# Evaluation and Treatment of Nonmonosymptomatic Enuresis

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## Practice Gap

Among children 7½ years old with enuresis, 31.6% will have evidence of concomitant lower urinary tract (LUT) dysfunction. This nonmonosymptomatic enuresis represents a separate clinical entity from monosymptomatic enuresis and requires addressing the LUT dysfunction before enuresis treatment to avoid high treatment failure rates.

Butler RJ, Golding J, Northstone K. Nocturnal enuresis at 7.5 years old: prevalence and analysis of clinical signs. *BJU Int.* 2005;96(3):404–410.

## Objectives After reading this review, the practitioner should be able to:

- Identify and use correct terms to accurately describe pediatric urinary incontinence.
- Take a thorough voiding and elimination history and differentiate between monosymptomatic and nonmonosymptomatic enuresis (NMSE)
- 3. Identify common comorbid conditions associated with NMSE.
- Describe and institute first-line therapy for monosymptomatic enuresis and NMSE.
- Recognize children with anatomical findings or children with refractory responses to first-line treatments that necessitate a specialist referral for lower urinary tract dysfunction and/or enuresis.

#### **BACKGROUND AND DEFINITIONS**

Parental concerns about urinary continence in children are commonly cited worries at primary pediatric appointments. A basic understanding of the classification and treatment of urinary incontinence and enuresis in otherwise neurologically normal children is thus essential for the practicing pediatrician. Many times, first-line behavioral modification techniques for encouraging proper bladder and bowel habits can be successful in primarily treating urinary symptoms without the need for referral to a subspecialist. The key to management AUTHOR DISCLOSURE Dr Roth has disclosed no financial relationships relevant to this article. Dr Austin has disclosed that he has research grants from Allergan and Warner Chilcott and is a consultant for Allergan. This commentary does contain a discussion of an unapproved/ investigative use of a commercial product/ device.

#### ABBREVIATIONS

BBD	bladder-bowel dysfunction
LUT	lower urinary tract
MSE	monosymptomatic enuresis
NMSE	nonmonosymptomatic enuresi

lies in accurately characterizing and classifying the type of incontinence and providing targeted medical therapy for each situation. Enuresis without other lower urinary tract (LUT) symptoms (nocturia excluded) and without bladder dysfunction is defined as *monosymptomatic enuresis* (MSE). Children with enuresis and any LUT symptoms are said to have *nonmonosymptomatic enuresis* (NMSE). For the purposes of this review, we focus on NMSE. Formerly termed *diurnal enuresis*, this term has been reclassified to *NMSE* by the International Children's Continence Society standardization documents. (I)(2)

Before delving further into the treatment of NMSE, a brief review of common terms that pertain to pediatric LUT dysfunction is essential to establish accurate communication among pediatric health care professionals. In addition, common terms assist in the determination of the appropriate characterization of the LUT function in tailoring treatment of these children.

**Urinary incontinence** is the involuntary leakage of urine. This can be either continuous or intermittent and can occur during the day or at night.

**Continuous incontinence** usually has an associated anatomic origin, such as an ectopic ureter, whereas **intermittent incontinence** usually has associated functional disturbances in the voiding process.

**Daytime incontinence** (usually simply referred to as incontinence) is involuntary leakage of urine during waking hours.

**Enuresis** refers to intermittent incontinence that happens while the child is asleep. This most often occurs at night but can also happen with daytime sleep, such as naps.

Other common urinary symptoms in children include increased frequency (voiding  $\geq 8$  times daily), decreased frequency (voiding  $\leq 3$  times daily), dysuria (pain or discomfort with urination), hesitancy (difficulty in initiating a void), intermittency (a stream that stops and starts during the micturition process), and urgency (sudden, unexpected strong desire to urinate). LUT dysfunction in a child with bowel function disturbances, such as constipation, encopresis, or fecal incontinence, represents a combined pathophysiologic condition termed bladder-bowel dysfunction (BBD). (I)(2)

Generally, urinary incontinence is not considered pathologic until a child reaches age 5 years as characterized by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* and the *International Classification of Diseases, 10th Revision.* (3)(4) Of course, there is variability in the maturational aspect of LUT function, and many children may have voluntary control over LUT function before age 5 years.

