Pediatric Enuresis Treatment Guidelines

Pediatric enuresis defined as involuntary urination that happens at night while sleeping, after the age when a person should be able to control his or her bladder. (In children ≥5 years of age)

In children less than 5 years of age, treatment is unnecessary because spontaneous cure is likely.

Pediatric enuresis is subdivided into the following categories:

- **Monosymptomatic enuresis**: enuresis in children without other lower urinary tract symptoms or bladder dysfunction
  - Primary enuresis: enuresis in children who have never been consistently dry throughout the night
  - Secondary enuresis: enuresis in patients who have resumed wetting after a period of dryness of at least 6 months in duration

- **Nonmonosymptomatic enuresis**: enuresis in children with other lower urinary tract symptoms (eg, urgency, frequency, daytime incontinence, genital or lower urinary tract pain)

**Pathophysiology**

Microstructural abnormalities and maturational delays of neuronal circuits have been identified in the frontal cortex of children with enuresis.

Physiological factors include:

1. Reduced bladder function and/or capacity
2. Altered arousal to a full bladder
3. Detrusor over-activity at night
4. Nocturnal polyuria from lack of circadian rhythm of nocturnal anti-diuretic hormone (ADH) secretion

Definitions applicable to pediatric patients are helpful in discerning the etiology:

- Bladder capacity: \( (30 + [30 \times \text{age}]) \text{ mL} \)
• Nocturnal polyuria: urine production >130% of expected bladder capacity for age
• Normal functional bladder capacity: maximum voided volume >70% of expected bladder capacity for age

Clinical Presentation and Diagnosis:

Proper assessment of the child or adolescent with enuresis should explore every aspect of urinary incontinence (UI), including the genitourinary and nervous systems.

The minimum assessment should include:

  o Interview of the child and parent(s), being sensitive to the emotional consequences of the enuresis.
  o Direct physical examination, looking for enlarged adenoids/tonsils, bladder distention, fecal impaction, abnormal genitalia, spinal cord anomalies, and abnormal neurologic signs (look for an organic cause amenable to surgery or medications; see table below).

  o Obtain urinalysis for glucose, protein, WBC, or leukocyte esterase; obtain urinalysis and urine culture if symptoms of UTI are present.
  o A 7 or more-day diary of wet and dry nights prior to intervention is useful to monitor the response to treatment.
- Nonmonosymptomatic enuresis may require a more extensive workup, including voiding cystourethrogram, renal and/or bladder ultrasound and urodynamics.

**Treatment - Desired Outcomes**

1. Reduction in the number of enuresis episodes and restoration of continence
2. Prevention of relapse and maintenance of treatment success
   - Continued success: No relapse in 6 months after the interruption of treatment
   - Complete success: No relapse in 2 years after the interruption of treatment
3. Prevention or minimization of disease complications (delay in childhood developmental milestones, adverse psychological effects on the child/caregivers)
4. Minimization of adverse effects and costs related to treatment
5. Improvement in the quality of life of the child and caregivers

**General Approach to Treatment:**

Management of primary monosymptomatic nocturnal enuresis in children may involve one or a combination of interventions.

The management of secondary nocturnal enuresis focuses on addressing the underlying contributing factor.

A general approach to therapy selection is:

1. Child with nighttime normal urine output, normal bladder capacity → either alarm or desmopressin therapy
2. Child with reduced bladder capacity → alarm therapy
3. Child with nocturnal polyuria, normal functional bladder capacity → Desmopressin
4. Child with excessive urine output and reduced nocturnal bladder capacity → combination of alarm and desmopressin therapy

Nonpharmacologic Treatment:

1. Urotherapy
2. Alarm Therapy

Urotherapy

- Education about the condition, fluid/diet modification, journal keeping, and behavioral or motivational therapy represent the first steps in managing pediatric enuresis (see Table 1).
• If motivational therapy fails to lead to improvement after 3 to 6 months, active interventions, such as enuresis alarms (Table 2) or desmopressin, may be added.

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**Enuresis alarms**

- The most effective and lasting first-line therapy
- Enuresis alarms are indicated for motivated families and children with frequent enuresis of > twice per week.
- Enuresis alarms can be combined with pharmacotherapy.

