The South African guidelines on enuresis: 2024 update

A Adam,[1,2] FC Urol (SA), MMed (Urol); **A Badenhorst,**[1] MB ChB; **F Claassen,**[3] FC Urol (SA), PhD;
T de Maayer,[4] MMed (Paed), Cert Gastroenterology (SA); **M Fockema,**[5] MB ChB, MSc, Med (Urol);
J Fredericks,[6] FC Paed, MMed (Paed); **E Gottlich,**[7] FC Paed, Cert Nephrology (SA); **J John,**[8,9] FC Urol (SA), MMed (Urol);
N Lala,[10,11] FC Paed (SA), Cert Nephrology (SA); **J Lazarus,**[12] FC Urol (SA), MMed (Urol);
S Leahy,[10,11] FC Paed (SA), Cert Nephrology (SA); **H N Lourens,**[13] FC Urol (SA), MMed (Urol);
S Maharaj,[14] FCORL (SA), MMed (ORL); **K M Mathabe,**[15] FC Urol (SA), MMed (Urol);
E M Moshokoa,[16] FC Urol (SA), MMed (Urol); **S B A Mutambirwa,**[17] FC Urol (SA), MMed (Urol);
K L Petersen,[10,11] FC Paed (SA), MMed (Paed); **M B Radzuma,**[17] FC Urol (SA), MMed (Urol);
A van der Merwe,[18] MMed (Urol), PhD; **I van Heerden,**[13] FC Urol (SA), MMed (Urol); **C A Zietsman**,[19] FC Urol (SA), MMed (Urol);
F Alyami,[20] MB ChB, FRCSC; **A Deshpande,**[21,22,23] FRACS, PhD; **G H H Smith,**[21,24] MBBS, FRACS

[1] *Division of Urology, Department of Surgery, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[2] *Department of Urology, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa; Wits Donald Gordon Medical Centre, Johannesburg, South Africa*
[3] *Department of Urology, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa*
[4] *Paediatric Gastroenterology, Rahima Moosa Mother and Child (Coronation) Hospital and Department of Paediatrics and Child Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[5] *Pelvic and Urotherapy Institute, Johannesburg, South Africa*
[6] *Department of Paediatrics and Child Health, Rahima Moosa Mother and Child (Coronation) Hospital and Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[7] *Paediatric Nephrology, Mediclinic Morningside, South Africa*
[8] *Division of Urology, Department of Surgery, Frere Hospital and Faculty of Medicine and Health Sciences, Walter Sisulu University, East London, South Africa*
[9] *Division of Urology, Department of Surgery, Faculty of Health Sciences, University of Cape Town, South Africa*
[10] *Division of Paediatric Nephrology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[11] *Department of Paediatrics, Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa*
[12] *Division of Urology, Red Cross War Memorial Children's and Groote Schuur hospitals and Faculty of Health Sciences, University of Cape Town, South Africa*
[13] *Pretoria Urology Hospital, Pretoria, South Africa*
[14] *Charlotte Maxeke Johannesburg Academic Hospital and Department of Otorhinolaryngology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[15] *Department of Urology, Steve Biko Academic Hospital and University of Pretoria, South Africa*
[16] *Mediclinic Midstream Hospital, Midstream, South Africa*
[17] *Department of Urology, Dr George Mukhari Academic Hospital and Sefako Makgatho Health Sciences University, Pretoria, South Africa*
[18] *Department of Urology, Tygerberg Hospital and Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa*
[19] *Discipline of Urology, School of Clinical Medicine, College of Health Sciences, University of KwaZulu-Natal, Durban, South Africa*
[20] *King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia; College of Medicine, Alfaisal Univeristy, Riyadh, Saudi Arabia*
[21] *Urology Unit, Department of Paediatric Surgery, The Children's Hospital at Westmead, Sydney, Australia*
[22] *Faculty of Medicine and Health, University of Sydney, Australia*
[23] *School of Medicine and Public Health, University of Newcastle, Australia*
[24] *Department of Paediatrics and Child Health, University of Sydney, Australia*

