Nocturnal enuresis (NE) is a common problem in children, and its prevalence rate is 20% among children aged 5 and subsequently, 15% of children recover every year. However, approximately 0.5% of adult populations remain unchanged.

The major pathogenic factors involved in NE are nocturnal polyuria, small bladder capacity and/or detrusor overactivity, and a high arousal threshold.

Desmopressin is the first-line medication for the patients with diuresis dependent nocturnal enuresis and its efficacy rates are nearly 70%. Enuresis alarm device is also commonly used especially for the patients with small bladder capacity and is effective for 65-70% of patients with NE.

For the patients who do not respond to desmopressin and enuresis alarm, anticholinergics or tricyclic antidepressants are used.

Japanese Society on Enuresis has recently revised the practical guideline for nocturnal enuresis in 2016.

Key words: nocturnal enuresis, bedwetting, enuresis alarm, desmopressin

Current concepts on nocturnal enuresis

By 5 years of age, 90-95% of children are nearly completely continent during the day, and 80-85% are continent at night. Subsequently, 15% of children recover every year. However, approximately 0.5% of children carry over the disorder into their adulthood.

Nocturnal enuresis refers to the occurrence of involuntary voiding at night after 5 years old, the age when volitional control of micturition is expected. Enuresis may be primary (estimated 75-90% of children with enuresis; nocturnal urinary control never achieved) or secondary (10-25%; the child was dry at night for at least a few months and then enuresis developed) (Figure-1).

Nocturnal enuresis is a heterogeneous condition that includes a spectrum of disorders with different underlying pathophysiological mechanisms.

Current evidence suggests that the major pathogenic factors involved in nocturnal enuresis are nocturnal polyuria, small bladder capacity and/or detrusor overactivity, and a high arousal threshold.

Enuresis is divided into monosymptomatic and non-monosymptomatic forms (Figure-2). Monosymptomatic enuresis (MNE) is defined as enuresis in children without any other lower urinary tract symptoms and without a history of bladder dysfunction.

Non-monosymptomatic enuresis (NMNE) is defined as enuresis in children with other lower urinary tract symptoms, including 1) consistently increased (≥8 times/day) or decreased (≤3 times/day) voiding frequency, 2) daytime incontinence,
3) urgency, 4) hesitancy (difficulty initiating voiding), 5) straining (application of abdominal pressure to initiate and maintain voiding), 6) a weak stream, 7) intermittency (micturition occurs in several discrete spurts), 8) holding maneuvers (strategies used to postpone voiding), 9) a feeling of incomplete emptying, 10) post-micturition dribble, and 11) genital or lower urinary tract pain.

The organic etiologies of non-monosymptomatic enuresis includes: ectopic ureter, neurogenic bladder, epispadias, posterior urethral valves strictures, paraureteral diverticulum, stone, tumor, foreign body, and sacral lipoma.

**Pretreatment evaluation**

Thorough history taking including the presence of 11 symptoms described above is an essential component for detecting underlying bladder dysfunction.
In addition, it is important to look for causes of nocturnal enuresis that may require additional evaluation and treatment (e.g., diabetes mellitus, obstructive sleep apnea, encopresis or constipation, bowel and bladder dysfunction, etc.).

It is difficult to successfully treat enuresis if coexistent constipation is not addressed. When evaluating for constipation, it may be helpful to ask about soiling in addition to the usual questions about bowel habits.

A brief but thorough physical examination also should be performed primarily to identify rare underlying anatomical (phimosis and labial agglutination) or neurogenic (spinal malfunction) causes.

The sole obligatory laboratory test in children with MNE is a urine dipstick test; glycosuria means that diabetes mellitus must be immediately excluded and proteinuria in repeat samples should prompt investigations for kidney disease. Both routine blood examinations and ultrasound of the kidneys and upper urinary tract are not warranted for MNE patients.

Management approach

Management of nocturnal enuresis may involve one or a combination of interventions, including, 1) education and advice (given the high rate of spontaneous resolution), 2) motivational therapy (e.g., sticker or star chart), and 3) active therapy (desmopressin and enuresis alarms).