How do they work?
• They condition the child or caregiver to wake to the alarm sound or vibration and stop urinating until they go to the toilet

• The alarm signals teach the child to wake enough to inhibit bladder contraction in response to the physiologic conditions present before wetting the bed completely

Follow-up should be assessed 1 to 2 weeks after initiating alarm therapy; however, a full response is not expected to occur until a trial of 3 to 6 months.

✔ If no improvement is seen in 3 months, alternative interventions should be considered

✔ Enuresis alarm can be reinitiated if a relapse occurs after discontinuation

◆ The advantage: Providing a real cure without adverse effects

◆ The disadvantages:

1. Slow in onset and require patience and motivation
2. Alarm failure
3. Inability to wake the child
4. Disruption of caregivers and family members
5. Cost since most are not covered by insurance policies
Pharmacologic Treatment

1. Desmopressin (DDAVP)

2. Imipramine

3. Anticholinergic

Desmopressin (DDAVP):

- An effective and ideal agent for the short-term control
- A synthetic analogue of vasopressin
- It is indicated for nocturnal enuresis:
  - who do not respond to initial management (Table 2), or
  - as an alternative for alarm therapy
- It is the drug of choice in pediatric enuresis
- It decreases urine production by enhancing water reabsorption in the collective tubules.
- It is most effective in a child with nocturnal polyuria and normal functional bladder capacity.
- It decreases the number of wet nights per week by about 1 night.
- The intranasal formulation was no longer FDA-approved due to post-marketing reports of seizures due to hyponatremia.

Oral tablets may be started at 0.2 mg (one tablet) 1 hour before bedtime to reach peak effects.

- If response is not achieved in 10 to 14 days, the oral dose may be increased by 0.2 mg to a maximum dose of 0.6 mg.
- If the child cannot swallow the tablet, it may be crushed and consumed with soft foods.

Sublingual tablets of 120 mcg are available. They may be given 30 to 60 minutes before bedtime.

- If response is not achieved after 10 to 14 days, the dose may be increased to a maximum of 240 mcg.
• The most serious complication of desmopressin therapy is water intoxication from dilutional hyponatremia and seizures (This occurs most frequently with the nasal formulation)
• Electrolyte monitoring in patients taking the oral formulation is recommended if comorbidities may exacerbate renal or electrolyte complications.
• To reduce the risk of water intoxication, children should drink no more than 240 mL of fluid from 1 hour before to 8 hours after administration of desmopressin.
• Treatment should be interrupted during episodes of fluid and/or electrolyte imbalance (eg, diarrhea, vomiting, vigorous exercise, fever, or dehydration).

**Imipramine**

• Considered a second-line pharmacotherapy option for mono-symptomatic enuresis.
• Tricyclic antidepressants (TCAs) are as effective as desmopressin but are associated with more adverse reactions.
• Their place in therapy is in a child who failed alarm and desmopressin therapies.
• Mechanisms of action of imipramine include anticholinergic and antispasmodic effects, as well as increasing plasma ADH concentrations, and/or lowering arousal threshold.
• Response to imipramine, defined as one less wet night per week, is expected in 50% of children. However, relapse rates are up to 67%.
• The usual initial dose is 10 to 25 mg at bedtime which may be increased if there is no response after 1 week.
• On average, the bedtime dose is 25 to 50 mg orally once a day.
• The dose should not exceed 50 mg in children between 6 and 12 years of age and 75 mg in children age 12 or older.
• After 1 month of successful response, the dose should be reduced to the lowest effective dose.
• As the patient continues the therapy, the medication is discontinued for a 2-week block every 3 months to reevaluate necessity of drug therapy.
• About 25% of children treated with TCAs experience gastrointestinal symptoms.
• Neurologic adverse effects including nervousness, personality change, or sleep disturbances are reported in approximately 5% of patients.
• Clinicians should monitor for the possibility of increased suicidality, particularly in children and young adults with preexisting depressive symptoms.
• The most serious adverse effects of TCAs are cardiac conduction disturbances, QT prolongation, and myocardial depression, particularly in cases of overdose.
• A history of sudden cardiac death in the family may preclude the use of TCAs unless cleared by a pediatric cardiologist. Therefore, safer options should be considered before starting any TCA for pediatric enuresis.