Corresponding author: *A Adam (ahmed.adam@wits.ac.za)*

Background. Enuresis, also referred to as nocturnal enuresis, is characterised by discrete episodes of urinary incontinence during sleep in children aged ≥5 years in the absence of congenital or acquired neurological disorders. This guideline is an update of the 2017 version.
Recommendations. The guideline provides recommendations and suggestions for various therapeutic options for enuresis available in South Africa (SA). These options include behavioural modification, urotherapy, pharmaceutical therapy, alarm therapy, alternative therapies, neuromodulation, psychological support and biofeedback. Additionally, it explores the role of a voiding diary, additional investigations and mobile phone applications (apps) in treating enuresis. The document also outlines standardised definitions for clarity.
Conclusion. This is an updated guideline endorsed by relevant key opinion leaders in SA, with additional input from international experts in the field.

Keywords: bedwetting, nocturnal enuresis, enuresis, South African, treatment guidelines, mobile phone applications (apps), expert review

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This updated guideline is intended for general practitioners, urologists, paediatricians, paediatric nephrologists and hospital administrators in South Africa (SA). Local challenges in implementing these guidelines include drug unavailability, lack of resources, high costs and medical staff shortages. Recommended dosages should be adjusted based on patient characteristics, weight and renal function. The dosages should be verified with an updated, reliable medical reference. This guideline provides an update to the previous comprehensive guideline published in 2017.[1]

Definitions and terminology[2,3]

Enuresis (also referred to as nocturnal enuresis (NE)) is defined as episodes of involuntary urinary passage during sleep in children aged ≥5 years without congenital or acquired neurological disorders. Enuresis would only be considered in children with developmental delays who are >5 years old once they reach the cognitive level of a 4-year-old.

Monosymptomatic enuresis (MSE). Bedwetting at night without other daytime lower urinary tract symptoms (nocturia excluded) and without bladder dysfunction is defined as MSE.

Primary enuresis (PMSE). Children who have never achieved a dry period of at least 6 months.

Secondary enuresis (SMSE). Children who achieved a dry period of ≥6 months, then incontinence resumed.

Non-monosymptomatic enuresis (NMSE). Children with enuresis with other lower urinary tract symptoms, such as daytime wetting or urgency, may also have bladder dysfunction, which can include abnormalities in emptying or storage.

For this guideline, PMSE will be discussed unless otherwise specified.

Severity of enuresis is defined based on the frequency of voiding: frequent (>4 per week) or infrequent (<4 per week).[4]

Expected bladder capacity (EBC) is determined with the widely used Hjälmås's formula to determine bladder capacity: EBC (mL) = 30 + (age in years × 30).[5]

Nocturnal (night-time) polyuria (NP) is defined as nocturnal urine production >130% of the EBC.[5] NP is present in <50% of bedwetting children.[6]

Nocturia is the complaint that the child wakes at night to void. Unlike enuresis, nocturia does not lead to incontinence, and nocturia does not necessarily indicate pathology.

Prevalence

The prevalence of NE decreases with increasing age.[7] Reviews conducted in Western countries revealed a prevalence of 8% among 7-year-olds, 3% among 11 - 12-year-olds, and 0.8% among 16-year-olds.[8] Higher rates of enuresis are seen in less developed countries owing to lower socioeconomic status, lack of efficient enuresis treatment, and late presentation.[9] A 2012 study in SA revealed that NE affects 16.0% of children, with 14.4% experiencing MSE and 1.6% having NE with daytime urinary incontinence.[10] Males are affected more than females, and the prevalence ratio is 2:1.[10] Poor school performance and learning problems are associated with NE. Additionally, NE may result in low self-esteem, which may lead to psychological issues.[10]

