Nocturnal Enuresis

Overview of
Prevalence and aetiology
Assessment
Management
Refractory enuresis

Janet Chase
Darwin 20th November 2014
Please

• NEVER say “he/she will grow out of it” without considering if treatment is necessary
• NEVER send a child away without assessment
Incontinence terminology

Incontinence

Continuous incontinence

Intermittent incontinence

Daytime incontinence

Nocturnal incontinence = enuresis

All ages

5 years or older
Nocturnal enuresis refers to …

- Emptying bladder during sleep
- Wetting day and night:
  - “incontinence”
- Primary NE (PNE):
  - never dry for 6/12 or longer
- Monosymptomatic NE (MNE):
  - no LUT symptoms during the day
- Non – MNE – night incontinence + day LUTS
•Primary mono-symptomatic enuresis

•Secondary mono-symptomatic enuresis

•Primary non mono-symptomatic enuresis

•Secondary non mono-symptomatic enuresis

•Important!

•Less important

Enuresis prevalence
Aged 6-7 years: more common among boys

Teenagers

Enuresis exists in all cultures

JC Darwin 20-11-2014
SEVERITY OF NE IN HK CHINESE CHILDREN AND ADOLESCENTS

Source: Yeung et al. 2006

JC Darwin 20-11-2014
Heredity of NE

- Phenotype modulated by environmental factors
- Multifactorial trait
- Gene mapping: polygenic, “major genes” on chromosome 13, 10q, 12 and 20
Nocturnal polyuria

Dry children

Some enuretic children

Dry night
Enuresis
Detrusor activity

Dry children

Some children with enuresis

Other children with enuresis

evening

night

morning

*= wet!

Normal bladder function
Overactive bladder
Subjective arousal thresholds

Dry children

Enuretic children

Answers to the question "How easily are you to awaken at night?"

Nevéus et al Acta Paediatr 1999

? = don’t know
A = very easily
B = easily
C = neither easy nor difficult
D = difficult
E = very difficult
F = almost impossible
Supraoptic nucleus

Locus coeruleus

Pontine micturition centre

Hypothalamus

Mesencephalon

Pons

Medulla oblongata

Essential for arousal:
upper station of the RAS

Essential for detrusor function:
Functional/anatomical overlap with pontine micturition center

Urine production function:
Links to vasopressin-producing nuclei
Pathological polyuria
Urethral obstruction

- Obstruction
  - Bladder overdistension
  - Overflow incontinence
  - Secondary enuresis
  - High intravesical pressure
    - Renal tubular damage
      - Renal concentration defect
        - Pathological polyuria
Obstructed breathing

Airway obstruction

- Persistent arousal stimulus
- Increased negative intrathoracic pressure

- Increased arousal thresholds (in order to preserve sleep)
- Increased secretion of atrial natriuretic peptide

Polyuria

Enuresis
Enuresis, sleep and psychiatry

Enuresis

Psychosocial problems
Enuresis, sleep and psychiatry

Enuresis

Psychosocial problems

It’s all just sexual frustration
Enuresis, sleep and psychiatry

Enuresis

Low self-esteem

Psychosocial problems

Low self-esteem → Psychosocial problems
Enuresis, sleep and psychiatry

Enuresis → Low self-esteem → Psychosocial problems → ADHD

ADHD → Low self-esteem → Psychosocial problems
Enuresis, sleep and psychiatry

Enuresis

Low self-esteem

Guilt and punishment
Cognitive problems due to disturbed sleep

ADHD

Psychosocial problems
Inter-relationship

Bladder

Constipation
- common cause

Daytime Incontinence

Urinary Tract Infections

Bowel

Enuresis

May be present in

Assessment

Good history taking means taking time

Who does it?
Doctor, nurse physiotherapist

Use voiding charts or bladder diaries

Look for mild or severe Warning signs
Mild warning signs

- Secondary enuresis
- Behavioural problems at home and school
- Voiding postponement
- Previous urinary tract infections

Severe warning signs

- Nausea, fatigue or weight loss
- Excessive thirst
- Voiding difficulties
- Poor urinary stream
- Need to strain in order to void
Primary evaluation: history

