

CLINICAL PRACTICE

Evaluation and Management of Enuresis

W. Lane M. Robson, M.D.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

The parents of an 8-year-old boy bring him to the pediatrician's office for evaluation of nightly bed-wetting. On half the nights, his urine soaks through a pair of absorbent disposable underpants into the sheets. He often does not void during school hours, and when he returns home after school, he usually rushes to the bathroom. He arrives home thirsty after school, and the majority of his daily fluid intake is in the 5 hours from 3:30 p.m. to bedtime. His physical examination is normal, apart from hard stool palpated in the left lower quadrant. In the office he voids 170 ml of urine and has urgency at this volume (average functional capacity for his age, 300 ml). How should this boy be evaluated and treated?

THE CLINICAL PROBLEM

Bed-wetting is common.^{1,2} According to a recent large, longitudinal study, at least 20% of children in the first grade occasionally wet the bed, and 4% wet the bed two or more times a week.¹ Enuresis is more common in boys than in girls. In a study of 10,960 children in the United States, the prevalence of enuresis in boys at the ages of 7 and 10 years was 9% and 7%, respectively, and in girls at those ages, 6% and 3%, respectively.²

The International Children's Continence Society has published standards of terminology and definitions for enuresis.³ Enuresis is categorized as monosymptomatic or nonmonosymptomatic. Monosymptomatic enuresis occurs in the absence of any daytime voiding symptoms, such as frequency, urgency, or daytime incontinence. Nonmonosymptomatic enuresis is more common; when a detailed history is obtained, the majority of children have at least subtle daytime symptoms.⁴

Enuresis can also be categorized into primary and secondary forms.^{3,5} Secondary enuresis is defined as wetting that develops after a minimum of 6 consecutive months of dryness. The clinical presentations of children with primary and secondary enuresis are otherwise similar, which suggests a common pathogenesis (Table 1).⁶ Factors implicated in the pathogenesis of enuresis include a disorder affecting arousal from sleep,⁷⁻⁹ nocturnal polyuria,^{10,11} and a reduced nocturnal bladder capacity.¹²

STRATEGIES AND EVIDENCE

EVALUATION

A careful history taking is fundamental to the evaluation of enuresis (Table 2). Symptoms that suggest a low functional bladder capacity include urinary frequency and nocturia. Some children void with a normal frequency or even a reduced frequency and yet have a low functional bladder capacity; these children often do not drink appreciably during the day, and urinary frequency is evident only after a fluid load. Most children in the age range for elementary school can relate an accurate voiding his-

From the Children's Clinic, Calgary, AB, Canada. Address reprint requests to Dr. Robson at the Children's Clinic, Suite 111, 4411 16th Ave. NW, Calgary, AB T3B 0M3, Canada, or at wlmrobson@gmail.com.

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Table 1. Conditions That May Precipitate Secondary Enuresis.

| Condition | Possible Mechanism |
|---|--------------------------|
| Cystitis | Reduced bladder capacity |
| Constipation | Reduced bladder capacity |
| Sleep-disordered breathing | Impaired arousal |
| Diabetes mellitus | Nocturnal polyuria |
| Diabetes insipidus | Nocturnal polyuria |
| Urethral obstruction | Reduced bladder capacity |
| Neurogenic bladder | Reduced bladder capacity |
| Seizure disorder | Neurogenic mechanism |
| Medications (selective serotonin-reuptake inhibitors, valproic acid, clozapine) | — |
| Psychological stress, sexual abuse | — |

tory for school days. An objective means of documenting voiding patterns is the voiding diary, which is especially useful when the history is not clear. A voiding diary kept by the parents should help to assess the times at which a child voids; the relationship between voiding and common events such as meals, breaks at school, and play activities; the occurrence of urgency or incontinence; and the volume voided (as often as is practical, and at least at common voiding times, such as on waking and after school). The history taking should include screening for symptoms of cystitis or constipation, since both conditions are associated with a reduced functional bladder capacity. Parents are often unaware of constipation in their child, and children in the age range for elementary school should be directly questioned about this problem. In one cross-sectional study of 277 children with enuresis, in which parental reporting of constipation was compared with a clinician's assessment, the prevalence of constipation reported was 14% and 36%, respectively.¹³ Keeping a 2- to 4-week calendar for bowel movements is helpful. The child should be instructed not to flush the toilet; the parent should record the time of movements and soiling, indicate whether the stool is soft or hard, and record the width.