Parental involvement and perceptions

Caregivers/parents may view enuresis as a behavioural issue, potentially causing psychological harm to children through punishment, shaming and lack of support.[10] Many parents have tried multiple treatment options, often without seeing substantial improvement in their child's progress. This leaves parents feeling hopeless and frustrated, causing them to discontinue treatment.[11] Research shows that parents who have a hostile and angry approach towards bedwetting are more likely to punish their child, whereas parents with a more positive approach are more likely to comfort and encourage their child.[12] Different cultures have varying beliefs and norms regarding their approach to enuresis.[11]

Parents' perception of NE also influences their likelihood of seeking medical treatment for their child.[11] Parents are often not very concerned, so most children do not receive treatment. Failure to seek treatment is partly because the condition usually gets better on its own, and partly because parents are unaware of available therapies. Families tend to try to treat their children with methods such as limiting fluids, waking the child at night to go to the bathroom, and counselling. However, these treatment methods are not successful on their own in some cases.[10] Parents also tend to prefer medication and behavioural treatments to bed alarms. They find that bed alarms disturb their sleep and are high maintenance, and stop using them.[11,13,14] Parental involvement is a crucial component in the treatment plan for enuresis. Healthcare practitioners should therefore try to understand parents' approach to bedwetting management to ensure the best treatment outcome for the child.[11]

Pathophysiology

The 'three systems model'

The model proposed by Butler and Holland[15] in 2000 provides a framework for understanding PMSE and helps conceptualise therapeutic interventions. PMSE is caused by one or more of the following three 'systems':

1. NP associated with an abnormal circadian pattern of antidiuretic hormone (ADH)/arginine-vasopressin
2. Overactive bladder (OAB)/small-capacity bladder
3. Lack of sleep arousal/abnormal sleep patterns.

The three systems model helps outline a management strategy:

1. Children with NP with normal bladder capacity may respond to desmopressin (DDAVP) or the bed alarm.[16]
2. Children with small bladder capacities for age are likely to be resistant to DDAVP; the alarm and/or anticholinergics can be considered.[17]
3. For children with polyuria and reduced capacity, combination therapy may be successful.[18]

The 'bladder-brain dialogue'

In their study, Yeung *et al.*[19] observed children with severe and refractory (refractory was defined as ≥5 wet nights per week) primary NE. They found that these children had a higher than expected cortical arousal index, resulting in failure to wake with a desire to void. The study concluded that the children had more light non-rapid eye movement sleep with frequent cortical arousals, but they could not wake up completely. It is speculated that complete awakening might be suppressed paradoxically by signals from the bladder through long-term overstimulation of the arousal centre.

Management

Behavioural modification[25]

Ideally, children aged >5 years should have acquired proper bladder and bowel behaviour that includes passing urine five to seven times during the day and passing a soft stool regularly (daily or on alternate days). To achieve optimal response to management of MSE, it is essential to explain to parents the importance of normal bladder and bowel emptying and to correct behaviour that may result in poor emptying.

The bladder diary

A bladder diary, also known as a frequency-volume chart, is a simple tool for monitoring urinary habits. It records the number of times the child voids and the volume of urine passed with each void. To gather accurate information, the diary should be kept for at least 2 - 3 days, although non-consecutive days are acceptable.

While a 3-day diary is more comprehensive, studies have shown that patient compliance and participation are improved with a 2-day diary compared with a 3-day diary.[20-22]

When investigating the possibility of polyuria or constipation, the diary should be extended to 7 days, as these issues may only become apparent after the initial 3 days. The enuretic voided volume is calculated by weighing the nappy for children wearing night-time nappies. With the sum of the first morning void, this volume will give the patient's nocturnal urine production.[23] It will help to identify whether nocturnal polyuria is present.[24]

The daytime portion of the diary helps to assess the presence of lower urinary tract dysfunction.[20-22] If present, there may be additional pathological contributions to enuresis.

