Voiding Dysfunction

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1. Introduction

This core curriculum section covers **Pediatric Lower Urinary Tract Dysfunction** and **Enuresis**.

1.1 Keywords

Bladder and bowel dysfunction (BBD), lower urinary tract (LUT) dysfunction, bladder overactivity (OAB), daytime incontinence, enuresis, dysfunctional voiding

2. Pediatric Lower Urinary Tract (LUT) Dysfunction

2.1 Introduction

LUT Dysfunction (LUTD) is a ubiquitous problem in the pediatric population and affects children of all ages. In many instances the problem will resolve with time but in other cases it can persist into adulthood. We now understand that pediatric lower urinary tract conditions consist of heterogeneous symptoms that involve a variety of pathophysiologic influences. In this chapter we will venture to classify the symptoms that make up LUTD as well as to clarify how to diagnose and treat the condition.

2.2 Terminology/Classification

The first step in defining a problem is establishing a common terminology. The International Children's Continence Society has published a standardization of terminology for LUTD which should be reviewed by all providers caring for children with BBD. Speaking a common language is important in properly characterizing these patients and tailoring treatment while making it easier to compare outcomes.[1] **Bladder and bowel dysfunction (BBD) is the comprehensive term of combined bladder and bowel disturbances** that can be subcategorized into lower urinary tract dysfunction and bowel dysfunction. **Lower urinary tract (LUT) dysfunction is a disturbance in urinary storage, emptying or both. Bowel dysfunction is a disturbance of the gastrointestinal tract in either storage, and/or elimination of stool; most commonly constipation and/or encopresis (ie, stool incontinence).**

2.2.1 LUT Symptoms

LUT symptoms of bladder storage are common and include variation in voiding frequency, altered sensation of bladder filling and continence. **Children who void > 8x per day have increased daytime urinary frequency whereas children who void < 3x per day have decreased daytime urinary frequency.** Urinary incontinence is defined as involuntary leakage of urine and can be subdivided as continuous incontinence, intermittent incontinence, daytime incontinence and enuresis.[1]

Continuous incontinence refers to constant urine leakage resulting from congenital malformations (e.g. ectopic ureter, exstrophy variant), functional loss of the external urethral sphincter function (e.g. external sphincterotomy) or iatrogenic causes (e.g. vesico-vaginal fistula). Intermittent incontinence is the leakage of urine in discrete amounts and may occur while awake or asleep. **Intermittent incontinence that occurs while awake is termed *daytime incontinence* whereas intermittent incontinence that occurs while asleep is termed *enuresis*.**

Other common LUT storage symptoms include urinary urgency and nocturia. **Urinary urgency refers to the sudden and unexpected experience of an immediate and compelling need to void.** The symptom of **urgency is often the hallmark of bladder overactivity (OAB)** but one must remember that even though urgency and OAB are often interchanged in studies/publications, the term urgency should only be used for the LUT symptom and can be secondary to idiopathic detrusor overactivity or other underlying etiologies (ie, urinary tract infection, cystitis, or bladder stone). **Nocturia is the complaint that the child awakens at night to void** and unlike enuresis, nocturia does not result in incontinence**.**

2.2.2 Voiding Symptoms

The presenting voiding symptoms are variable in pediatric LUT dysfunction. Hesitancy denotes difficulty in initiating voiding when the child is ready to void. When the child complains of needing to make an intense effort and increase intra-abdominal pressure (e.g. Valsalva) in order to initiate and maintain voiding this is called **stranguria**. Intermittency is voiding that is not continuous but rather has several discrete stops and starts. Some children may report a **weak stream** that will prompt further investigation and others may complain of burning or discomfort during voiding termed **dysuria. Dysuria at the start of voiding suggests a urethral source of pain distal to the external sphincter, whereas dysuria at the completion of voiding suggests a bladder or proximal to the external sphincter source**.

2.2.3 Other LUT Dysfunction Symptoms

Holding Maneuvers are observable behavioral strategies used to postpone voiding or suppress urgency that may be associated with bladder overactivity. Common holding maneuvers include standing on tiptoes, forcefully crossing the legs, grabbing or pushing on the genitals or abdomen and placing pressure on the perineum with the heel of the foot (Vincent's Curtsy) or edge of a chair. Holding maneuvers represent a defense mechanism to prevent OAB and incontinence by contraction of the pelvic floor or stimulation of genital/perineal afferent pathways to negatively inhibit spinal efferents to the bladder. These maneuvers are often observed by the child's caregiver who may not associate them with voiding until specifically asked about them during the office visit.

Feeling of incomplete emptying refers the child's complaint that the bladder does not feel empty after voiding and may result in the need to return to the toilet to void again.

Urinary retention refers to the sensation of an inability to void despite persistent effort in the presence of a fully, distended bladder. Duration of time is particularly beneficial in characterizing retention.

Post micturition dribble is used when the child describes involuntary leakage of urine immediately after completion of voiding. This symptom **may be associated with vaginal reflux in girls or syringocele (**cystic dilation of the Cowper's gland ducts) **in boys**. It can also be seen in both males and females with either bladder neck dysfunction or external sphincter dyssynergia.

Spraying (splitting) of the urinary stream refers to the complaint that urine passes as a spray or a split rather than a single discrete stream. It **usually implies a mechanical obstruction at or just below the meatus (e.g. meatal stenosis).**

Genital pain refers to pain in the genitals. In girls, vaginal pain and vaginal itching are commonly seen with localized irritation from incontinence but can also be from trigonal irritation as well as from constipation. Penile pain and episodic priapism may be seen in young boys as referred symptoms associated with a full bladder, constipation or the result of urine trapping inside a phimotic foreskin.

2.3 Epidemiology

In two large population-based studies, most girls are toilet trained by age 2-2.5 years old whereas most boys are toilet trained at 2.5-3.0 years old.[2,3] The **age for attaining bladder and bowel continence, however, is variable.** In the most recent ICCS terminology and standardization document,[1] the **reference point for LUT symptoms is > 5 years of age** as this age is used by the DSM-5 and the International Classification of Diseases-10 (ICD-10) to characterize urinary incontinence disorders.[4,5] For functional bowel dysfunction, the minimum age is 4 years. **Other influences impacting bladder function and continence include the developmental level of the child**[6] **as well as behavioral disorders**.[7]

LUTD in children and adolescents is common and prevalence rates are similar across cultures and ethnicities, with several studies finding rates of 15-20% amongst school aged children.[8,9] **Another study of Swedish children, found that approximately 25% of 7-year-old healthy children have mild to moderate symptoms of LUT dysfunction** and more significant LUT dysfunction such as **daytime wetting occurs in 6% of girls and 4% of boys.**[10]

