or rule out the presence of dysfunctional voiding. EMG lag time is assessed and in the presence of pelvic floor discoordination, I will typically direct the child to our Physical Rehabilitation Department for pelvic floor rehabilitation with biofeedback exercises. These are taught by the staff and are to be continued at home. Our Physical Rehabilitation Department is staffed with some 20 trained physical and occupational therapists located at the main hospital campus as well as at satellites in the surrounding counties. This program has been of major help in preventing patients from traveling long distances and thus remaining compliant with their therapy. 6 – 8 sessions are usually required.

Should constipation remain a persistent problem we will again refer the patient to Rehabilitation Therapy for transcutaneous electrical stimulation with interferential current therapy as described by Clarke, Chase et al. for slow transit constipation. We have modified their regimen to suit patients with retentive constipation with very satisfactory responses.

Rationale of Bowel Management in LUT Dysfunction

The etiological role of constipation in LUT dysfunction has slowly emerged over the past three or four decades. Pediatric urologists and gastroenterologists have taken a closer look at the role of constipation with regard to urinary incontinence, urinary tract infection and vesicoureteral reflux. In 1973 Neumann et al. demonstrated clinical (continued on next page)
BRISTOL STOOL FORM SCALE (BSF-Scale)

A diagnostic aid to classify stool into 7 groups. Because stool form depends on the time it spends in the colon, there is a correlation between colonic transit time and BSF type. Lewis SJ, Heaton KW, Scand J Gastroenterol. 1997; 32:920

Evidence for an association between constipation and urinary tract infection (UTI) in 34% of children with UTI. O’Regan et al. further demonstrated that recurrent UTI and urodynamically demonstrated OAB were associated with constipation. The presence of constipation in these children was denied by 50% of mothers, whereas direct questioning of the children revealed that they had only 2-3 bowel movements per week. The frequency of urinary incontinence, and UTI in 234 constipated children was evaluated by Loening-Baucke before and after the management of constipation. Successful resolution of constipation occurred in 52% at 12-month follow-up with concomitant resolution of daytime incontinence in 89% and enuresis in 63%. Recurrent UTI also resolved in all children who had normal urinary tract anatomy. In 1987 O’Regan et al. subjected 17 constipated children with vesicoureteral reflux (VUR) to urodynamic and rectal manometric studies. All had evidence of OAB and abnormal dilatation of the rectum. In 1998 Koff et al. showed that constipated children with recurrent UTI and VUR had a higher rate of recurrent infections and a lower rate of reflux resolution than in controls. Children with this syndrome, which was termed ‘Dysfunctional Elimination Syndrome’ (DES) were more prone to unsuccessful surgical outcomes or development of contralateral reflux. They also manifested more postoperative UTI’s despite having undergone successful reimplantation.

A retrospective review of 482 children aged between 4-17 yrs seen in health maintenance clinic in Iowa during a 6-month period and followed from birth revealed a prevalence rate for constipation of 22.6%. The prevalence for urinary incontinence (all types in all children) was 10.5%. Those without constipation comprised 7.3% whereas those with constipation constituted 21.9% of the group.

Although additional evidence is continually being brought to light linking constipation to voiding dysfunction, the exact mechanisms of this relationship remain unclear. Whether it is the mere pressure effect of rectosigmoid distension with stool on the bladder and pelvic nerves or some other triggering mechanism remains a subject for conjecture. A presentation at the recent 2009 Section of Urology Meeting of the AAP by Burgers et al. concluded that “In nearly 70% of children with LUTS, painless rectal distension with a rectal balloon significantly but unpredictably affects bladder capacity, bladder sensation and detrusor overactivity regardless of whether or not children have constipation and independent of their urinary symptoms, clinical features or baseline urodynamics.” These results justify further research regarding rectal-bladder dynamics as well as the pathophysiology underlying the coexistence of rectal fullness and LUTS in children.”

A central mechanism that regulates the brain-bladder and brain-gut axis has recently been invoked. Studies of PET scans of the brain have demonstrated responses in different areas of the brain to changes in bladder volume and urge to void. Similar vascular phenomena were demonstrated in response to bowel distension and expectation to defecate.

Therefore, it appears prudent to me that a therapeutic approach to voiding dysfunction should start by assessing the bowel status in relation to bowel habits, frequency and consistency of bowel movements, dietary habits particularly relating to fiber intake. Several methods are available to assess bowel function; pediatric gastroenterologists have extensively debated the matter with only a few publications taking into consideration the impact of constipation on the urinary tract. While it may be some consolation that many constipated children do not have urinary symptoms, when these make their appearance in the form of frequency, urgency, enuresis, UTI’s (mostly afebrile), it is more than likely that an underlying constipation problem will be uncovered.