# EPIDEMIOLOGY, PATHOPHYSIOLOGY, AND TARGETS OF THERAPY

The British Avon Longitudinal Study of Parents and Children Study, the only prospective longitudinal study of voiding habits in more than 8000 children, found that approximately 15% of all children 7½ years old experience enuresis, or nighttime wetting. (5) For many children, this is a solitary event (termed *MSE*); however, the prevalence of daytime urinary symptoms increases with the frequency of enuresis. Roughly one-third of children with 2 or more nights of enuresis per week will also have daytime urinary symptoms and thus have NMSE. (6)

MSE is thought to arise from 3 primary physiologic disturbances that involve the kidney, brain, and bladder. First, there is nocturnal polyuria present in a subset of children, diminished sleep arousal in another, and nocturnal bladder overactivity or reduced nocturnal bladder capacity in a final cohort. Treatments of enuresis are traditionally based on the predominant component of these 3 physiologic processes. (7) There may also be overlap of these 3 physiologic causes of enuresis, necessitating combination therapy. In children with NMSE, there is concomitant LUT dysfunction that renders traditional therapies ineffective. Children with NMSE will often have bowel issues, and constipation is a known contributor for LUT dysfunction. Thus, treatment of NMSE is based on addressing any BBD, which often results in improvement and sometimes resolution of the accompanying enuresis. (8)

#### COMORBID CONDITIONS

Although less frequent than other functional elimination disorders, children with enuresis have approximately a 20% to 30% incidence of comorbid behavioral conditions, such as attention-deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder. (9) These comorbid conditions should be addressed in conjunction with the enuresis to optimize treatment.

#### **EVALUATION OF THE PATIENT WITH ENURESIS**

#### History

The primary evaluation approach for evaluating enuresis in a pediatric patient is a thorough elimination history. Of particular importance is the clarification of the LUT dysfunction symptoms (eg, frequency of enuresis, the presence or absence of daytime urinary symptoms, presence of comorbid behavioral issues or constipation, and whether the enuresis has been continuous since toilet training or is a new development after an initial period of continence). Children who begin having enuresis after a dry period of greater than 6 months (termed *secondary enuresis*) should be questioned about any responsible social stressors.

An elimination history should include information on the typical daily bladder- and bowel-emptying habits of the child. When possible, having parents keep a bladder and bowel diary for a 1-week period before the appointment can improve the accuracy of the assessment of the child's voiding and stooling patterns. A complete bladder diary consists of a 7-night recording of incontinence episodes and nighttime urine volume measurements and is used to evaluate enuresis. A 48-hour daytime frequency and volume chart is used to evaluate LUT dysfunction. This detailed 48hour assessment provides information on the fluid intake volumes, the voided volumes, and the presence or absence of incontinence and is useful in differentiating idiopathic urinary frequency from polyuria. This 48-hour daytime frequency and volume chart is usually kept during a weekend to make adherence easier for the family. Many parents and children are unaware of LUT dysfunction on routine questioning, and symptoms may not be apparent without an adequate voiding history and diary.

Another relevant question is the posture of the child while voiding. Young girls will often slump while sitting on the toilet without an upright posture or inadequately spread their legs apart during voiding. Petite girls may also fall through the toilet seat, preventing good egress of urine from the urethra. A footstool at the base of the toilet or having the child sit astride and face the toilet will allow them to use better posture and correct these problems. Finally, some children will exhibit leg crossing, squatting on the floor, or sitting on the edge of a chair to compress their perineum. These posturing maneuvers are compensatory responses to counter bladder spasms when the bladder is too full or overactive and the perineal pressure inhibits bladder contraction through the sacral reflex arc.