2.4 Co-morbidities with LUT Dysfunction

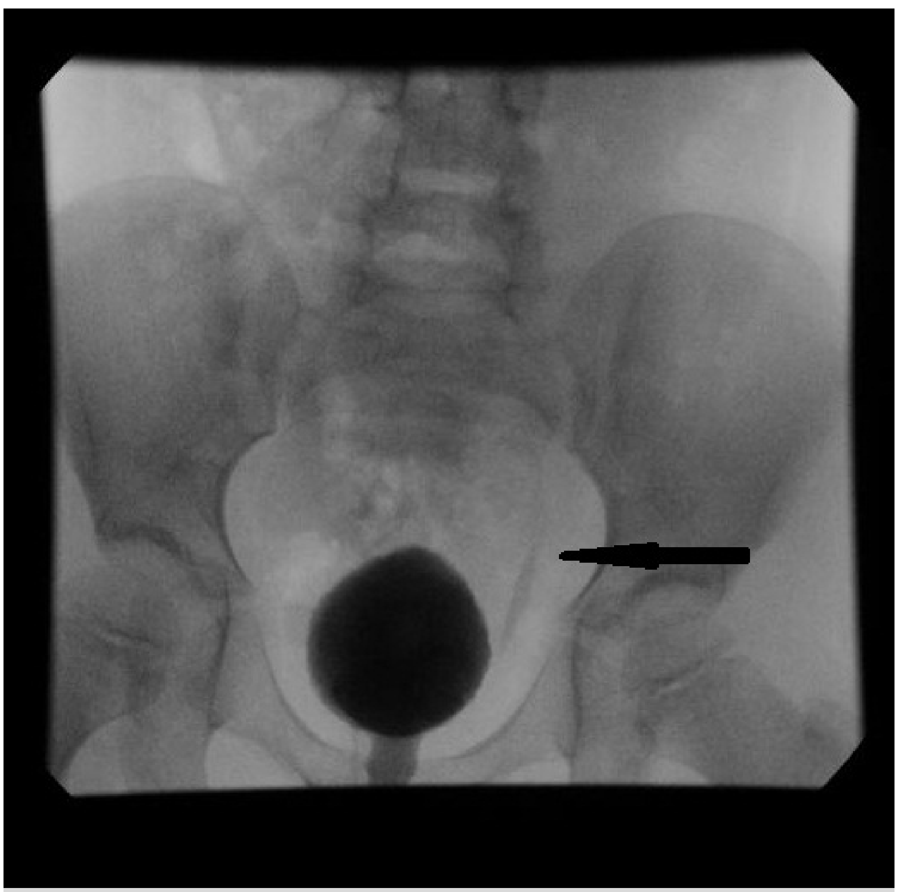

Figure 1

2.4.1 UTIs

There is an elevated risk and association of UTIs with LUT dysfunction particularly with incomplete emptying. **The association is attributed to stasis of urine and inability to effectively evacuate urine from the bladder, which occurs most commonly in patients with one of two LUT conditions: voiding postponement and dysfunctional voiding (see Section 2.6 LUTD conditions below for details).**[11]

2.4.2 Vesicoureteral Reflux (VUR)

Also see Core Curriculum: **Vesicoureteral Reflux**

There is a strong relationship between LUT dysfunction and VUR, which is often **termed secondary reflux** to denote the distinction from primary VUR that is related to the inadequate submucosal tunnel length of the ureter. **Secondary reflux from LUT dysfunction is thought to be due to high pressure voiding (e.g. dysfunctional voiding with detrusor sphincter dyssynergia, can be either bladder neck or external sphincter dysfunction) or alteration in the bladder wall that affects the submucosal ureteral tunnel** (**Figure 1**).

2.4.3 Neuropsychiatric Associations

There is a high rate of comorbid clinical behavioral disorders associated with LUT dysfunction. **The incidence of associated psychological conditions is 20-30% with nocturnal enuresis, 20-40% with daytime urinary incontinence and 30-50% with fecal incontinence.**[7] **The most common psychological condition seen with LUT dysfunction is attention deficit hyperactivity disorder** (ADHD). Other specific psychological conditions associated with BBD include oppositional defiant disorder (ODD), anxiety and depression. Emerging data from brain imaging in urology place the control of urge in the prefrontal cortex and anterior cingulate gyrus. Similarly functional MRI studies identify similar regulatory brain areas in both children and adults with depression, anxiety and ADD/ADHD.[12] This association substantiates the link between neuropsychiatric problems and voiding issues. Pharmacologic therapy for the specific neuropsychiatric condition often leads to improvement in BBD.

2.4.4 Bowel Dysfunction (e.g. constipation)

The association of constipation with LUT dysfunction is related to the shared physiologic control of these pelvic organ systems. The presence of both bladder and bowel dysfunction (BBD) necessitates a comprehensive elimination treatment approach. [13]

2.4.5 Neurologic causes

One pitfall to avoid in evaluating the pediatric patient with LUTD is to rule out potential neurogenic causes such as spina bifida occulta, spinal cord injury, and tethered spinal cord. Transverse myelitis and multiple sclerosis can also manifest as LUT dysfunction and should be considered in the setting of sensory issues or other motor issues (ie, muscle weakness). The examination of every patient with LUTD should include an examination of the lower back and sacrum and obtaining spinal MRI and/or urodynamic study may be necessary in specific situations.

2.4.6 Physical or Sexual abuse

Unfortunately, the pediatric urologist and team must remember that physical or sexual abuse may manifest as recurrent UTIs and/or LUT dysfunction. A careful consideration of the patient's social situation is crucial at initial evaluation and any suspicion should be reported to the appropriate authority (often based on state laws/guidelines).

2.5 Daytime Urinary Incontinence and Bladder Dysfunction

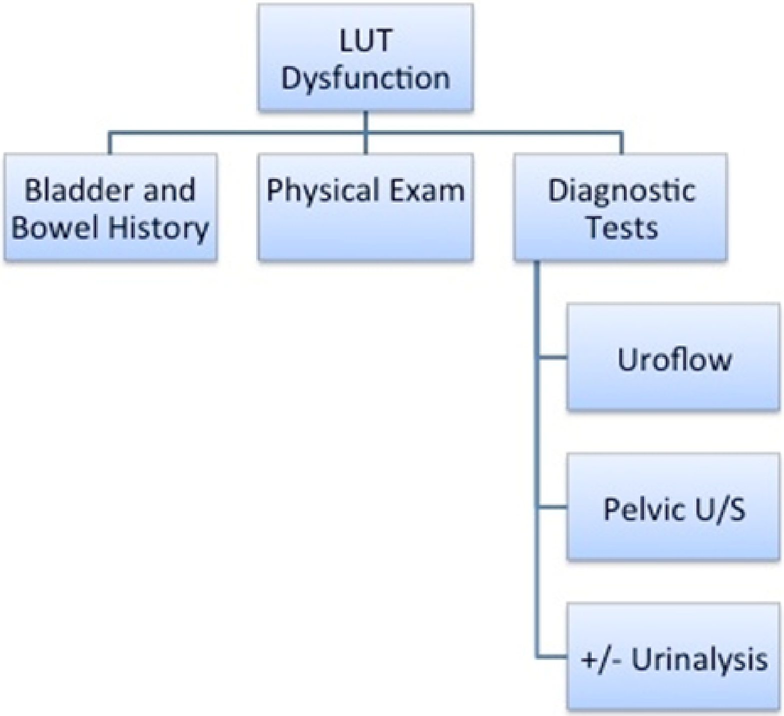

Figure 2: Algorithm for Evaluation of Pediatric LUT Dysfunction

2.5.1 Evaluation

(Figure 2)