A history of soaking absorbent disposable underpants suggests nocturnal polyuria, and in such cases, a history of daily diet and fluid intake is helpful. Many children do not drink appreciable amounts of fluids during the morning and early afternoon, especially on school days. These children often arrive home from school thirsty, and most of their daily fluid intake occurs during the

late afternoon and evening, a pattern that favors nocturnal polyuria.

The physical examination should include palpation of the abdomen for stool, examination of the lower spine for cutaneous stigmata of spinal dysraphism (midline pigmentation or hair tuft, or a dimple above the cleft), assessment of the anal wink, and evaluation of the motor strength, tone, reflexes, and sensation in the legs for evidence of a neurogenic bladder (Table 2). Children who have daytime urinary symptoms or who do not have improvement with therapy should be referred to a specialist.⁴

LABORATORY TESTING AND IMAGING STUDIES

A urinalysis is warranted in all children to rule out urinary tract infection and glycosuria. A high specific gravity in a urine specimen obtained in the afternoon suggests low fluid intake during the day.

Ultrasonography of the pelvis is helpful in children with daytime symptoms and should be performed routinely as part of a specialty assessment. Ultrasound examination of the bladder, performed when the child feels the bladder is "full," can be used to estimate functional bladder capacity, which can be compared with norms for bladder capacity according to age.^{14,15} Ultrasonography performed after voiding can be used to assess the patient for a thick bladder wall (>5 mm after voiding³) and elevated residual urinary volume (>5 ml),³ both of which suggest nonmonosymptomatic enuresis. The use of transabdominal ultrasonography of the rectum to measure the transverse rectal diameter has reportedly been helpful in screening for constipation,¹⁶ but its use for this purpose has not been well validated.

MANAGEMENT

Conventional therapies for enuresis include behavioral therapy, alarm therapy, and pharmacologic therapy. The evidence for the efficacy of much of the care provided to children with enuresis is weak.⁴ The only therapies that have been shown to be effective in randomized trials are alarm therapy and the use of desmopressin or imipramine.

The decision to defer treatment should not be based on the belief that the problem is likely to resolve over time. Enuresis that occurs as infrequently as once a month is associated with reduced self-esteem, and treatment has been reported to improve self-esteem, regardless of the type or the success of therapy (although successful therapy

Table 2. Important Aspects of the History and Physical Examination in Enuresis.

| Symptom, Sign, Condition | Possible Interpretation | Referral to Specialist |
|---|--|------------------------|
| Urinary frequency | Reduced bladder capacity | Yes |
| Nocturia | Reduced bladder capacity | Yes |
| Urinary urgency | | Yes |
| Daytime incontinence | | Yes |
| Interrupted or otherwise abnormal stream | | Yes |
| Absorbent underpants soaked (vs. damp or average wetness) | Nocturnal polyuria | No |
| Soaking through absorbent underpants into sheets | Nocturnal polyuria | No |
| Large volume of urine on first voiding in morning, despite enuresis | Nocturnal polyuria | No |
| Low daytime fluid intake, thirst at end of school day, majority of fluid intake in late afternoon and evening | Nocturnal polyuria | No |
| Thirst, polyuria | Nocturnal polyuria, possibly diabetes mellitus or diabetes insipidus | No |
| Cystitis | Reduced bladder capacity | Yes |
| Constipation or encopresis | Reduced bladder capacity | Yes |
| Snoring | Impaired arousal from sleep | Yes |
| Hard stool in abdomen | Constipation | Yes |
| Patulous anus, absence of anal wink | Neurogenic bladder | Yes |
| Dimple above cleft or other cutaneous abnormalities over lumbosacral spine | Neurogenic bladder | Yes |
| No improvement with therapy | — | Yes |

results in greater improvement).^{17,18} The decision about when to start treatment should generally be guided by the degree of concern and motivation on the part of the child rather than the parents.