Prior documentation of urinary tract infection suggests some component of urinary stasis or incomplete emptying. Many children with LUT dysfunction may experience symptoms consistent with cystitis, such as dysuria, urinary frequency, and suprapubic pain or discomfort related to voiding, although urine culture is sterile. These children may have urinalysis findings of pyuria, hematuria, and amorphous debris that reflect chronic inflammation and irritation in response to urinary stasis. Children with enuresis who have had a history of cystitis or recurrent cystitis symptoms should be considered to have LUT dysfunction and should be treated as having NMSE rather than MSE. Evaluation should also include a brief screening for new neurologic symptoms, such as a change in coordination or gait disturbances. Finally, it is also helpful to discuss voiding problems sensitively and openly with the parents and child to remove any stigma associated with any LUT dysfunction.

#### **Physical Examination**

A general physical examination should be performed for children who present with NMSE, including a genital examination. The pertinent findings for each portion of the examination are summarized below.

Examination of the abdomen should include assessment of any abdominal distention or bloating that might indicate underlying bowel dysfunction. Palpation should be performed, looking for any palpable abdominal masses or abdominal tenderness, especially the suprapubic region, which would suggest urinary retention. In smaller children with severe constipation, the sigmoid colon may be palpable in the left lower quadrant.

A neurologic examination should include an assessment of strength, sensation, and coordination of all extremities. Careful examination of the spine through inspection and palpation is important to exclude underlying occult neurologic conditions. Any bony abnormalities of the vertebrae or sacrum should be further investigated. Any central cutaneous abnormalities overlying the spine, such as a sacral dimple, gluteal cleft, or lipoma or hair tuft, should also prompt further consideration for investigation because these may signify occult spinal cord anomalies (eg, tethered cord, diastematomyelia, and lumbosacral defects).

Pertinent findings on genital examination include appearance of the external genitalia and presence of irritation or dampness of the underwear or perineum. Blood or a bulge at the urethral meatus may indicate a urethral polyp or anatomical cause for voiding symptoms. The vaginal introitus should be examined for pooling of urine or irritation. If there is continuous incontinence, examination of the introitus for an ectopic ureteral orifice should be performed. If a patient has chronic irritation of the genitalia and perineum, skin changes or labial hypertrophy may be observed. (7)

#### Ultrasonography and Uroflow

Although not within the scope of practice for primary care practitioners, noninvasive urodynamic measurements determined by an office pelvic ultrasonography and uroflow can assist in differentiating MSE from NMSE and are commonly used in pediatric urology consultations. Findings on prevoid and postvoid ultrasonography consistent with NMSE include an enlarged bladder capacity (>150% expected for the child's age), incomplete emptying (a postvoid residual of >10% expected capacity), or a thickened bladder wall suggestive of increased workload on the bladder muscle (detrusor muscle) during emptying due to increased bladder outlet resistance and pelvic floor muscle tone. A rectal diameter greater than 30 mm in a child without the urge to defecate is suggestive of concomitant bowel dysfunction. Uroflowmetry allows the pediatric specialist to assess the urinary flow pattern, and the shape of the flow curve may indicate underlying disease because shape is determined by detrusor contractility and influenced by abdominal straining, coordination with the bladder outlet musculature, and any distal anatomical obstruction. The urinary flow curve of a healthy child is bellshaped, and other flow patterns are suggestive of underlying LUT dysfunction and NMSE. (10)(11)

#### THERAPY

Therapy for NMSE is based on the following principles.

- 1. Address any underlying constipation or fecal incontinence.
- Address any LUT dysfunction and daytime voiding symptoms.
- 3. Address any comorbid behavioral conditions.
- 4. If enuresis is still present after addressing the above, institute standard therapies for MSE.

Although treatment of severe fecal incontinence and behavioral conditions are outside the scope of this article, many validated techniques exist for treatment of these comorbidities that may accompany enuresis. We review these treatment concepts in further detail.