The emptying and storage patterns for both bladder and bowel are explored in detail. The elimination frequency and presence of regularity are important to document. Any **LUT symptoms** are explored.

Bladder and bowel diaries are particularly useful in the objective evaluation of bladder and bowel dysfunction.[1] Mobile apps are increasingly used to document BBD. For the evaluation of a child with enuresis, a **full bladder diary** is used for documentation and consists of a 7-night recording of incontinence episodes and nighttime urine volume measurements. In contrast, a **48 hours daytime frequency and volume chart** is recommended for the evaluation of LUT dysfunction. Bowel function is explored using a **7-day bowel diary** along with the **Bristol Stool Form Scale**. The clinical diagnosis of constipation is controversial and the most accepted definition is derived from the **Rome-IV criteria of functional constipation.**[14]

Questionnaires are recommended to provide semi-quantitative data for BBD. Several questionnaires are available. The **Dysfunctional Voiding Symptom Score (DVSS)**[15] quantifies severity of LUTS and has been widely published. Similarly, the **Pediatric Urinary Incontinence Quality of Life Score (PIN-Q)**[16] measures the emotional impact that urinary incontinence has on a child. Because of the association of BBD and neuropsychiatric conditions, any validated, normed broadband behavioral questionnaire is recommended to screen for comorbid psychological conditions. [7]

Clinical history taking should also include evaluation of any social stressors, as stress in children and adolescents can manifest as LUTD. In particular, new social stressors that correlate to onset of LUTD should be investigated. Common stressors include starting at new school, birth of new sibling, parent separation/divorce, and bullying.

2.5.2 Physical Exam

A complete physical exam should be performed with emphasis on the inspection of the abdomen, external genitalia, perineum and sacral region. At minimum, neurological status should be assessed determining normal perineal sensation and intact perineal reflexes. During the abdominal exam, any masses (e.g. distended bladder or colon with stool) as well as any tenderness should be noted. Any findings of lower musculoskeletal abnormalities including sacral skin changes should be noted e.g. flattened-appearing sacrum, gluteal cleft, tuft of hair and skin pigmentation.

During the genital exam, meatal stenosis is assessed when there are complaints of a deflected urinary stream. Labial adhesions and introital erythema reflect localized irritation and inflammation from incontinence in girls. Finally, inspection of the introitus for an ectopic ureteral orifice is warranted with a history of continuous urinary incontinence.

2.5.3 Investigative Tools

Urine studies are part of the investigation of LUT dysfunction. A urinalysis (U/A) is helpful for screening for diabetes mellitus or insipidus, hematuria, proteinuria and infection. When a urinary tract infection is suspected, a urine culture and sensitivity is warranted.

Non-invasive urodynamics are employed in the investigation of pediatric BBD. Uroflowmetry allows characterization of a child's voiding dynamics and assessment of their flow pattern. There are **five major types of flow patterns (Figure 3)**. A bell-shaped curve (**Figure 3a**) is the normal urinary flow curve of a healthy child. A tower-shaped (**Figure 3b**) curve suggests an overactive bladder producing an explosive voiding contraction whereas a staccato-shaped curve (**Figure 3c**) suggests sphincter overactivity during voiding and is characteristic of dysfunctional voiding. An interrupted-shaped curve (**Figure 3d**), in which the uroflow rate hits 0 for 1-2 seconds between peak rates, suggests an underactive bladder with abdominal straining. A plateau-shaped curve suggests an underactive bladder with abdominal straining and a plateau-shaped curve (**Figure 3e**) suggests a bladder outlet obstruction (BOO). The BOO can be anatomical (e.g. posterior urethral valves or urethral stricture) or dynamic (e.g. continuous, tonic sphincter contraction). Electromyography of the perineal muscles has been used to identify potential bladder neck issues. A delay in the start of urination can be noted on a uroflow EMG. If such delay exceeds 6 seconds, there is likely bladder neck dysfunction. [17] Two to six seconds are considered normal time for urine to begin to flow. This time between the relaxation of the sphincter and the initiation of flow is called the EMG lag time (**Figure 3f**).[18] There is growing evidence that flow shapes are not readily reproducible with low inter-rater and intra-rater reproducibility on international surveys and numerous published studies at same centers. There has been an introduction of the concept of the Flow Index in children which has been shown to be a more quantitative measure of voiding efficiency based on thermodynamic principles. Utilizing this concept of measuring the actual flow rates/expected flow rate based on the bladder volume derived from normal bell voids we can predict if patients are hypo-efficient (plateau shape) efficient voiders (bells) or hyperefficient voiders (tower voiders). Interrupted and staccato voiders are categorized as fractionated voiders and can then be subdivided based on the prior efficiency. This system is agnostic of variations in flow rates related to age, sex and voided volume making comparisons easy across all groups and standardizing outcomes.[19,20]