To facilitate accurate tracking, suggested bladder diary templates are available. Links to PDF documents are provided.

https://www.rch.org.au/uploadedFiles/Main/Content/clinicalguide/guideline_index/Bladder%20Diary.pdf

or

https://www.ruh.nhs.uk/patients/patient_information/URO037_Bladder_Diary.pdf

or

http://www.monashchildrenshospital.org/wp-content/uploads/2016/10/15050_Bladder_diary_form.pdf

or

https://www.bbuk.org.uk/wp-content/uploads/2022/08/Baseline-bladder-diary-paediatric-Bladder-Bowel-UK.pdf

or

https://www.evelinalondon.nhs.uk/resources/patient-information/bladder-bowel-diary.pdf

- Toilet time after breakfast and before going to school is required to reduce the need to hold urine and stool passage while at school.
- Explanation of the ideal position for children to sit on an adult toilet (leaning forward with feet slightly apart and resting on a low bench so that the knees are slightly higher than the hips, and use of a toilet ring, if necessary, so that the child does not feel as if they are falling into the toilet).
- Discussions with teachers to encourage children to go to the toilet during school breaks (such as recess and lunch) and to ensure that school toilets are acceptable.

Parents of children with primary enuresis should be counselled as follows:

- Restrict fizzy drinks, caffeine and drinks with colourants. Water is the choice for fluids. A guide on recommended fluid intake in children is available (https://www.ouh.nhs.uk/patient-guide/leaflets/files/120806fluidmanagement.pdf).
- Waking the child up and lifting them from bed should not be encouraged. Create a schedule for frequent voiding.
- Only remove nappies once the child has had consistent dry nights.
- Understand the child's condition and avoid critical comments if the child's bed is wet.
- Use a star chart, with the child's involvement, to demonstrate scheduled voiding and fluid intake.
- Explain to the child, in simple terms, why medication is being used.

Pharmaceutical therapy

Desmopressin

DDAVP is a synthetic version of the posterior pituitary hormone vasopressin, also known as ADH. DDAVP monotherapy is recommended in cases of NP (with normal bladder capacity). Success rates of 70% can be obtained.[26] It is recommended to start treatment when the child is ≥6 years old.[27] Although water intoxication and hyponatraemia are rare, limit fluids to an hour before and 8 hours after medication.[28]

When response to treatment with DDAVP is poor, be aware that poor parental compliance may be a factor.[29] The starting MELT dosage of 120 µg is recommended. A structured titration increase of up to 240 µg is effective and safe.[30]

DDAVP can be used as monotherapy or in combination with alarm therapy.[26,27] A recent meta-analysis has shown that structured withdrawal results in better relapse-free rates.[27]

Formulations available:

- **Oral tablet.** Initial dose 0.2 mg (maximum 0.4 mg) daily 1 hour before bedtime.
- **Nasal spray.** No longer recommended owing to the increased risk of overdose, nasal discomfort, nasal bleeding and headaches.
- **MELT (sublingual desmopressin lyophilisate),** dosage 60 µg,120 µg, 180 µg and 240 µg, daily 1 hour before bedtime. Children preferred the MELT formulation in a randomised study of MELT v. tablet formulation.[31]

Contraindications: Hyponatraemia, renal failure, known hypersensitivity[26]

Anticholinergics

Monotherapy with anticholinergics is not indicated in the management of PMSE.[26,32] They may be helpful as combination therapy with DDAVP in the management of refractory PMSE or in children with NE and daytime urinary incontinence if there is no post-void residual urine and constipation is excluded or successfully treated. In patients with overactive or small-capacity bladders, the addition of anticholinergic therapy is recommended.

Types of anticholinergics

Oxybutynin and propiverine hydrochloride are the only anticholinergic agents registered for use in children in SA. Tolterodine and solifenacin, newer agents with fewer side-effects, have been combined with DDAVP elsewhere. These drugs can be expected to become available for label prescription soon.