Behavioral Therapy

Data from randomized trials of the efficacy of behavioral therapy (other than alarm therapy) are lacking, but clinical experience suggests that this approach is beneficial.⁴ The fundamental goal of behavioral therapy is the achievement of good bladder and bowel habits. For example, the child should be encouraged both to void frequently enough to avoid urgency and daytime incontinence and to have a bowel movement every morning after breakfast, before leaving for school. Behavioral therapy requires a supportive parent, a motivated child, patience, and time (an average of 6 months) (Table 3). Although the influence of the clinician's behavior has not been formally studied, clinical experience suggests that the ability to establish a rapport with the child and to engender and sustain motivation is important for successful behav-

ioral therapy. In practice, compliance improves when parents and children understand the problem to the extent that the suggested behavioral modifications make sense. A personalized calendar for recording daytime incontinence and enuresis and the frequency and timing of bowel movements and encopresis helps the family and the child to follow progress. Families should be counseled that there is "no race for dryness" and that slow but steady improvement is more realistic. Parents might choose to offer rewards appropriate for the age of the child. On the basis of the information recorded on the personalized calendars, physicians can challenge children to improve specific behaviors between visits, such as reducing the number of episodes of daytime incontinence, increasing the number of daily bowel movements, or increasing the number of days on which there is a morning movement. Regular follow-up every 1 to 3 months is helpful in sustaining motivation.

Treatment of constipation may also reduce enuresis, although this approach has not been studied in randomized trials. In an uncontrolled study,

Table 3. Recommendations for the Use of Behavioral Therapy.*

| |
|---|
| Remove underpants and have child void in toilet at start of every day |
| Encourage child to avoid holding urine |
| Encourage voiding at least once every 2 hr, at least several times during school day, and often enough to avoid urgency and incontinence† |
| Facilitate easy access to school toilets with a note to the teacher |
| Have child drink a liberal amount of water during morning and early afternoon hours, a total of at least 30 ml per kilogram of body weight† |
| Minimize intake of fluids and solutes after dinner unless child is participating in evening sports or social activities† |
| Encourage a daily bowel movement, preferably after breakfast and before child leaves for school |
| Have child use optimal posture to relax pelvic-floor muscles, facilitating good emptying of bowel‡ |
| Encourage the child to eat foods that soften stool and to avoid foods that harden stool |
| Encourage the child to engage in physical activity and discourage prolonged sitting in front of television or computer† |

* These recommendations are based on clinical experience rather than the results of randomized trials.

† This recommendation is from Nevéus et al.⁴

‡ The optimal posture involves sitting in the middle of the toilet with heels flat on the ground or on a footstool.

successful treatment of constipation, without any other intervention, resulted in resolution of enuresis in 63% of 41 patients.¹⁹ A stool softener is helpful to increase the regularity of bowel movements as well as optimize emptying. Polyethylene glycol, which is tasteless for most children and has minimal side effects, has been shown to be effective as compared with placebo.^{20,21} The optimal posture for relaxing the pelvic-floor muscles, and for emptying the bladder and the bowel, involves sitting in the middle of the toilet with the legs apart and with the heels flat on the ground or on a footstool. Clinical experience suggests that small children — usually preschool children and those in the early grades of elementary school — benefit from the use of an over-the-toilet seat and a footstool, and they should be counseled not to rush or push.

Neither bladder holding nor “stretching” exercises are efficacious.²² In contrast, behavioral therapy to relax the bladder and the pelvic-floor muscles has been shown to improve outcomes in children with frequency, urgency, and daytime wetting.²³ Biofeedback techniques that help children to recognize and relax the pelvic-floor muscles are helpful in addition to optimal posture.

Alarm Therapy

With alarm therapy (Table 4), the child is awakened precisely at the moment of wetting. Alarm therapy is presumed to improve arousal from sleep either by classical conditioning or avoidance-con-

ditioning effects.²⁵ In up to a third of children successfully treated with alarm therapy, nocturia replaces bed-wetting.²⁶ In this situation, arousal from sleep is presumably improved, but the children still have a reduced nocturnal bladder capacity.

A Cochrane review of 56 randomized trials that involved 3257 children concluded that alarm therapy is beneficial.²⁴ About two thirds of children were dry (bed-wetting had stopped) with alarm therapy (relative risk of failure, 0.38; 95% confidence interval [CI], 0.33 to 0.45). Almost half of those for whom alarm therapy was successful remained dry after therapy was stopped. Successfully treated children usually begin to have a response in the first month, with regular dryness typically requiring a total of 3 to 6 months of continuous therapy. Once a child has been consistently dry for several months, the therapy can be discontinued. If there is no improvement at 1 month, it is reasonable to discontinue therapy.