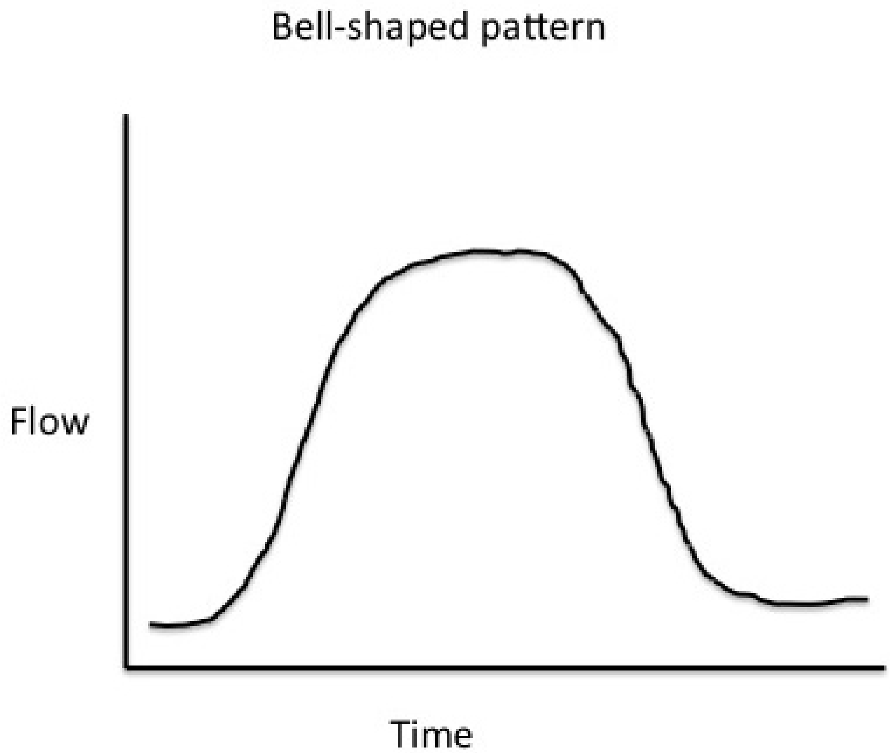

Figure 3A: Bell-shaped pattern

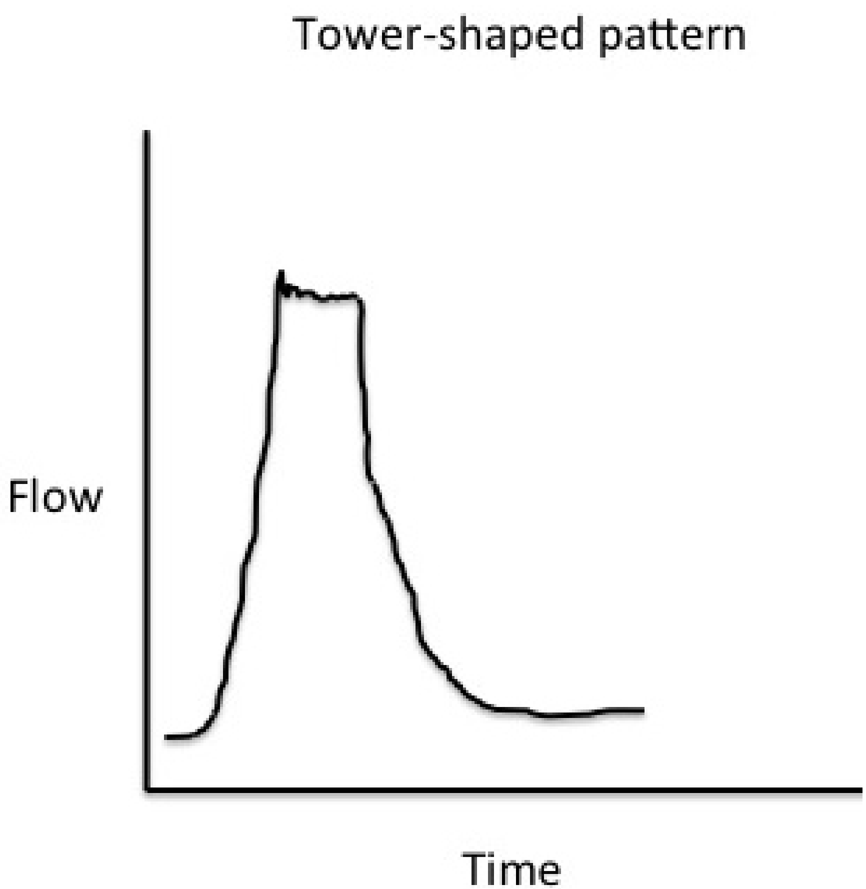

Figure 3B: Tower-shaped pattern

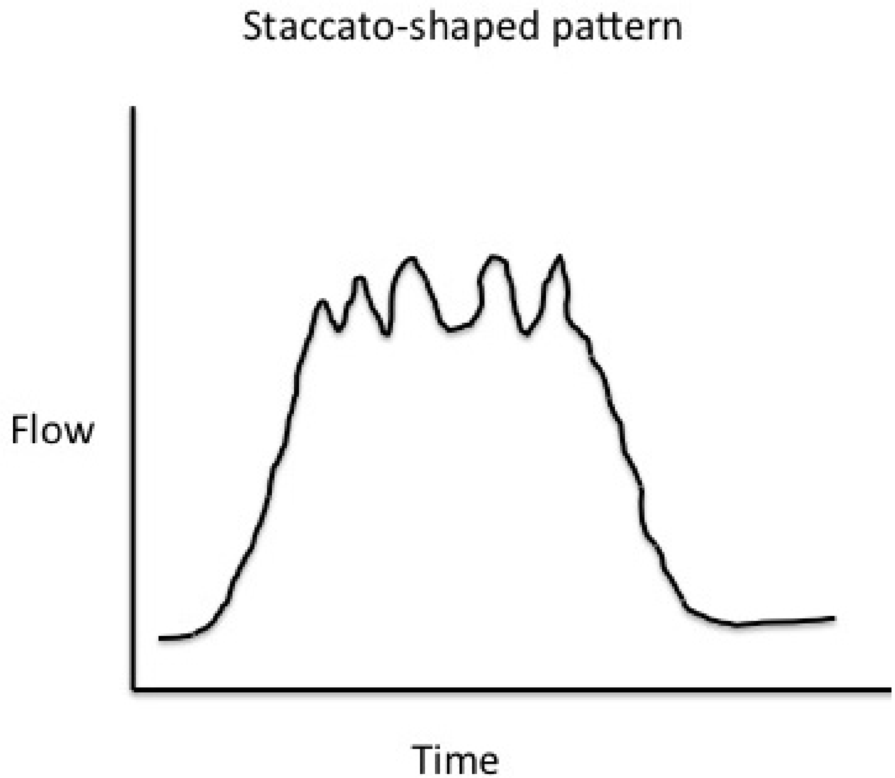

Figure 3C: Staccato-shaped pattern

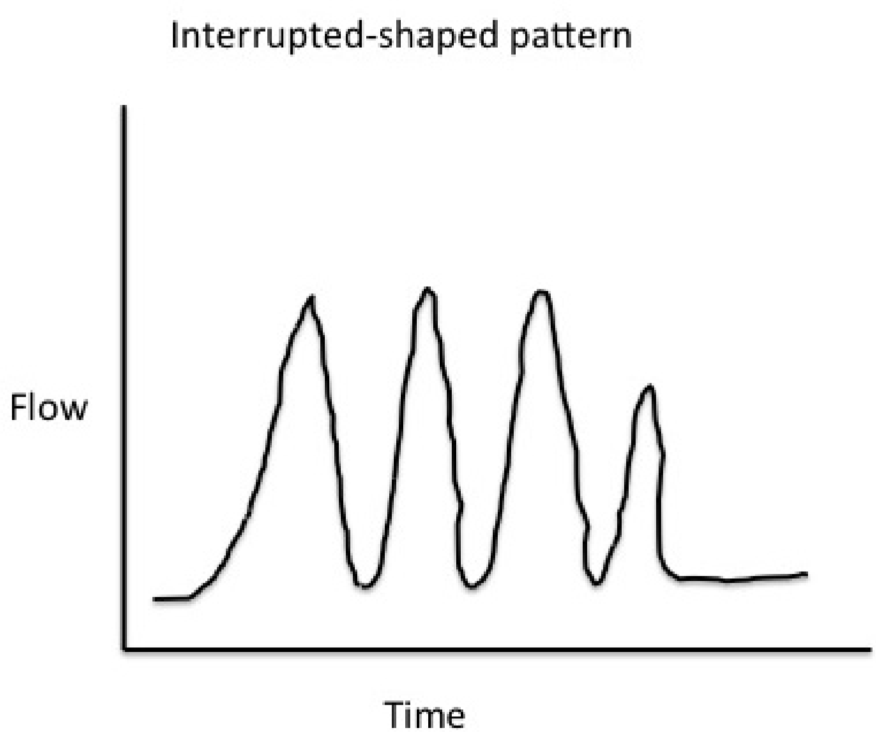

Figure 3D: Interrupted-shaped pattern

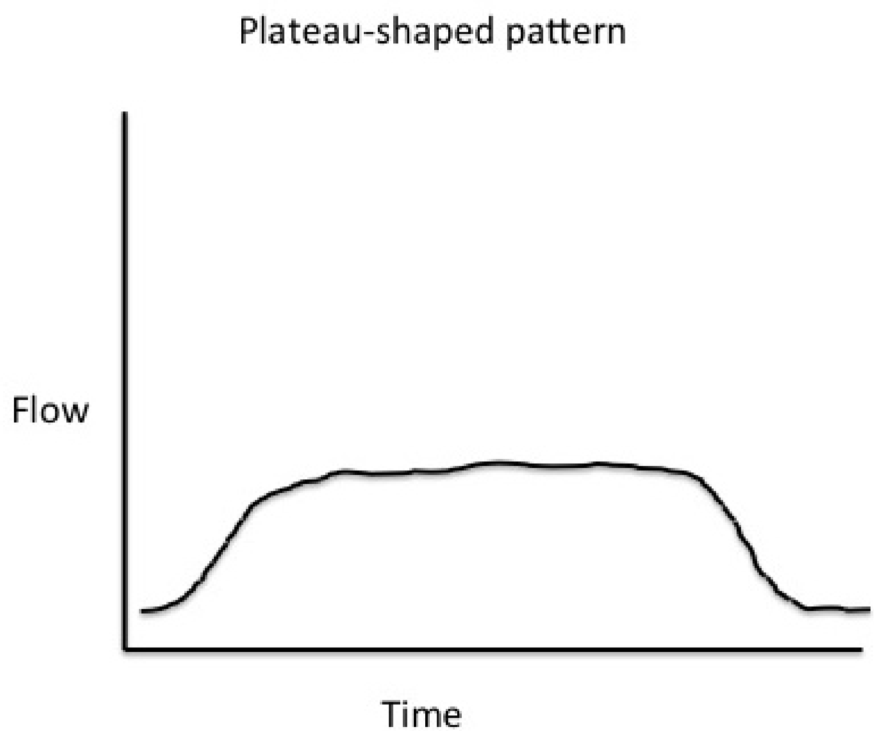

Figure 3E: Plateau-shaped pattern

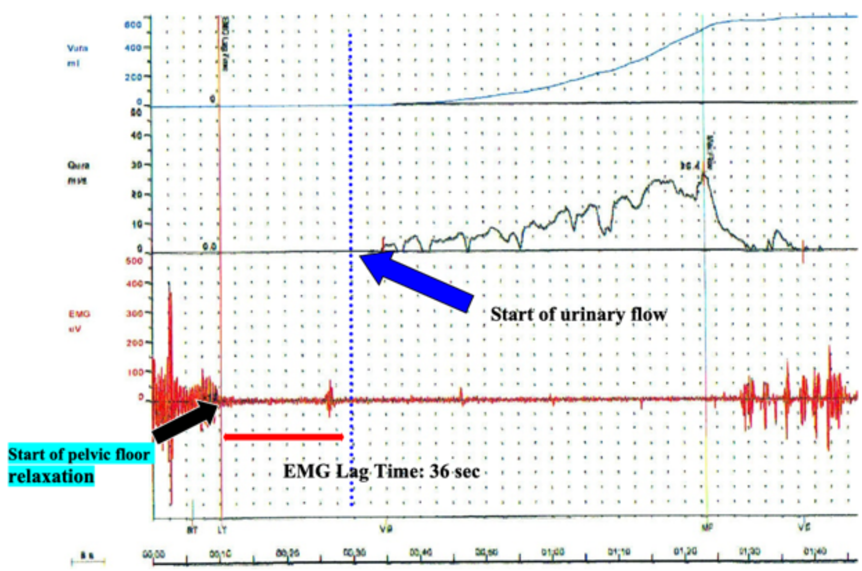

Figure 3F. Example of how to calculate EMG lag time

Flow Index Method of Evaluation Uroflowmetry

In a worldwide survey of professionals involved in the care of children with voiding problems, the intra and inter-rater reproducibility of uroflowmetry utilizing the above flow shapes has been found to be marginal, if not poor for the most part. [21] An alternative method of defining flow has been sought and the concept of the flow index[19,22] has been introduced as a means of comparing the actual flow to an ideal flow. An ideal flow would be considered a bell-shaped curve with no post void residual and the child voiding with a bladder not filled beyond 115% of estimated capacity.[20] Utilizing a system of equations to define the estimated flow rates both for maximal and average flow rates, the actual flow rate is divided by the expected flow rate and a volume normalized flow index is produced. This normalized flow index can be used to compare all flows regardless of the voided volume or the individual since the volumes have been normalized to 1 and are corrected for sex as well. As a result, we can compare any patient to itself and its peers. Additionally, flow index is actually a measure of voiding efficiency which is more accurate than the method measuring post void residual.[19,20] In this same publication it was shown that flow index can be a better method of defining shapes than the shapes themselves. The authors have advocated for the use of a bimodal classification system to define flows. In this system flows should be defined as smooth or fractionated and the flow index can be reported to define voiding efficiency.[19,20] The pediatric flow equations are as follows:

Males 4-12
Qave =3.412+0.052*TBC-0.0000061*TBC2
Qmax =11.26+0.0701*TBC-0.0000513*TBC2
Females 4-12
Qave = 3.37+0.048*TBC-0.0000354*TBC2
Qmax =10.723+0.073*TBC-0.0000423*TBC2
(TBC= Voided volume +PVR)

Since flow curves are arbitrarily defined, the flow index definitions have been set with the following parameters defined on a consensus basis from large datasets. Plateau voids or hypovoids are generally found to occur at or below an index of 0.7 and hypervoiders or tower voids occur above 1.25. These ranges tend to be around the area of 1 standard deviation from the norms and this has been identified in both pediatric and adult studies where pathologic states are recognized.[19,22]

A pelvic ultrasound (U/S) is another non-invasive tool used to evaluate BBD. The pelvic U/S is used to calculate the bladder volume, post-void residual (PVR) and evaluate parameters such as bladder wall thickness, presence of ureteral dilation, presence of stool and any rectal dilation (e.g. > 3 cm). The bladder should not be under distended (< 50%) or over distended (> 115%) in relation to the expected bladder capacity.

2.6 LUT Dysfunction Conditions

The classification of daytime LUT conditions is complex due to the heterogeneity of symptoms of LUT dysfunction and the considerable overlap between conditions. A helpful framework to classify daytime LUT dysfunction includes the assessment and documentation of the following parameters:

1. Incontinence (presence or absence, volume and symptom frequency)
2. Voiding frequency
3. Voiding urgency
4. Voided volumes
5. Fluid intake

An **overactive bladder (OAB) is characterized by urinary urgency** in the absence of a urinary tract infection (UTI) or other obvious pathology and is usually accompanied by frequency and nocturia. OAB may occur with or without urinary incontinence.

In the setting of children who habitually postpone micturition using holding maneuvers, their bladder behavior is termed **voiding postponement**.

In children who need to raise intra-abdominal pressure to initiate, maintain or complete voiding i.e. straining, they are considered to have an **underactive bladder**. **Underactive bladder** is characterized by a weak slow urinary stream which can present as any of the aforementioned urinary flow patterns. If there is a need to raise intra-abdominal pressure mid void, a staccato or interrupted flow pattern may be seen.

Dysfunctional voiding (DV) is one of the most common causes of LUT dysfunction seen in children. DV is characterized by the habitual contraction of the urethral sphincter or pelvic floor during voiding. DV is characterized by a fractionated uroflow pattern, commonly seen as staccato with or without an interrupted flow on repeat uroflow when EMG activity is concomitantly recorded.

Stress incontinence is the involuntary leakage of small amounts of urine with effort or physical exertion that results in increased intra-abdominal pressure e.g. coughing or sneezing.

Vaginal reflux, in which urine collects in the vagina, may occur in the setting of toilet-trained girls who consistently experience daytime incontinence in moderate amounts shortly after voiding and have no other LUT symptoms or nighttime incontinence.

Giggle incontinence is a rare condition in which extensive emptying or leakage occurs during or immediately after laughing. Bladder function is otherwise normal when there is no laughter.

Extraordinary daytime only urinary frequency applies to a toilet-trained child who reports the frequent need to void solely during the day and is associated with small micturition volumes. The daytime voiding frequency is at least once per hour (with a voided volume <50% of estimated bladder capacity) and incontinence is rare and nocturia is absent. One should exclude co-moboridities such as polydipsia, diabetes mellitus, nephrogenic diabetes insipidus, UTI, or viral syndrome. Extraordinary daytime only urinary frequency is often self-limited.

2.7 Treatment

See **(Figure 4)**

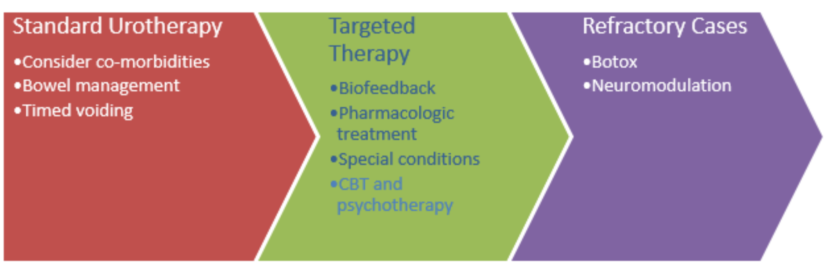

Figure 4: Algorithm for Management of Pediatric LUT Dysfunction

2.7.1 Urotherapy

Urotherapy is used to describe the treatment of LUT dysfunction and is divided into standard therapy and specific interventions. **The hallmarks of standard urotherapy are education and behavioral modification.** Behavioral modification consists of regular voiding habits, proper voiding posture, avoidance of holding maneuvers, proper diet and fluid intake. **Key features of behavioral modification include:**

1. **Timed voiding** at regular intervals. Initially, it is suggested for the child to start voiding on a two to three hour interval.
2. **Reminder alarms--** e.g. vibratory or audible alarms during the day via a time keeping device provide positive reinforcement to adhere to time voiding programs.
3. **Relaxation techniques** with deep breathing during voiding.
4. **Voiding diaries** for the child care provider

5. **Treatment of bowel dysfunction** is vital to the successful outcome in the setting of BBD.

Specific interventions of urotherapy beyond standard therapy are often used as second and third line therapies and include pharmacotherapy, physiotherapy and neuromodulation.

2.7.2 Pharmacotherapy

Pharmacological therapy is considered an ancillary measure to improve bladder emptying and storage in children with LUT dysfunction (**Table 1**). The selection of a specific pharmacologic agent is tailored toward the characteristics of the LUT dysfunction.[23,24] The medical therapy used in pediatric LUT dysfunction is common to adult urology and very few medications have FDA labeling and are thus used off-label; this information should be imparted to parents.

Table 1. Medications used for treatment of LUT Dysfunction

Name	Example	Mechanism of action	Targeted LUT treatment
Anticholinergic/antimuscarinic	Oxybutynin, tolterodine, and solifenacin (recently FDA approved in children >2 years old)	Antagonizes binding of acetylcholine to the muscarinic receptor	OAB
b3-agonists (off label)	Mirabegron	Activates the b3 adrenergic receptors in the detrusor muscle	OAB
Alpha-adrenergic antagonist (off label)	Doxazosin, Terazosin, Tamsulosin, Alfuzosin, Silodosin	Blockade of alpha-adrenergic receptors	Smooth muscle relaxation of bladder neck and proximal urethra
Botulinum toxin (off label)	OnabotulinumtoxinA	Inhibits release of acetylcholine at the neuromuscular junction	1) Refractory OAB 2) Refractory dysfunctional voiding
Antidiuretic hormone (vasopressin analogue)	Desmopressin	Reduction in urinary output	Kidney polyuria with enuresis
Tricyclic antidepressant	Imipramine	Not fully known. Mixed mechanism of action including anticholinergic effects. Increases cerebral dopamine and norepinephrine levels	Secondary agent for enuresis

Antimuscarinics

Antimuscarinic agents are effective in treating OAB. Antimuscarinics are **not as effective in treating OAB associated with incomplete emptying, stasis of urine and UTIs**. Antimuscarinics are approved for the treatment of neuropathic detrusor overactivity (NDO) and many are used off label for pediatric LUT dysfunction. Only three antimuscarinic agents have been approved by the FDA for use in children: oxybutynin, tolterodine, and solifenacin.