Oxybutynin

Oxybutynin reduces the risk of non-response to treatment by 57% compared with placebo.[33] A similar response was observed in a randomised controlled trial comparing oxybutynin and tolterodine in patients with primary enuresis.[34]

- **Dosage** 5 mg 1 hour before bedtime.[3]

The anti-enuretic may not be immediately apparent, so the therapy should be evaluated after 1 - 2 months.[30] If there is a good response, we recommend that drug withdrawal be attempted regularly, approximately every 3 months.[3]

Daytime incontinence and NE:

- In children aged >5 years, oxybutynin 5 mg twice (or three times) daily, preferably 5 - 10 mg 1 hour before bedtime.
- In children aged >6 years, extended-release oxybutynin, starting at 5 mg daily for a week and increasing to 10 mg daily, can be

considered. Tablets should be swallowed and not chewed, crushed or divided.
- Oxybutynin is used as an off-label drug to control OAB in children aged 1 - 5 years, with a dosing regimen of 0.2 mg/kg orally administered two to four times daily.

Propiverine hydrochloride

This drug has recently been registered for use in SA in the paediatric population.
- **Dosage** 0.8 mg/kg per day in two to three divided doses.
- The coated tablets come in a dose of 5 mg per tablet.
- A minimum body weight of 12 kg is required before use.

Children weighing ≥35 kg have the same maximum dose as adults, 15 mg twice daily.

Contraindications to anticholinergic therapy

Anticholinergics are contraindicated in infants aged <6 months, in patients with known hypersensitivity, and in those with myasthenia gravis, closed-angle glaucoma, pyloric stenosis, paralytic ileus or toxic megacolon.

Adverse effects

Anticholinergics are safe, and adverse effects are much less common in children than in adults.[30] Common clinically relevant side-effects in children are constipation (which may in turn influence lower urinary tract function), increased post-void residual urine (with a risk for urinary tract infections), dry mouth (which may lead to dental caries), and altered behaviour, including night terrors.[35] The effects on the central nervous system raise greater concern, and symptoms can include hallucinations, sedation, agitation, amnesia and confusion.[35] Propiverine has a better tolerability profile than oxybutynin.[36] All these side-effects resolve when the medication is stopped.

Mirabegron (beta-3 adrenoreceptor agonist)

The beta-3 agonist mirabegron was initially developed in 2007 to treat bladder overactivity and its associated symptoms of frequency, incontinence and urgency in adults.[37,38] Use in the paediatric population has never been evaluated to the same degree. However, in 2016, Blais *et al*.[39] published the first research demonstrating efficacy and safety in children with OAB, with a median patient age of 10.1 years. Data on the use of mirabegron in the setting of enuresis are scant and primarily based on adult literature describing off-label use. The treatment of enuresis with mirabegron has only been evaluated in a single study, the design of which did not include a control arm.[40] Data from this study showed complete and partial response in 31.3% and 40.6% of patients, respectively, with about one-third (28.1%) being non-responders after 6 months of treatment. Other limitations of this study included the small number of participants and the concomitant use of anticholinergic agents to improve continence.[40]

The side-effect profile of mirabegron is similar to that of anticholinergic agents, but to a lesser degree, and includes constipation and xerostomia. One specific side-effect is hypertension, and guidelines in the adult literature recommend routine measurement of blood pressure after initiation of treatment.

As no prospective data are currently available, mirabegron should be used with caution and in settings where other pharmacological options have failed, by physicians with experience in managing complicated enuresis.
- **Dosage** 25 mg per day 1 hour before bedtime in children aged >10 years.

Tricyclic antidepressants

Tricyclic antidepressants (TCAs), mostly imipramine, have been used for >60 years with proven benefits in enuresis.[41] However, mainly owing to cardiotoxicity, they are used as a third line of therapy initiated by specialists experienced in the use of TCAs. These drugs can be fatal if overdosed or if the patient has long QT syndrome.[30] The therapeutic-to-toxic ratio can be as low as 1:2. The mechanism of action of TCAs is unclear, but is thought to involve a combination of noradrenergic, serotoninergic and anticholinergic actions on the bladder, urine production, and arousal mechanisms.