#### CONSTIPATION

Even in children without pathologic constipation or fecal incontinence, addressing subclinical constipation can result in marked improvement in LUT dysfunction. Multiple observational studies report improvement of urinary tract dysfunction in 60% to 90% of children treated for underlying constipation. (12) Although increased dietary fiber and adequate hydration are the first-line therapy for constipation, many children will require further treatment. Secondline therapy is typically a fiber supplement and an osmotic laxative, such as polyethylene glycol, titrated to give a smooth, daily bowel movement that does not require straining or cause pain. A pictorial scale, such as the Bristol stool scale, can be useful in communicating accurately with families regarding the child's bowel habits. (13) Severe cases of constipation may require hospital admission and fecal disimpaction. This should only be undertaken after consultation with a gastroenterologist, and the children should be evaluated for possible pathologic causes of bowel dysfunction,

such as underlying neurologic conditions or Hirschsprung disease. (12)

#### **BEHAVIORAL CONDITIONS**

Addressing behavioral comorbidities in conjunction with LUT dysfunction should be in accordance with existing therapeutic approaches. Although some conditions may be amenable to management in a primary setting (such as stimulant medication and counseling for attentiondeficit/hyperactivity disorder), many may require further expertise, such as referral to a psychiatrist or psychologist. (9)

#### UROTHERAPY

Urotherapy is conservative-based therapy and the mainstay of treatment for LUT dysfunction. The hallmark of urotherapy is parental and patient education on normal elimination habits and institution of a structured behavioral program designed to improve bladder and bowel function. In our practice, we routinely use an educational handout for parents with information about managing constipation and encouraging good posture and voiding habits. Both the child and parents keep diaries to monitor and record the elimination patterns. For the child, the voiding diary is also a reward chart for children to color or place stickers for each attempted void. Parents record a week-long elimination diary about their child's elimination patterns and any symptoms of BBD during weeks 1 (baseline), 6, and 12 of the program. These scheduled time points allow for accurate assessment of the child's progress from the behavioral modification and indicate need for any further follow-up or additional treatment. For most children with LUT dysfunction, this behavioral modification program is the only necessary treatment. When children are refractory to standard urotherapy, evaluation for possible underlying neurologic abnormalities and referral to a pediatric urologist should be considered before instituting more advanced therapeutic techniques.

#### ADVANCED UROTHERAPY TECHNIQUES

Advanced urotherapy techniques include biofeedback techniques for assessing pelvic floor musculature and pelvic floor musculature physiotherapy. In addition, neurostimulation with sacral transcutaneous electrical nerve stimulation and posterior tibial nerve stimulation are alternative methods of modulating the sacral nerves responsible for control of the pelvic floor. These advanced techniques are generally performed by pediatric subspecialists and involve specialized



Figure 1. Algorithm for evaluation and management of children with enuresis.

physical therapists with expertise on pediatric pelvic floor dysfunction.

#### OTHER ADVANCED TECHNIQUES

#### $\alpha$ -Blockers

For children with evidence of functional bladder outlet obstruction who do not improve with first-line therapy,  $\alpha$ -adrenergic antagonists ( $\alpha$ -blockers) are sometimes used to facilitate more coordinated bladder emptying. Initially designed for treating men with LUT dysfunction secondary to benign prostatic hypertrophy, these medications have also been used for treatment in pediatric LUT dysfunction. (10) Selective  $\alpha$ -blockers improve bladder emptying by their targeted relaxing effect on the bladder neck and proximal urethra (internal sphincter under autonomic innervation) during micturition. The Food and Drug Administration has not formally evaluated these medications for this indication, and use in children should not be undertaken without disclosure to the family about off-label use.

#### **Botulinum Toxin**

Botulinum toxin A is another promising pharmaceutical agent for management of refractory LUT dysfunction. This is investigational at this time and should only be used under the supervision of a pediatric urologist in a research setting.

#### ENURESIS-SPECIFIC TREATMENTS

Once constipation, behavioral comorbidities, and LUT dysfunction have been addressed, standard enuretic therapies can be instituted if enuresis is still present. Each of the below therapies has strong research evidence for recommended use in children converted from NMSE to MSE.