Beta-3-agonists

An emerging treatment for OAB is β3-agonists but the pediatric usage for OAB is off-label. Mirabegron is FDA approved from use for NDO in patients ≥3 years old.

Alpha-adrenergic blockade (alpha-blockers)

Use of alpha-blockers in children with LUT dysfunction is currently off-label but may facilitate bladder emptying in select patients, especially those with bladder neck dysfunction.[25,26] There is some evidence that non selective alpha-blockers may be valuable in ameliorating bladder overactivity in adult patients as well as in children.

Botulinum-A toxin (BTA)

Use of BTA is off-label and can be used to treat emptying and storage issues. BTA may be used in the bladder to treat OAB and for the external urethral sphincter to facilitate emptying in select patients with refractory dysfunctional voiding.[27] BTA has an effect duration of between 3 and 12 months in most patients and therefore requires repeat treatment at regular intervals.

SSRIs

Use of SSRIs is off-label and may facilitate treatment of LUT dysfunction in select patients with associated psychological conditions.[28] Fluoxetine is approved for the use in several psychiatric disorders in children, most notably anxiety and or depression. Duloxetine (SSRI/NERI) is approved in Europe in adults for the treatment of mild stress incontinence but is not approved in the United States.

Recent basic science findings and potential future therapeutic targets

Models of LUTD in rodents have led to improved understanding of the central nervous system control of volitional voiding. Recently, the role of corticotropin-releasing hormone (CRH) in the pontine micturition center (PMC, the “control center” for voiding in the brainstem) has been studied and CRH has been shown to be inhibitory to the voiding pathway in mice.[29] Activation of CRH-neurons in the PMC reversed the overactive voiding phenotype in a mouse model of bladder overactivity, suggesting that CRH or CRH receptors may be a potential target for future therapy for OAB. Interestingly, two recent clinical studies found significantly lower serum CRH level in children with nocturnal enuresis (i.e., bedwetting) compared to control children,[30,31] suggesting that enhancing the influence of CRH in this pathway may be a novel therapeutic strategy for nocturnal enuresis.

Given CRH’s role as a neurostress hormone, these findings compliment the association between LUTD and neuropsychiatric disorders, including post-traumatic stress disorder.

2.7.3 Physiotherapy

Physiotherapy involves assessment of the abdominal/pelvic floor muscle interaction with pelvic floor muscle training that includes biofeedback.[32] Computer games software are often employed for pediatric pelvic floor physiotherapy as they may improve the efficacy of biofeedback for younger children.[33] Studies show that biofeedback reduces symptoms of LUTD, expedites resolution of VUR, and prevents recurrent UTIs. In their systematic review of biofeedback in children with BBD (27 studies included, 1 RCT), Desantis et al found a 83% improvement in UTI risk, 80% improvement in daytime urinary incontinence, and 67-100% improvement in urinary frequency.[34]

2.7.4 Neuromodulation

Neuromodulation refers to therapy that reduces LUT symptoms or restores LUT function by the alteration and modulation of nerve activity through central and/or peripheral electrical stimulation or chemical agents to targeted sites. Role of neuromodulation for pediatric LUTD and BBD is controversial given lack of controlled trials and lack of understanding of specific mechanism of action. Studies have shown that neuromodulation can increase bladder capacity, decrease severity of urgency, improve continence and decrease UTIs. Neuromodulation has also been shown to improve urodynamic parameters.

Transcutaneous electrical nerve stimulation (TENS) is the most common neuromodulation and involves stimulation with surface electrodes on the lower back or sacrum that modulates the S2 and S3 sacral nerve route. These results may indicate that the stimulation allows the patient to become accommodated to the stimulus of bladder filling. [35] TENS sessions typically last 20-30 minutes and are repeated three time per week. If feasible, patients can purchase their own electrical stimulator for home use which allows for more sessions each week. Studies in children with refractory OAb have shown TENS to have a cure rate of 0-63% and an improvement rate of 20-90%.

Percutaneous tibial nerve stimulation (PTNS) involves stimulation through the tibial nerve to the sacral plexus via a needle electrode placed near the tibial nerve posterior to the medial malleolus in the lower leg. The posterior tibial nerve is a mixed sensory and motor nerve that orginates from the L4-S3 spinal segments. Correct placement of the needle electrode is confirmed by ipsilateral plantar and toe flexion or fanning. Typical treatment involves 30-minute sessions once a week for 12-weeks initially. Studies using PTNS for pediatric DV and/or OAB have reported cure rates of 25-86% and improvement rates of 35-100%. Despite these high reported success rates, use is often limited by intensive time commitment and costs (as PTNS is often not covered by insurances and often requires significant documentation to get approval).

Sacral nerve modulation (SNM) via implantable devices is FDA-approved for patients older than 18 years of age with urinary urge incontinence, urinary retention and significant symptoms of urgency/frequency who failed or could not tolerate more conservative forms of treatment. Implantation occurs in two stages with the first being a trial to determine efficacy. Use is off-label in children and revision rates range from 7-18%. Complications include wound infection, electrode migration, and lead fracture. Roth et al reported outcomes in 20 patients aged 8-17 years old with BBD who underwent SNM and found improvement or resolution of urinary incontinence in 88%, urinary frequency in 89%, nocturnal enuresis in 69%, and constipation in 71%.[36] The authors did report a 20% rate of repeat surgery for complications.

3. Enuresis

3.1 Terminology/Classification

Enuresis is the involuntary release of urine during sleep in a child greater than five years of age. It can be considered primary in a child who has never been dry for at least a six month period. Secondary enuresis is classified as a recurrence of night time wetting after a period of being dry at a minimum of six months.