Pharmacologic Therapy

Medications used to treat bed-wetting include desmopressin, anticholinergic agents, and tricyclic agents (Table 5). Desmopressin reduces overnight production of urine. A Cochrane review of 47 randomized trials that included 3448 children concluded that desmopressin reduces bed-wetting.³⁴ Children treated with desmopressin, as compared with those receiving placebo, had an average of 1.3 fewer wet nights per week (95% CI, 1.1 to 1.6).

Table 4. Recommendations for the Use of Alarm Therapy.*

| |
|--|
| Use as first-line therapy — consider before prescribing medication |
| Continue therapy for at least 2 to 3 months |
| Have child wear alarm every night |
| Motivate child and parents to participate |
| Have both parents and child arise each time the alarm goes off — children quickly learn to turn off alarm and fall back to sleep |
| Have child go to bathroom and void each time alarm goes off |
| Inform family that first few weeks of therapy are the most difficult — arrange an early follow-up appointment to monitor progress and address any problems |
| Inform family that failure of child to wake or of parents to wake child are the most common reasons for failure of alarm therapy |

* Recommendations are from Glazener et al.²⁴ Alarm therapy is effective in approximately two thirds of children (relapse rate, 4 to 55%).

There was a wide range of efficacy among the studies, most likely because of different patient populations (monosymptomatic vs. nonmonosymptomatic), differences in concomitant behavioral therapy recommendations, and differences in the dosage or formulation of desmopressin.²⁷⁻²⁹

The only serious adverse event reported with desmopressin is symptomatic hyponatremia with water intoxication.³² On evenings when desmopressin is taken, children should be instructed not to drink during the 2 hours preceding bedtime or for the rest of the night. Parents should be advised not to administer the medication on nights when there is excess fluid intake, such as during evening sports or social activities. Desmopressin should be discontinued if headache, nausea, or vomiting develops, since these symptoms may suggest water intoxication.

The majority of the reported episodes of water intoxication are associated with the nasal-spray formulation of desmopressin, which has a prolonged half-life.^{33,35} The nasal spray has a black-box warning from the Food and Drug Administration and is no longer recommended. The fast-melting oral formulation has a shorter duration of pharmacodynamic action, which approximates the average duration of sleep for a child in the age range for elementary school.^{31,36}

The most common cause of unresponsiveness to desmopressin is a reduced nocturnal bladder capacity.^{12,37} Another cause is persistent nocturnal polyuria,³⁸ which may result from poor compliance with evening fluid restriction, increased nocturnal solute excretion, or a reduced pharmacodynamic effect of desmopressin.^{39,40}

Pharmacologic therapies to improve bladder capacity or reduce detrusor overactivity include anticholinergic medications such as oxybutynin and tolterodine.^{40,41} Although evidence of efficacy from randomized trials is lacking, uncontrolled studies show improvement in some children with nonmonosymptomatic enuresis, presumably because many of these children have a reduced functional bladder capacity.^{41,42} Clinical experience suggests that some children benefit from a combination of desmopressin to reduce nocturnal polyuria and an anticholinergic medication to increase functional bladder capacity.⁴¹ When these medications are prescribed, the child should be followed closely for constipation and increased residual volume after voiding, since these adverse effects, especially the former, might worsen enuresis.

A Cochrane review of 58 randomized trials that included 3721 children concluded that both imipramine and other tricyclic medications have been proved effective in reducing bed-wetting.³⁰ Treatment with a tricyclic agent, as compared with placebo, reduced bed-wetting by about 1 wet night per week (weighted mean difference, -0.9; 95% CI, -1.4 to -0.5). About a fifth of children became dry. However, owing to the unfavorable adverse-event profile (which includes association with mood changes and sleep disturbances) and the risk of death with an overdose, the International Children's Continence Society recommends that imipramine be used only when all other therapies have failed.⁴

Reboxetine, a noradrenaline-reuptake inhibitor, is pharmacologically related to imipramine but is

Table 5. Pharmacologic Therapy.