**Enuresis data**
How often? Primary/secondary?

**Micturition data**

**General health**
Growth/development OK? General health OK? Thirsty?

**Treatment strategies**
Earlier treatments and their effects. Coping strategies

**Psychological data**
Behavior problems? Bothered by enuresis?
Primary evaluation: FV charts

Why should we use them?
• Objectifies history data, eliminates recall bias
• Gives valuable prognostic information
• Assists in the detection of children who need extra evaluation
• Detects families with low compliance

What should they measure?
• Voided volumes: minimum 2 days
• Enuresis and other symptoms: minimum 1 week
• Fluid intake: minimum 2 days (recommended)
• Bowel movements: minimum 1 week (recommended)
• Diurnal/nocturnal urine production (optional at this stage)
# Voiding diary

## Daily Voiding Diary

<table>
<thead>
<tr>
<th>Time of Day</th>
<th>Type &amp; Amount of Food</th>
<th>Type of Fluid</th>
<th>Amount of Fluid</th>
<th>Amount Voided Oz or CC</th>
<th>Amount of Leakage Ml/Ml/MLG</th>
<th>Was Urge Present</th>
<th>Activity With Leakage</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11:00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **EBC** (Expected Bladder Capacity): $EBC = (age + 1) \times 30$ milliliters

- **Teenagers**: approximately 400 mm

- **Diapers**

- **First morning void**

- **Nocturnal urine production**

JC Darwin 20-11-2014
<table>
<thead>
<tr>
<th></th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
<th>Sunday</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time I went to bed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time I got up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I am dry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I am wet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I got up in the night to pee</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the morning, my diaper weighed (g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The volume of my first pee in the morning (mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[urine volume + change in diaper weight]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooed today</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Primary evaluation: physical examination

Usually completely normal in uncomplicated MNE

Otherwise

• Neurological exam
• Inspection of back and legs
• Inspection of genitals
• Rectal examination if any suspicion of constipation
Primary evaluation: blood/urine tests

Urine test
• Glucose?
• Exclude diabetes mellitus* (obviously)
• Leucocytes or nitrite positive?
• Send for culture! Consider UTI*
• Protein or erythrocytes?
• Consider kidney disease*

Blood tests
• No

* Rare as causes of MNE
Primary evaluation: radiology
Not helpful

Primary evaluation: urodynamics
Not necessary
But what if you haven’t got enough time?
What is really important?

• Exclude serious disease
• Find out if more examinations are needed
• If not, find out which treatment to start
The five most essential questions to the child who seeks your help for the first time for enuresis

**Question 1:**

• Is the general health and growth of the child OK?

**Reason for asking:**

• If no, make sure to exclude diabetes or kidney disease
The five most essential questions to the child who seeks your help for the first time for enuresis

Question 2:
• Is this a new problem?

Reason for asking:
• If yes, make sure to exclude diabetes or kidney disease
The five most essential questions to the child who seeks your help for the first time for enuresis

Question 3:

- Are there day-time micturition problems as well?

Reason for asking:

- If yes, make sure to exclude UTI
- Day-time incontinence needs to be addressed first, and additional bladder and bowel data needs to be obtained
- Urgency/incontinence indicates detrusor over-activity as the likely cause, and desmopressin is then unlikely to help
The five most essential questions to the child who seeks your help for the first time for enuresis

**Question 4:**

• How often is the bed wet?

**Reason for asking:**

• If enuretic episodes are infrequent or intermittent, then the alarm is not first-line treatment
• If every night is wet, prognosis without treatment is poor
The five most essential questions to the child who seeks your help for the first time for enuresis

Question 5:

• Is this a big problem for the child?

Reason for asking:

• If no, then compliance with the alarm will be low and perhaps we can wait with treatment altogether. Also, psychiatric comorbidity more common
So what do we do...
Minimal primary evaluation: 1

Requirements: basic history and a urine sample

Background data

• **Age <6 years?**
  Only general advice, no active treatment

• **Enuresis every night?**
  Prognostically unfavourable. Consider referral to specialist

• **Is the child not bothered by the enuresis?**
  Risk for therapy-resistance. Consider postponing treatment until child is motivated
Complicating factors, comorbidity

- Daytime incontinence, urgency, holding maneuvers, suspected voiding frequency <4 or >7 times per day?
  Suspect NMNE. Have the family complete a FV-chart

- Faecal incontinence, hard stools, infrequent bowel movements?
  Suspect, and treat for, constipation before proceeding

- Problems with behaviour and peer relations?
  Risk for psychiatric comorbidity and/or therapy resistance. Consider parallel psychological evaluation
Minimal primary evaluation: 3

Warning signs

• **Straining, continuous incontinence, weak stream?**
  Suspect neuropathic bladder or anatomic abnormality. Send to secondary center

• **Glucosuria, proteinuria, leukocyturia, hematuria?**
  Consider diabetes, UTI, kidney disease

• **Excessive thirst, need for nighttime drinking?**
  Consider polydipsia or kidney disease. Measure fluid intake.