1. Education and advice

The education and advice typically includes the following information:

i) Enuresis resolves on its own in the majority of children.

ii) Enuresis is the fault of neither the child nor the caregivers; children should not be punished for bedwetting.

iii) The child should attempt to void regularly during the day and just before going to bed (a total of four to seven times); if the child wakes at night, the caregivers should take him/her to the toilet.

iv) High-sugar and caffeine-based drinks should be avoided in children with enuresis, particularly in the evening hours.

v) Daily fluid intake should be concentrated in the morning and early afternoon; fluid and solute intake should be minimized during the evening.

vi) Keeping a calendar of wet and dry nights helps to determine the effect of interventions.

2. Motivational therapy

Once the child agrees to accept some responsibility for the treatment program, he or she can be motivated by keeping a record of progress.

Initial rewards should be given for agreed-upon behavior (e.g., going to the toilet before bedtime) rather than dryness.

Successively larger rewards, agreed upon in advance, are given for longer compliance with agreed-upon behavior and, eventually, for longer periods of dryness (e.g., a sticker on a calendar for each dry night, a book for seven consecutive dry nights).

Penalties (i.e., removal of previously gained rewards) are counterproductive.

Motivational therapy is a good first-line therapy for nocturnal enuresis in younger children who do not wet the bed every night.

Motivational therapy is estimated to be successful (14 consecutive dry nights) in 25 percent of children and to lead to significant improvement (decrease in enuretic events by ≥80 percent) in more than 70 percent.

If motivational therapy fails to lead to improvement after one month, the addition of active interventions may be warranted.

3. Addition of active therapy

Enuresis alarms and desmopressin are effective active therapies for nocturnal enuresis.

i) Enuresis alarms

Enuresis alarms are activated when a sensor, placed in the undergarments, detects moisture; the arousal device is usually an auditory alarm and/or a vibrating pager.

The alarms work through conditioning: the child learns to wake or inhibit bladder contraction in response to the physiologic conditions present before wetting.

Enuresis alarms work best for well-motivated families and children with frequent enuresis (more than twice per week).

Enuresis alarms are the most effective means of controlling nocturnal enuresis and preventing
relapse\(^7\).

In a meta-analysis of 56 randomized trials (3,257 children), 66 percent of children became dry for 14 consecutive nights during alarm use versus only 4 percent of no-treatment controls (relative risk [RR] for treatment failure \(0.38, 95\%CI 0.33-0.45\) \(^7\)).

Alarm treatment should be continued until the child has had a minimum of 14 consecutive dry nights \(^8\).

This usually takes between 12 and 16 weeks, with a range of 5 to 24 weeks \(^9\), however, alternative interventions may be warranted if there has been no improvement after 6–8 weeks of alarm therapy \(^8\).

### ii) Desmopressin treatment

Desmopressin (a synthetic vasopressin analog) is a first-line treatment for enuresis in children older than five years whose bedwetting has not responded to advice about fluid intake, toileting, or an appropriate reward system.

It is an alternative to enuresis alarms for children and families who seek rapid or short-term improvement of enuresis; have failed, refused, or are unlikely to adhere to enuresis alarm treatment; and for whom an enuresis alarm is unsuitable.

Desmopressin works best for children with nocturnal polyuria and normal functional bladder capacity.

Nocturnal polyuria is defined \(^2\) by nocturnal urine production greater than 130 percent of expected bladder capacity for age which is estimated with the following formula: \(30 \times \text{[age [in years] + 1]}\) \(^2\).

Approximately 30 percent of patients achieve total dryness using desmopressin, with perhaps another 40 percent exhibiting a significant decrease in nighttime wetting \(^10\).

Regularly, oral melt tablets are given 30 to 60 minutes before bedtime.

The initial dose is 120 mcg; if needed after 10 to 14 days, the dose may be increased by 120 mcg to a maximum dose of 240 mcg \(^10\).

If effective, it should be used for 3–6 months, and then an attempt should be made to taper the dosage.

Training to control urination previously provided to enuretic patients in order to increase functional bladder control. Specifically, when patients feel the need to urinate after coming home from school, the patient should be asked to hold it as long as they can. Although accumulated data showed that the maximal voided urine volume increased with this training, the effectiveness for the treatment of enuresis by the training has not yet been established to date.

### Treatment options for the refractory patients

#### 1. Anticholinergics

For therapy-resistant enuresis or children with symptoms of an overactive bladder, anticholinergic therapy is indicated. Oxybutynin 5 mg or tolterodine 2 mg at bedtime often are prescribed. If the medication is ineffective, the dosage may be doubled.