Classifying enuresis as monosymptomatic vs. non-monosymptomatic is critical in determining the most effective treatment modality (Table 2). If a child has enuresis without any other LUT symptoms (excluding nocturia) and no underlying bladder dysfunction, then it is considered monosymptomatic. Non-monosymptomatic enuresis occurs with any of the other LUT symptoms.[37]

Table 2. Classification of enuresis with corresponding pathophysiology and treatment		
Major Classification	**Pathophysiology**	**Treatment Approach**
Monosymptomatic	CNS arousal (brain) or Polyuria (kidney)	Moisture alarm or desmopressin
Non-monosymptomatic	CNS arousal (brain) LUT dysfunction (bladder) with or without CNS arousal (brain)	LUT targeted therapy, moisture alarm, imipramine

3.2 Pathophysiology

Enuresis has been most commonly attributed to the occurrence of polyuria, arousal disorders and nocturnal detrusor overactivity. All may exist in a patient, but determining the predominant pathophysiology guides the most effective treatment.

3.2.1 Polyuria

Large urine output at night, may contribute to enuresis. Quantifying the amount fluid intake during the day is paramount to identify as a contributing factor. Polyuria is calculated by weighing the soaked pads or sheets and adding the first morning void to measure the overnight urine production. Polyuria is defined as a nighttime urine volume > 130% of the maximum voided volume (MVV). Circadian rhythm of urine production, regulated by nocturnal vasopressin secretion, normally reduces nighttime urine output and results in a maximal concentration of the urine. Primary nocturnal enuresis is often a result of a disturbance of this pattern.

3.2.2 Arousal Disorders

Sleep disorders for those children afflicted with enuresis have been extensively studied. Anecdotally parents report extreme difficulty in awakening a child who has bedwetting. Associations with obstructive sleep apnea, parasomnias or other sleeping disorders are continued areas of research.[38] Emerging research supports that restless sleep and poor-quality sleep increase the risk for enuresis.

Obstructive Sleep Apnea (OSA)

There is a high association of enuresis with OSA. This has led to consideration of adenotonsillectomy but only in patients with well documented OSA. Although the short-term reports are good in selected patients, the long-term durability remains mixed and controversial.[39,40]

3.2.3 Nocturnal Detrusor Overactivity

Often these children are refractory to many routine measures taken to treat nocturnal enuresis. Functional bladder capacity is reduced in these children when wetting during nighttime. Polyuria is not a contributing factor and volume of voids during daytime is often normal.

3.3 Epidemiology

Enuresis is twice as common in boys as it is in girls. An estimated 15-20% of children between the ages of four to six years have some component of enuresis. As children age and garner more social skills, the incidence decreases. Those children who have enuresis that persist into adulthood tend to exhibit classic LUT symptoms.

3.3.1 Familial Inheritance

Nocturnal enuresis has been well described to occur across generations of family members and within siblings of the same generation. The mode of inheritance is usually autosomal dominant in nature. If both parents are affected, then risk for the child is significantly increased. Recent studies suggest nocturnal enuresis may have a familial component.[41]

3.4 Evaluation

3.4.1 History and Physical Examination

The history and physical examination should mirror the evaluation for LUT dysfunction as described in the previous section on **bowel-bladder dysfunction**.

3.4.2 Laboratory Tests

Urinalysis may be useful in those patients whom urinary tract infection may be a culprit in the etiology of enuresis. In addition, it can be a screening tool for other medical disease processes like diabetes mellitus, diabetes insipidus or kidney disease.

3.4.3 Voiding Diary

A **full 7-day bladder diary** similar in the evaluation for LUT dysfunction is equally useful in the evaluation of enuresis. This allows an objective quantification of the amounts voided (particularly the MVV to define nocturnal polyuria), timing on micturition, and when enuresis occurs. [1]

3.4.4 Radiologic Studies

Imaging has a limited role in the general work-up of the patient with enuresis. Specifically, it should be obtained in those patients with history of recurrent febrile urinary tract infections, genitourinary anomalies or in suspected structural anatomic abnormalities, which may be associated with enuresis. In those particular cases, ultrasound of the kidneys/bladder and/or a voiding cystourethrogram (VCUG) may be warranted.

3.5 Treatment

See (**Table 1** and **Table 2**)

3.5.1 Bed-wetting Alarm

Use of the **bed-wetting alarm** remains the most effective treatment for nocturnal enuresis. It is associated with the least likelihood of failure following discontinuation of treatment and increasing efficacy with duration of therapy. It requires a highly motivated child and family to commit to its proper use. It is estimated be most effective when used consistently over a three-month period.[42] In a recent metaanalysis of randomized control trials, the efficacy of alarms is hampered by the high dropout rate and therefore, the overall proportion of patients who had a > 50% reduction in wet nights were comparable between the alarm and desmopressin groups in intent to treat analysis. The enuresis alarms outperformed desmopressin in achieving a sustained response (alarm: 67.8%, 78/115; desmopressin: 45.5%, 60/132; P = 0.005) and lower relapse rate (alarm: 12.9%, 37/287; desmopressin: 37.6%, 118/314; P = 0.0001) which are in line with the results of the previous studies. The results suggested that the alarm could have a better long-term treatment success rate than desmopressin. [43]

3.5.2 Pharmacologic Therapy

Desmopressin, an analog of vasopressin, has increased antidiuretic activity without any of the vasoconstrictor effect. Ideal candidates are children who have nocturnal polyuria. It may be used nightly or selectively for special social occasions like sleepovers and summer camps based on parental and child preference.[42,44] The antidiuretic mechanism of desmopression is now not thought to be the sole mechanism for how the medication works. [45] Animal studies indicate that there is a stimulatory effect in the CNS with an associated increase in activation of the locus coereulus, this area is critically involved in awareness.

Anticholinergics/antimuscarinics agents block the muscarinic receptors in the bladder that promote detrusor overactivity. This is most effectively used in patients with non-monosymptomatic enuresis or with nocturnal detrusor overactivity. These agents may also be efficacious in combination with other treatments (i.e. oxybutynin and desmopressin).[44]

Tricyclic antidepressants (TCA) used for enuresis are considered a secondary treatment modality. Imipramine is the most common TCA used in treatment of enuresis. While the exact mechanism of the therapy is not known, its efficacy may be related to its mild anticholinergic properties, changes in brain dopamine or norepinephrine levels or alterations of sleep cycles. Its use has been limited due to fears of cardiotoxic effects, even though it is only a problem in patients with conduction defects, or patients taking other sympathomimetics and in cases of overdosing.

Atomexitine a serotonin reuptake inhibitor has been found to be of value in treating refractory nocturnal enuresis as well as patients with ADHD and nocturnal enuresis.[46,47] The mode of action is likely due to increased central norepinephrine levels. This mode of action would make the mode of action of imipramine more likely due to norepinephrine rather than due to a weak anticholinergic effect especially when oxybutynin by itself has not been a good method of treatment of nocturnal enuresis.

Other medications, like **non-steroidal anti-inflammatory drugs (NSAIDs)** and **benzodiazepines**, have been used off-label with very limited efficacy.[48]

Presentations

VOIDING DYSFUNCTION Presentation 1

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