The most common side-effects are mood swings, nausea, anxiety, dizziness, drowsiness, lethargy, dry mouth, anorexia and vomiting, as well as hepatotoxicity and cardiotoxicity. Teenagers with suicidal ideation have also been described, especially if they have depressive symptoms.[41] Before treatment with a TCA can commence, other modes of treatment should have been tried and have failed, or be contraindicated. The patient should have an electrocardiogram to exclude long QT syndrome. Parents need to be counselled to keep the medication away from siblings. There has been a rapid increase in the overall growth of antidepressant use in children, especially those aged >6 years, imposing a risk of unintentional ingestion by younger siblings.[42]

Dosage regimen:
- Imipramine is given 1 hour before bedtime.
- The initial dose is 25 - 50 mg daily.
- The lower dose is for children aged 5 - 8 years, and the higher dose is for older children.
- The dose is titrated, watching out for ineffective dose and side-effects.

Therapeutic response is evaluated after 1 month. If treatment is successful, the dose is titrated to the minimum effective dose. Tolerance to imipramine is known to develop, and it is recommended to let the patient have a drug holiday. One suggestion is after 3 months to have at least 2 weeks of a drug-free period.[30,41] It should be noted and explained to the patient and parents that the dose needs to be decreased gradually when stopping the drug by halving the dose for 1 or 2 weeks. This is to reduce side-effects. On cessation of therapy, the relapse rate is as high as 96%.[41]

Alternative treatment/complementary therapies

Minimal advances in this area have been observed. No efficient or direct comparative data are available for any alternative therapies. There are no measurable outcomes data or placebo-controlled data available. Various forms of acupuncture, acupressure, chiropractic therapies and psychotherapies have been trialled. Hypnotherapy has one study indicating efficacy above placebo but below imipramine and alarm therapies (unfortunately not all medical diagnoses were excluded, as they were largely unknown at the time of the study).[43] Medicinal herbs are regularly used in naturopathic and homeopathic therapies, but no data are available to identify the biochemical action that may constitute cholinergic, antidiuretic and other properties, so no recommended therapies can be brought to the fore in these guidelines.[44,45] These therapies can be seen as complementary. Acupressure has been proven safe in children,[46] while herbal medication still needs several randomised controlled trials to be proven safe for use.

Urotherapy

Urotherapy is part of the conservative adjustments and behavioural modifications that patients and parents can make with support from various health professionals.[20] It is explicitly indicated if dysfunctional voiding is part of the enuresis problem.

Bladder control can be improved in the following three domains: increasing the capacity of the bladder
- decreasing urine output at night time
- heightening awareness of the unconscious sensation of bladder filling.

The following techniques can be used:[47]
- increase daytime fluid intake
- reduce night-time fluid intake
- avoid caffeine and drinks with a high sugar content
- empty the bladder regularly
- pre-bedtime voiding
- functional awareness training
- daily bowel movements.

Urotherapy includes the following components:[48]
- demystification and educational information
- scheduled voiding habits
- lifestyle advice, e.g. drinking habits
- voiding posture
- registration of voiding habits and symptoms using a bladder diary or app
- support and feedback from the caregiver.