#### **Behavioral Modification**

Data from randomized trials on the efficacy of behavioral therapy are lacking, but clinical experience (ie, level IV evidence) would suggest that this approach is beneficial. All patients with enuresis receive education and strategies to optimize bladder behavior. Children should attempt to void regularly during the day and just before going to bed for a total of 6 to 7 times daily. High sugar- and caffeine-based drinks should be avoided, particularly in the evening hours. Daily fluid intake should be concentrated in the morning and early afternoon, and fluid and solute intake should be minimized during the evening. Parental waking of the child to void when the parents go to bed is generally unreliable because the children will wet the bed randomly throughout the sleep cycle. Similarly, results from bladder-stretching exercises are mixed and generally anecdotal.

#### Moisture Alarm

Commercially available moisture alarms, when used properly, are effective treatments for MSE. The moisture alarm aims to strengthen the relationship between the full bladder and the sleeping brain and represents classic conditioning therapy. The alarm will sound as soon as moisture is detected in the child's underwear; however, it is crucial that parents use the alarm as a tool to fully awaken the child and have the child void before returning to sleep. With repetition, the child will learn to suppress micturition or may awaken spontaneously with a full bladder, obviating the need for the alarm. With proper use, 50% of children will be dry and have a durable response after several weeks of alarm therapy. (7)

#### Desmopressin

Desmopressin is the first-line pharmaceutical option for enuresis. The medication is an analog of vasopressin (also known as antidiuretic hormone) and works at the level of the nephron to decrease overall urine production. It does not have any central effect and does not increase spontaneous arousal with the sensation of a full bladder. Approximately 30% of children will be dry with this treatment, and another 40% will partially respond. Identification of children with nocturnal polyuria will markedly improve the response rate by selecting ideal candidates for desmopressin. Nocturnal polyuria is determined by weighing overnight pads and measuring the first morning void and is defined as nocturnal urine production greater than 130% of age-expected bladder capacity. (1)(2) The medication is generally safe and well tolerated, and adverse effects are rare. It is up to the discretion of the family whether to institute daily treatment or symptomatic management under situations where

enuresis would be problematic or socially unacceptable, such as slumber parties, camp, or school trips. (7)

#### Imipramine and Centrally Acting Medications

Imipramine, a tricyclic antidepressant, was the first medication noted to improve enuresis. Multiple randomized studies have found its efficacy to be approximately 50%. It has some direct anticholinergic activity on the bladder and may increase storage capacity to a small degree, but its primary mechanism is its central activation on the brain. The postulated mechanism of imipramine is the selective inhibition of neurotransmitter reuptake, but the exact central action of imipramine is poorly understood. It is no longer recommended as primary therapy for MSE because of concerns of cardiac toxic effects and the interaction of tricyclic antidepressants with many commonly prescribed medications. Thus, therapy with imipramine should only be instituted as a second-line agent after failing management with desmopressin and alarm therapy. (7)(8)

Other centrally acting medications, specifically norepinephrine reuptake inhibitors, also have promise in treating enuresis; however, these should not be routinely prescribed outside a tertiary care setting.

#### **Anticholinergics**

Monotherapy with anticholinergic drugs, such as oxybutynin or tolterodine, has been found not to be effective as a firstline of treatment for MSE in a placebo-controlled trial. (14) Although evidence of efficacy from randomized trials is lacking, uncontrolled studies have revealed improvement in some children with NMSE, presumably because many of these children have a reduced functional bladder capacity or nocturnal detrusor overactivity. (15) The therapeutic role of anticholinergics is clearer in combination therapy in the treatment of children with MSE who are refractory to desmopressin monotherapy. In a double-blinded, randomized, placebo-controlled study, children with primary MSE in whom the maximal dose of desmopressin monotherapy has failed received either extended-release tolterodine or placebo with desmopressin. With a generalized estimating equation approach, there was a significant 66% reduction in the risk of a wet episode compared with the placebo group. (16)

Alternative Therapies. Other drugs, including indomethacin, ephedrine, atropine, furosemide, and diclofenac, have been tried in the treatment of enuresis. A recent systematic review of randomized trials of drugs other than tricyclic antidepressants and desmopressin found that although indomethacin, diclofenac, and diazepam were better than placebo in reducing the number of wet nights, none of the drugs was better than desmopressin. (17) A second review of complementary approaches, such as hypnosis, psychotherapy, and acupuncture, found limited evidence from small trials with methodologic limitations to support the use of such modalities for the treatment of enuresis. (18)