• **Nausea, weight loss, fatigue?**
  Consider kidney disease. Consult paediatrician
How many children can we help?

The alarm (cure)

Refractory nocturnal enuresis

Desmopressin (treatment success)

All enuretic children
How many can we help?

The alarm (cure)

Desmopressin (treatment success)

All enuretic children

Anticholinergics + Desmopressin

? Anticholinergics

Imi + desmo

Imipramine

Laxatives
Primary treatment strategy

**Alternative 1:**
Present the pros and cons and let the family chose, but not in Australia. If one treatment does not work, the other is tried.

**Alternative 2:**
FV chart with diurnal/nocturnal urine measurements. Give desmopressin to children with nocturnal polyuria and normal voided volumes, provide the alarm to the rest.
Suggested protocol

First try
Proper evaluation, proper bladder advice and desmopressin or the alarm

Second try
The alarm or desmopressin

Third try
Extended evaluation (voiding charts, flowmetry etc)
Exclusion/treatment of complicating bowel/bladder factors
Anticholinergics + desmopressin or Imipramine
Primary treatment: basic strategies

• Explanation, demystification, removal of guilt/blame.
• Stop doing things that don’t work.
• Regular voiding. Regular (but non-excessive) fluid/solute intake.
• Treat co-existing constipation
• Treat allergy and obstructed airways
• Household management strategies
• Troubleshooting
• Consider psychosocial factors
• Support parents
Primary treatment: the alarm

**Evidence based**

**Pros**
- Curative
- Harmless
- Cheap
- Helps 50-80%

**Evidence level Ia**

**Cons**
- Requires hard work
- Requires time
Primary treatment: the alarm

For the professional
• use reliable equipment
• explain the time-frame
• written instructions/charts
• explain the signs of progress
• regular review to trouble-shoot and maintain motivation
Primary treatment: the alarm

For the family

• the first step in the process is learning to wake
• help child to wake (but the child turns off the alarm)
• as necessary help to get child to toilet to finish void, to change sheets, clothing and reset alarm
• chart every night
• attend regular review
• Use consistently every night without interruptions
• Use until either 14 consecutive dry nights or 2-3 months without effect
Primary treatment: desmopressin

**Evidence based**  
**Evidence level Ia**

**Pros**
- Easy to use
- Quick effect
- Almost harmless
- Full response 30%, IR 30%

**Cons**
- Not curative
- Expensive
Both are given 30-60 minutes before going to sleep.
How useful is it?
Desmopressin: antienuretic mechanism

or CNS effects?

Desmopressin
To whom is desmopressin useful?

Positive predictors
• Nocturnal polyuria
• Normal voided volumes
• Absence of day-time bladder symptoms

Negative predictors
• Small voided volumes
• Urgency, day-time incontinence or high voiding frequency
• Very frequent enuresis

No predictive value (?)
• Sex, heredity, arousability, primary/secondary enuresis, psychosocial factors, neuropsychiatry, calcium excretion
To whom should desmopressin be given?

Prerequisites

• Monosymptomatic enuresis (at least no day-time incontinence)
• Age 6 or more
• Enuresis considered a problem for the child
• No underlying medical/urological condition

• Start with the alarm or desmopressin?
• Let the family chose! (Not in Australia!)
How should desmopressin be used?