One can use one of several methods to assess the presence or absence of constipation. The Rome II, Rome III and Paris Consensus on Childhood Constipation Terminology Group (PACCT) criteria rely on a questionnaire as to the number and consistency of bowel movements. Although these criteria are the result of extensive discussions among pediatric gastroenterologists, I find them of limited use in my practice because of the difficulty parents often have in describing their children’s bowel habits. However, they do have their place and many clinicians like to use them. I find plain abdominal X-rays of little value on a routine basis except in obese children and rectal manometric studies are relatively invasive. A few years ago I became aware of the Bristol Stool Form Scale which has been validated in some 1900 individuals and was found to be simple and reliable not only at the initial assessment but also on follow-up visits to assess progress. Most children often show a vivid interest in comparing their stool to the pictorial diagrams provided in the Bristol Scale and end up being more reliable historians than their parents/guardians in this respect! Several versions of the diagram are available on Google by searching Bristol Stool Form Scale.

Further confirmation of constipation is determined by pelvic ultrasonography at the time when post-void residual volume is measured with pre and post-voiding images. Treatment is instituted with a high-fiber diet and a stool softener and resistant cases are treated by transcutaneous electrical stimulation with interferential therapy.

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Q6: What is the duration of treatment that you anticipate for patients with LUT dysfunction? Is the treatment duration different amongst patients with LUT dysfunction?

PH: The minimal treatment duration is around 6 months for most children with just overactive bladder and normal emptying. With dysfunctional voiding and underactive detrusor the treatment duration is 1 year or longer. If no result is obtained after one year, we will sent the patients for more intensive treatment like in voiding camps and voiding school (which is inpatient training for 2 weeks) and eventually for more invasive treatments like botulinum toxin injection in sacral nerve stimulation. In these decisions the age of the patient is important. Only children of 8 years and older are considered eligible.

ZR: I keep turning back to the theory that there is a wide spectrum of patients with LUT dysfunction, and it is difficult to correlate the results of various centers, because we have patients who are neglected by some physicians and over-treated by others. As to the prognosis of such patients, in some the disease will spontaneously resolve, while in others placebo treatment can bring improvement or cure. Generally speaking, an honest physician will be uncertain whether the result is due to treatment effects or to the influence of both factors. There are no studies which could competently and with certainty confirm the success of certain therapies.

At the other end of the spectrum there are patients who must be on drugs (permanently or quite frequently) so as to control their problems, and whose LUT function presents a locus minoris. Unfortunately, we have also patients whom, at this point of time, despite permanent treatment, we cannot offer objective help.

How long do we treat certain patients? I think that the question should be for how long and how often should we keep such patients under follow-up. There is always the danger that the patient has LUT dysfunction but without symptoms; thus, they should be approached with additional caution.

IF: I tell my patients that have been started on alpha-blockers or imipramine that they will be on therapy for 6 months after they have been completely dry. I then taper the meds slowly and if they become symptomatic again then we go back to the last dose that worked and restart the 6-month cycle all over again. Some kids are able to come of the meds right away and others linger for long periods of time. In other cases they come off and a couple of months later they are back again with the same symptoms. This speaks to a problem that is probably going to be a life-long issue for these patients that recur after coming off medication. In many instances where there are anxiety issues I make sure that the patients do not come off treatment just before going to camp or the start of the school year which can be very stressful and lead to significant voiding issues.

KG: In general, patients are told that they will be followed by us for several months to more than a year or two which depends on the severity of their disorder, how long it has been present prior to them being treated and what effect, if any, the disorder has had on the bladder and upper tracts. Anticholinergic medications usually are maintained until the patient is dry and symptoms are relieved, which in general amounts to several months or more. Families who understand the importance of timed voiding for the recovery from LUT symptoms and are able to follow through with our recommendations usually see their children recover faster. One factor which impedes recovery or can even cause a relapse is the development of constipation. Aside from treating constipation when present before starting anticholinergic therapy (since that alone may cure them), it is advisable to diagnose and start treating constipation before initiating anticholinergic therapy since it may make the constipation worse. Proactive treatment is also advisable since anticholinergics can lead to constipation when none existed before.