## Summary (Figure 1)

- On the basis of some research evidence and consensus, up to one-third of patients with enuresis will have daytime urinary symptoms indicative of lower urinary tract (LUT) dysfunction. (8) (9)
- On the basis of international consensus, children with enuresis and LUT dysfunction are correctly identified as having nonmonosymptomatic enuresis (NMSE) (formerly termed *diurnal enuresis*). (1)(2)
- On the basis of some research evidence and consensus, an adequate voiding and elimination history is the primary tool in differentiating between MSE and NMSE. (2)(7)(8)
- On the basis of some research evidence and consensus, therapy for NMSE is based on addressing underlying LUT dysfunction, constipation, and comorbid behavioral conditions before addressing enuresis. (2)(8)(9)(12)
- On the basis of some research evidence and consensus, treatment of underlying BBD and comorbid conditions will often result in improvement or resolution of enuresis. (2)(8)(9)(12)
- On the basis of international consensus, if enuresis is still present and a concern after treatment of underlying LUT, specific medical or behavioral therapy for enuresis should be offered to the family. (2)(8)

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# PIR Quiz

- 1. A 5-year-old girl has always been continuously incontinent for urine and is continent for bowel. She is wet throughout the day and night. She has a history of constipation, but this has decreased with increase in dietary fiber. She sleeps soundly during the night and is difficult to wake when her parents have tried to awaken her at night to void. Her parents are recently separated. The MOST likely cause of her incontinence is:
  - A. Chronic constipation.
  - B. Diminished sleep arousal.
  - C. Ectopic ureter.
  - D. Nocturnal polyuria.
  - E. Social stressors.
- 2. A 6-year-old boy was continent both day and night at 4 years. In the past 6 months, he has had bedwetting several nights per week. His physical examination findings are normal. He has no constipation with daily soft bowel movements. His teacher has noted changes in his behavior in the classroom; he has been impatient with his classmates and has had several altercations on the playground. Which of the following history elements is MOST likely to assist in identifying the cause of his nocturnal enuresis?
  - A. Leg crossing or squatting on the floor.
  - B. Daily fiber intake.
  - C. Inattention and impulsivity in the classroom.
  - D. Dampness of the underwear.
  - E. Social stressors.
- 3. A 7-year-old girl has secondary enuresis; she was toilet-trained at age 3 years. She has been inattentive in the classroom, and her teacher has requested a psychoeducational evaluation in school. She has grown 4 cm in the past few months, and her mother believes she is tripping more. On physical examination, you are MOST likely to note:
  - A. Mouth breathing.
  - B. Labial hypertrophy.
  - C. Pooling of urine in the vaginal introitus.
  - D. Blood at the urethral meatus.
  - E. Sacral hair tuft.
- 4. An 8-year-old boy has nocturnal enuresis. He and his family have completed a 7-day bladder diary and a 48-hour daytime and volume frequency chart, which reveal normal bladder capacity for an 8-year-old. He has low postvoid residual. He has no constipation with daily soft bowel movements. He sleeps very soundly and is difficult to awaken. His neurologic examination findings are normal. You are MOST likely to recommend:
  - A. Late night voiding.
  - B. Moisture alarm.
  - C. Referral for biofeedback training.
  - D. Trial of nightly imipramine.
  - E. Use of an anticholinergic medication.
- 5. The parents of a 7-year-old girl are frustrated by her nighttime bedwetting. They have heard about a medication, desmopressin, used to treat enuresis. They would like to know whether she is a candidate for use of the medication. She has daily bowel movements and no daytime voiding accidents. She is an average student. Her physical examination findings are normal. You are MOST likely to recommend:

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- A. Biofeedback training.
- B. Bladder ultrasonography.
- C. Psychoeducational evaluation.
- D. Spinal radiography.
- E. Weighing of nighttime pad and first morning void.

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