The clinician should monitor for constipation as a potential side effect.

| Amount of nocturnal urination (cc) | Polyuria type | Bladder type | Mixed type | Normal type |
|-----------------------------------|---------------|--------------|------------|-------------|
| 6-9 years                          | Polyuria with hypoosmolar urine | ≥ 200 (≥ 0.9 ml/kg/h) | ≤ 200 (≤ 0.9 ml/kg/h) | ≥ 200 (≥ 0.9 ml/kg/h) | ≤ 200 (≤ 0.9 ml/kg/h) |
| 10 years or more                   | Polyuria with hyperosmolar urine | ≤ 200 (≤ 0.9 ml/kg/h) | ≥ 200 (≥ 0.9 ml/kg/h) | ≤ 250 (≤ 0.9 ml/kg/h) | ≤ 250 (≤ 0.9 ml/kg/h) |
| Osmolality of the first morning urine (mOsm/l) | ≤ 800 | ≥ 801 | ≥ 801 | ≤ 800 | ≥ 801 | ≥ 801 |
| Specific gravity of the first morning urine | ≤ 1.022 | ≥ 1.023 | ≥ 1.023 | ≤ 1.022 | ≥ 1.023 | ≥ 1.023 |
| Functional bladder capacity (cc) | 6-9 years | ≥ 200 (≥ 5 ml/kg) | ≤ 200 (≥ 5 ml/kg) | ≥ 200 (≥ 5 ml/kg) | ≤ 200 (≥ 5 ml/kg) |
| 10 years or more                   | ≥ 250 (≥ 5 ml/kg) | ≤ 250 (≥ 5 ml/kg) | ≥ 250 (≥ 5 ml/kg) | ≤ 250 (≥ 5 ml/kg) | ≤ 250 (≥ 5 ml/kg) |
| Daytime incontinence               | Rare | Common | Common | Rare |
2. Tricyclic antidepressants

Another option is imipramine, which is a tricyclic antidepressant. This medication has mild anticholinergic and α-adrenergic effects, reduces urine output slightly, and also might alter the sleep pattern. The dosage of imipramine is 10–25 mg. Reported success rates are 30–60% and the side effects include anxiety, insomnia, and dry mouth, and heart rhythm may be affected. If there is any history of palpitations or syncope in the child, or sudden cardiac death or unstable arrhythmia in the family, long QT syndrome in the patient needs to be excluded.

The use of tricyclic antidepressants seemed common in Japan previously, however, since they are potentially cardiotoxic and an overdose may

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**Figure 3**

**Previous treatment for polyuric type**

- **Lifestyle guidance**
  - Low urine osmolality
  - Normal urine osmolality
- **Desmopressin**
  - Low bladder capacity at night
- **Tricyclic anti-depressant**
  - Low bladder capacity at night
- **+Tricyclic anti-depressant**
  - Alarm
- **Refer to specialists**
  - Follow-up
  - Refer to specialists

![Diagram showing treatment options for polyuric type]

**Figure 4**

**Previous treatment for bladder type**

- **Lifestyle guidance**
  - Low bladder capacity at night
- **Anti-cholinergics**
  - Low bladder capacity at night
- **Alarm**
- **Refer to specialists**
  - Follow-up
  - Refer to specialists

![Diagram showing treatment options for bladder type]
prove fatal\(^{10}\), the cautious use of them is warranted in Europe and United States\(^{8}\).

**The treatment guidelines by Japanese Society on Enuresis**

Japanese Society on Enuresis issued the 1\(^{st}\) edition of clinical guidelines in 2004\(^{1,11}\). In that guideline, the clinicians were requested to define the patients’ subtypes of nocturnal enuresis (polyuric-type, bladder-type, mixed-type, and normal-type) according to the clinical parameters obtained at the early stage of the treatment (Table–1). Then, they started the therapy for each subtype of the patients (Figure–3 is for polyuric-type patients and Figure–4 for bladder-type patients. The mixed-type patients were treated with both protocols.).

We have recently issued the revised guideline in 2016\(^{12}\), in which we discarded the pretreatment subtyping of the patients and proposed the algorithm (Figure–5).

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