An improvement took place in >70% of cases when urotherapy was used before initiating pharmacological or alarm therapy.[47]

Alarm therapy

Enuresis alarms, consisting of a moisture sensor and an arousal alarm, work by conditioning the child to wake, get up and void or inhibit bladder contraction in response to a moisture sensor.[30,49] The alarm can be auditory or vibrating in nature (electric shock options are not recommended).[50] The child associates the alarm with a full bladder and will eventually awaken before voiding, breaking the bedwetting cycle.[49] Alarm therapy improves arousal and can increase bladder reservoir function.[49]

Alarm therapy has been reported to achieve impressive success rates of 60 - 80% in various studies; however, there is a 50% relapse rate once it is discontinued.[30,49] Alarm therapy is similarly effective in reducing wet nights compared with DDAVP, as demonstrated in a meta-analysis of randomised trials.[50] Adverse effects of alarm therapy are uncommon and include alarm failure and false alarms.[50] The child's inability to wake up when the alarm goes off is the most common cause of failure.[49]

Alarm therapy is best suited for children with at least two episodes per week of monosymptomatic NE and with normal or small-capacity bladders.[30,49] This treatment modality needs to be demonstrated to the child and family for best results, and it should be used continuously with minimal interruption.[30] Response to treatment can take 2 - 3 months. This treatment therefore best suits motivated families who agree to active therapy, where immediate improvement is not a priority.[30,49] Withdrawal of alarm therapy is suggested after 2 weeks of consecutive dry nights.[30,49]

The device is often bought commercially, with an average cost between ZAR400 and ZAR4 000. Wireless options are available. Sensor options include pads under the sheets or in the child's underwear.[49] The alarm has several variations available on the market: a buzzer, a bell, a vibration, or even a visual signal, e.g. light.[50] The alarms can be set to different intensities and tones and operate intermittently or at various intervals.[50] Reviews suggest that an immediate alarm performs better, and that children prefer a body-worn alarm to a bed pad.[50]

Neuromodulation[51-53]

There is a role for neuromodulation in adolescents and older children with refractory enuresis that causes severe psychological distress. Transcutaneous electrical neurostimulation is non-invasive and stimulates the sacral nerves over S2 - S4, controlling detrusor contractions. This modality should only be considered by experts in dealing with refractory enuresis. We do not routinely suggest using neuromodulation therapy for children with NE, although it was found to be safe and effective in a meta-analysis compared with placebo/control in some cases of refractory enuresis. The risk of relapse and the optimal type of electrical stimulation in comparison with other interventions for NE are uncertain.

Pelvic floor muscle training

The use of pelvic floor muscle training (PFMT) is based on the hypothesis that daytime and night-time enuresis in children may be due to pelvic floor muscle imbalance between contraction and relaxation and overactivity. Even though PFMT may have a role in NE management, there is no standard exercise protocol (number of repetitions, duration of contraction and relaxation, and length of treatment course). In randomised trials, PFMT increased bladder capacity, but it was not associated with improved enuresis or an improved response rate to subsequent treatment with an enuresis alarm.[54,55] A systematic review of simple behavioural and physical interventions for NE in children found contradicting results of PFMT and concluded that it had no additional effect to standard urotherapy.[25] We believe, based on the literature, that PFMT cannot be used as a single first-line therapy for MSE in children, although it can be one component of multimodal therapy programmes.

Biofeedback[56-58]

Biofeedback is an interactive, non-invasive subset of urotherapy that targets the pelvic floor muscles. It assists in teaching children how to control their lower urinary tract and relax their pelvic floor when voiding. It has been proven effective in treating children with functionally small bladder capacities. This method allows children to retain larger volumes for more extended periods without leakage.

Mobile phone applications (apps) in enuresis

Technology should be embraced, as it is evolving daily and can play a role in the effective treatment and follow-up of enuresis. An electronic 'bladder diary' has shown superiority over the conventional 'pen and paper' bladder diary.[59]

There are apps designed to manage enuresis. These apps are available on both the Google Play Store (Android) and the iOS (Apple).[60] Available apps include: 'Drydawn Bedwetting Diary', 'Rodger app', 'BeDry Bladder Diary', 'DreamDry', and 'Bed Wetting Calendar'.