Anticholinergics
• Since anticholinergic agents increase bladder capacity during sleep, they are the primary therapy for a child who has low bladder functional capacity.
• Monotherapy is ineffective so these agents are used in combination therapy only. (Combination of anticholinergic + desmopressin)
• These agents should be used only if the child has nocturnal enuresis + daytime incontinence.
• Initial doses of immediate-release (IR) oxybutynin are 5 mg and titrated upward based on clinical response.
• Maximal therapeutic effects can be seen within 2 months.
• Children should be monitored for potential adverse events, such as urinary retention (may lead to UTIs), constipation (worsens urinary tract dysfunction), and decreased saliva secretion (dry mouth).

Combinations of Therapies
- In children who fail to respond to one therapy or who have frequent relapses \(\rightarrow\) combinations of urotherapy, imipramine, oxybutynin, desmopressin, and/or alarm therapy can improve treatment response.
In a child with small bladder volumes and refractory enuresis → combination therapy with desmopressin and anticholinergic agents is more effective than desmopressin alone.

**Comparison of Therapies**

- Data suggest that use of enuresis alarms is the most effective treatment method
- The initial rate for success is 66%, with 55% long-term success rate after discontinuation
- Alarm therapy is at least as effective as desmopressin, but with a significantly lower relapse rates (46% vs 60%–70% for desmopressin)

### Therapies for Pediatric Enuresis

<table>
<thead>
<tr>
<th>Therapy (FDA approval)</th>
<th>Dosage form</th>
<th>Dose (generic)</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enuresis alarms</td>
<td>Sound and/or vibration</td>
<td>0.2 mg, increased to 0.4 mg (Maximum 0.6 mg)</td>
<td>• Best response • Low relapse rates</td>
<td>• Requires motivation • Slow-acting • Low response rate • High rate of relapse</td>
<td>Sleep disruption</td>
</tr>
<tr>
<td>Desmopressin (&gt; 6 years of age)</td>
<td>Oral, tablet 0.1 mg, 0.2 mg (generic)</td>
<td>0.4 mg</td>
<td>• Reduces urine volume at night • Faster acting than enuresis alarms</td>
<td></td>
<td>Water intoxication, hyponatremia, seizures</td>
</tr>
<tr>
<td>Imipramine (&gt; 6 years of age)</td>
<td>Oral, tablet 10 mg, 25 mg, 50 mg (generic)</td>
<td>10 mg to 25 mg (Maximum: 50 mg if &lt; 12 years of age; 75 mg if &gt; 12 years of age)</td>
<td>• Reduces bladder contractions • Equally effective to desmopressin</td>
<td>• High rate of relapse</td>
<td>Cardiac conduction disturbances; myocardial depression Constipation, dry mouth</td>
</tr>
<tr>
<td>Anticholinergics: oxybutynin (&gt; 5 years of age)</td>
<td>Oral, tablet 5 mg; Syrup 5 mg/mL (generic)</td>
<td>5 mg once or twice a day</td>
<td>• Reduces bladder contractions • Effective in patients with low functional bladder capacity</td>
<td>• Ineffective as monotherapy, use in combination therapy</td>
<td>Constipation, dry mouth</td>
</tr>
<tr>
<td>Anticholinergics: Tolterodine (not approved in children)</td>
<td>Oral, tablet 1 mg, 2 mg (generic)</td>
<td>1–2 mg per day</td>
<td>• Reduces bladder contractions • Effective in patients with low functional bladder capacity</td>
<td>• Ineffective as monotherapy, use in combination therapy, limited data in children</td>
<td>Constipation, dry mouth</td>
</tr>
</tbody>
</table>

### Treatment of Relapse

**Relapse defined by more than 1 wet night per month after a period of dryness.**

- When it occurs, consider reinitiation of the intervention which was previously effective.
- For children with multiple recurrences after discontinuation of desmopressin, gradual dose tapering of desmopressin may be helpful.
• If relapse occurs following successful treatment with alarm therapy, the addition of desmopressin may be effective.
• When motivated children and families do not respond to at least 3-month therapy of enuresis alarm and/or desmopressin, referral to a specialty clinic (eg, developmental-behavioral pediatrician, pediatric urologist) may be warranted.

Outcome Evaluation

- Evaluate the patient for adverse events, allergies, and interactions (drug–drug and drug–disease) and adherence.
- Evaluate treatment response in 1 to 2 weeks after therapy initiation. Adjust medication dosing if needed.
- Allow at least 3 months to assess efficacy of treatment.

References:


Done by Pharm D students: Batool Mohammad & Rana Banat

Under Supervision of Dr: Eshraq Al-Abweeny.