| Characteristic | Desmopressin | Anticholinergic Agent | Imipramine and Other Tricyclic Agents |
|-------------------|--|--|--|
| Evidence based | Yes | No | Yes |
| Mechanism | Reduces nocturnal polyuria | Increases bladder capacity, reduces detrusor overactivity | Not clear ⁴ |
| Considerations | Use as first-line pharmacologic therapy ⁴ ; consider using for special occasions (sleep-overs, camp) | Use as second-line pharmacologic therapy for children who do not have a response to other therapies ⁴ ; consider using in combination with desmopressin | Use only as third-line therapy, when all other therapeutic options have failed ⁴ |
| Efficacy | Cessation of bed-wetting in 3 to 48% of study subjects ²⁷⁻²⁹ ; works as a control, not a cure — relapse expected after medication is stopped | Works as a control, not a cure — relapse expected after medication is stopped | Cessation of bed-wetting in about 20% of study subjects ³⁰ ; works as a control, not a cure — relapse expected after medication is stopped |
| Dose* | Tablets: 200–600 μ g 1 hr before bedtime; fast-melting formulation: 120–360 μ g 30–60 min before bedtime (consider this formulation for younger children who prefer not to swallow tablets) ³¹ | Oxybutynin tablets or syrup: 5 mg before bedtime; tolterodine tablets: 2 mg before bedtime | Tablets: 25–50 mg before bedtime ⁴ ; do not exceed 75 mg before bedtime ⁴ |
| Adverse events | Water intoxication with headache, nausea, vomiting, decreased level of consciousness, seizure ^{32,33} ; nasal-spray formulation labeled with black-box warning regarding increased risk of water intoxication — not recommended | Constipation, dry mouth, blurred vision, facial flushing, heat intolerance, mood change, increased residual urine | Mood changes, nausea, sleep disturbance; cardiotoxicity, with potential for death with overdose — medication should be securely stored, out of reach from children |
| Drug interactions | Nonsteroidal antiinflammatory medications and antidepressant medications may cause additional fluid retention ⁴ | | |

* The doses for both formulations of desmopressin have been approved by the Food and Drug Administration (FDA) for children 6 years of age or older, and the doses for both formulations of oxybutynin have been approved by the FDA for children 5 years of age or older. Tolterodine has not been approved by the FDA for use in children.

without apparent cardiovascular toxicity. In one study, reboxetine monotherapy resulted in dryness in 32% of 22 children who had enuresis that was resistant to other therapies; reboxetine combined with desmopressin resulted in dryness in another 27%.⁴³ Further study is needed to define the role of this agent in clinical practice.

AREAS OF UNCERTAINTY

Why children with enuresis do not wake up to a full or contracting bladder is not understood. The factors that control arousal from sleep and changes in arousal with age are poorly understood. Arous-

al from sleep is mediated by the reticular activating system, and voiding is mediated by the pontine micturition center; these functions converge in the locus ceruleus in the upper pons.^{8,9} Limited evidence suggests that children with enuresis might have abnormalities in this area.^{8,9}

The mechanisms by which constipation might cause enuresis are not well defined. The bladder is located in the narrowest dependent portion of the pelvis. The volume of a child's pelvis is small, and the presence of stool might cause enuresis either by reducing bladder capacity or by triggering nocturnal colonic motility that stimulates a detrusor contraction at a lower volume.

Although behavioral therapy is considered helpful, randomized trials are necessary to clarify which aspects are most efficacious.

GUIDELINES

The International Children's Continence Society recently published recommendations for the evaluation and treatment of monosymptomatic enuresis.⁴ The recommendations in this article are consistent with those of the society.

CONCLUSIONS AND RECOMMENDATIONS

The child described in the vignette has nonmonosymptomatic enuresis that probably results from both reduced functional bladder capacity, which might be caused by constipation, and nocturnal polyuria, given his substantial fluid intake in the afternoon and evening. He does not wake to void,

which suggests a problem with arousal. Referral to a specialist should be considered. Evaluation should include a urinalysis; I would also recommend pelvic ultrasonography to assess the thickness of the bladder wall and residual urinary volume after voiding and to determine the transverse rectal diameter as an indicator of the presence or absence of constipation. A good preliminary approach to management would be to follow the behavioral-therapy recommendations in Table 3. If enuresis does not diminish within several months, I would recommend a trial of alarm therapy, which has proved effective in randomized trials and offers the possibility of a cure. If alarm therapy is not successful, then a trial of desmopressin (tablet or fast-melting oral formulation) should be considered, since randomized trials have also shown that this therapy can be effective.

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