Biofeedback for dysfunctional voiders usually requires 3 or 4 sessions before the patients learn to consistently keep their pelvic floor muscles relaxed during voiding. Session are scheduled every week or so until the child “gets it”, then are brought back at 1, 3 and 6 months to make sure they are continuing to void normally. In our hands we find that biofeedback therapy works best when we integrate into the therapy with the actual motor unit sound emission generated by the EMG, as well as the EMG graph appearance and its effect on the flow curve. Patients are taught the difference between the muscles being tight and relaxed, usually by first demonstrating this to them by placing the EMG patches on our own hands and manipulating the muscles. Then, with patch EMG electrodes placed at the 3 and 9 o’clock positions at the margin of their external sphincter, this concept is transferred to controlling their pelvic floor by teaching the child to voluntarily squeeze and relax their external anal sphincter. Some do not respond as quickly and need more than 3-4 sessions to achieve consistent control; most are treated with anticholinergics as well and as outlined above with alpha blockers if concomitant secondary BNO is also associated. In addition, we also teach the children to verbalize the principles of effective relaxed voiding and give them homework exercises for pelvic floor therapy which can be practiced with their parents. We occasionally use computer games for pelvic floor therapy in patients who have difficulty grasping the concepts involved.

Patients with constipation often tend to relapse after successful therapy and, therefore, should not be discharged from follow-up too soon. Sometimes it is even the anticholinergic therapy itself which causes or exacerbates the constipation. One should also be aware that encopresis can occur without constipation. In our experience this is especially true in patients with severe detrusor overactivity and interestingly, often resolves with anticholinergic therapy.

References
While alpha blocker therapy for secondary BNO has a finite treatment endpoint (usually 6-12 months) its use in PBND is another story. In the majority of patients with PBND, the condition is chronic and very few of our patients can be taken off of alpha blockers without resumption of pre-alpha blocker symptomatology and abnormal uroflow-EMG parameters. We consider a trial of discontinuing blockers after 2 years of successful therapeutic response.

**YH:** Treatment duration varies from individual to individual and may be as short as 2 months or longer than one year. Patients with severely overactive bladders may require a trial of different anticholinergics until a suitable one is found to be of help. Some patients will require Botox injections to the detrusor in non-responsive OAB. In some cases Botox injection to the external sphincter may be required when there is severe and resistant discoordination that does not respond to alpha-blockers. Alpha-blockers have also been successful in managing the underactive bladder and in significantly reducing high post-void residuals even in the absence of documented external sphincter discoordination.

**Q7:** How do you define successful treatment?

**PH:** No more symptoms, more specifically no incontinence and if possible no urge. For those with recurrent UTI, then I use the criteria of no UTI during at least 2 years.

**ZR:** Above all, clinical success is that which defines success. Established continence, absent UTI and decreased dilatation (at least no deterioration) are the key elements which will convince the parents that treatment is successful. We have made the assessment of the results based on IUT, voiding curves, EMG activity during voiding, post voiding residual and VCUG. However, clinical improvements with the shape of flow pattern curve/EMG activity and PVR are basic parameters in children for the evaluation of treatment effect.

Of diagnostic procedures, normal parameters alone, without clinical findings, are rarely sufficient to define a successful therapy. No single diagnostic parameter has such high specificity and sensitivity to be sufficient to define the problem of LUT dysfunction. To sum-up (in scoring system), we define this problem more precisely (our unaccepted report submitted for publication). DVSS has been accepted and can define well the problem and the stage of dysfunction symptoms. However, the patients who have the problem but without symptoms can be overlooked or qualified as milder cases. A score which would also encompass parameters obtained by diagnostic procedures could better define the problem, making the follow-up of such patients easier, comparing results and helping in defining treatment.

If we could be brave enough, we should ask ourselves whether we might be on a wrong track with the whole concept of understanding LUT dysfunction and its treatment. Perhaps a new era in the understanding of this problem begins with a concept underlined by Israel Franco (J Urol 178: 761-774, 2007, September 2007 and AAP 2008 Boston) on a central disorder in the patients with overactive bladder. Also, the results of Dr Xiao, Chuan-Guo (AAP 2008 Boston) on the reinnervation of the urinary bladder (for now in patients with neurological problems) could be milestones of the new era in the treatment of LUT dysfunction patients.

**IF:** In my opinion a success is when the child is completely dry and or infection free. In cases which have elevated post void residuals I need to see a PVR of less than 10 cc in 2-3 consecutive visits to declare them cured. Everyone comes back 6 months later for f/u since I have found that these kids have short memories and they go back to doing what they were doing before and this helps reinforce that they continue the right voiding habits.

**KG:** It is essential that one recognizes that relief of LUT symptoms is only one aspect of what is needed for us to consider treatment a success. We also focus on the importance of normalization of abnormal uroflow-EMG parameters, e.g., Qmax and Qave, the uroflow pattern, a quiet EMG during voiding, an age appropriate bladder capacity and the EMG lag time. Resolution of bladder wall thickening can take a long time and is not a goal per se, focusing instead on how the detrusor behaves, not its appearance. Other parameters are cessation of urinary tract infections, resolution of reflux and complete bladder emptying.

**YH:** Successful treatment is a relieved family with no more wetting issues, complete bladder emptying, absence of recurrent UTIs and freedom from constipation.