• 0.2-0.4 mg oral or 120-240 ug quick-melt
• Start with full dose, then decrease (or the other way around)
• If no effect in 14 days, stop treatment
• Every evening or just before ”important nights”?
• Let the family chose!
• Regular medicine-free intervals
• No medication when the child has been drinking very much!
• Long-term treatment is safe, if needed
Desmopressin problems

• (No toxicity, few side-effects)
• (Small) risk for water intoxication
• Small or absent curative effect (like all other antienuretic therapies except the alarm)
• Desmopressin is expensive
• Only a minority will be dry every night that they take the drug
Therapy-resistant enuresis: background

• Many enuretic children (25%?) are not helped by standard treatment (the alarm and desmopressin)

• Most of these children wet their beds because of combined nocturnal detrusor overactivity and low arousability
Treatment of therapy-resistant children

Re-assess

First step
• Exclude/treat constipation
• Retry the alarm if it was incorrectly used

Second step
• Anticholinergics (+/- desmopressin)

Third step
• Imipramine (+/- desmopressin) with caution

And
• New attempts with the alarm every second year or so
Studies on anticholinergics in enuresis

Several open, noncontrolled, nonrandomised studies showing 40 - 70% response

One randomised placebo-controlled study (Lovering 1988): no significant effect

**Studies on anticholinergics in refractory enuresis**

Evidence level Ib

One open, nonrandomised study (Nevéus -99): 60% response if combined with desmopressin

One randomised study (Nevéus & Tullus -07) comparing tolterodine 1 mg, imipramine and placebo: tolterodine not better than placebo. Better results if combined with desmopressin

One randomised study (Austin 2008) comparing tolterodine 4 mg + desmopressin with desmopressin alone. Combination treatment better
Anticholinergics; background

• Good effect against day-time incontinence due to detrusor overactivity

• Alternatives: oxybutynin, propiverine, tolterodine

• Anticholinergic and detrusor relaxant effects

• Largely atoxic, but side effects occur

• Tolterodine has fewer side effects than oxybutynin
Anticholinergics; assets and drawbacks

**Assets**
Helps (?) approx 40% of therapy-resistant children
Not dangerous

**Drawbacks**
No immediate effect
UTI risk (girls > boys)
Side effects (constipation!)
Treatment usually needed for a long time
Elaborate follow-up needed (residual urine)
Usually needs to be combined with desmopressin
Anticholinergics; practicalities

Dosage (in isolated enuresis)
- Tolterodine 2 mg 1-2 (-3) tablets at bedtime
- Combine with desmopressin 240 ug oral melt

Guidelines
- First exclude or treat constipation
- Evaluate therapy after 1-2 months
- Good effect; check if desmopressin is needed
- Treatment usually needed for 6-12 months or more
- Taper gradually
- Regular toilet habits important.
- UTI: stop therapy and check for residual urine
- Check residual regularly during long-term treatment
- Assure good oral hygiene (salivation inhibitor)
Studies on Imipramine in enuresis


Approx 50% response

Studies on Imipramine in refractory enuresis
Evidence level Ia

One retrospective evaluation (Gepertz & Nevéus -04)
Approx 60% response if desmopressin added

One randomised study (Nevéus & Tullus -07) comparing tolterodine, imipramine and placebo: imipramine better than placebo. Still better results if combined with desmopressin
Is there a role for Imipramine?

Evidence based
Approximately 50% of enuretic children are helped; more if desmopressin is added

Somewhat unclear mode of action
Noradrenergic, sympathomimetic component (not the serotoninergic, antidepressant or anticholinergic effects)

*Cardiotoxic if overdosed*
Background

Imipramine

• Tricyclic antidepressant drug with central noradrenergic and serotonergic effects

• Proven effect against enuresis

• Anticholinergic side-effects, cardiotoxic if overdosed

• Reason for antienuretic effect unclear but distinct from the antidepressant action
Conclusions: Imipramine

Still an evidence-based therapy of enuresis

• Still has a role to play in therapy-resistant enuresis

• Side-effects (nausea, mood changes) quite common

• The reason for imipramine’s antienuretic effects is not its anticholinergic action, but probably central noradrenergic facilitation of arousal
Disclaimer

Imipramine should only be considered if…

… standard treatment has been fully tried and failed

… there are no cardiac risk factors (child and family)

… the parents keep the pills securely locked

… dosage is kept low (25 - 50 mg)

… you know what you are doing
Imipramine should *only* be considered if...

... standard treatment has been fully tried and failed

... there are no cardiac risk factors (child and family)

... the parents keep the pills securely locked

... dosage is kept low (25-50 mg)

... you know what you are doing