Treatment outline and algorithm

A suggested treatment algorithm was included in the 2017 guideline.[1]

Associated factors

Bladder and bowel dysfunction and constipation

The functioning of the lower urinary tract and anorectum are inter-related. The association between detrusor overactivity and constipation has been clearly described.[61,62] The combination has been termed bladder and bowel dysfunction,[20] and may be explained by rectal distension interfering with bladder function or shared innervation pathways. The association between constipation and enuresis is more controversial, and appears to be limited to children

with NMSE.[63] Treatment of constipation without treating enuresis has also been shown to have a poor effect on MSE.[64,65]

The diagnosis of functional constipation is often elusive, and the history and examination of a child with enuresis should include looking for features as described by the Rome IV criteria.[66] The combination of constipation and enuresis should also prompt a careful neurological and spinal examination. The treatment of constipation is challenging and consists of education and pharmaceutical treatment. Education and de-mystification are essential; caregivers and children must understand the central role of withholding behaviour in the pathogenesis of functional constipation.[67] Osmotic laxatives such as polyethylene glycol or lactulose are the first-line medications to induce and maintain soft stools while toilet training/retraining is ongoing. Second-line options include stimulant and lubricant laxatives or rectal enemas.[67] If disimpaction is required, a combination of laxatives in relatively high doses is often required before starting maintenance therapy.

Psychological issues[68]

Psychological issues are well described as being associated with the pathogenesis of enuresis. Subclinical symptoms include sadness, moodiness, embarrassment and guilt. Enuresis leads to a lower quality of life for the patient and caregivers.

Several clinical conditions are associated with enuresis:

- externalising disorders (attention deficit/hyperactivity disorder (ADHD), conduct disorder)
- internalising disorders (depression, anxiety)
- mixed disorders (autism spectrum disorder, anorexia).

Psychological screening. There are validated psychological screening modalities available that can be performed in waiting rooms before consultation:

- Short Screening Instrument for Psychological Problems in Enuresis (SSIPPE)[69]
- Child Behaviour Checklist (CBCL).[70]

In refractory cases, a high suspicion of non-adherence is essential and psychological screening is critical.

Early referral

A multidisciplinary approach is essential if an underlying psychological disorder is suspected. Early referral should be done for a formal psychological assessment and early management if indicated.

High-risk groups for a negative impact on quality of life are female gender and patients at an older age.[71] These patients may require expedited psychological referral.

Enuresis and ADHD

Studies have consistently shown an increased prevalence of enuresis among children with ADHD. Systematic reviews and meta-analyses have found that the pooled prevalence of enuresis in ADHD patients can be up to 30%, significantly higher than the 5 - 10% reported in the general population.[72]

There are controversies regarding the association of ADHD and enuresis and the multifactorial aetiologies, but several factors are thought to contribute:

- **Genetic predisposition.** Both enuresis and ADHD have been shown to have a significant genetic component, with specific genetic variants increasing the risk of both conditions.[73]
- **Neuroanatomical abnormalities.** Functional magnetic resonance imaging (MRI) studies have identified differences in brain structure and function between ADHD patients with and without enuresis, including altered activity in regions involved in bladder control and arousal regulation.[74]
- **Sleep disturbances.** ADHD patients often experience sleep disturbances, which may contribute to enuresis by disrupting the normal sleep-wake cycle and increasing nocturnal bladder contractions.[75]
- **Executive function deficits.** ADHD-related deficits in executive function, including planning, organisation and self-regulation, may impede the development of adequate bladder control mechanisms.

Studies report an average of 14.9% of children with NE as having associated psychiatric disorders, with ADHD being the most prevalent.[76] The child may have ADHD and other co-occurring psychological or developmental conditions, such as autism spectrum disorder or learning disabilities, which may complicate the management of enuresis. In general, patients with enuresis often present with comorbid symptoms of ADHD, including inattention, hyperactivity and impulsivity.[77]

Research suggests that enuresis in ADHD patients is often associated with poorer treatment outcomes, including reduced response to pharmacological interventions and an increased risk of relapse. Early identification and management of comorbid enuresis in ADHD patients may help improve treatment outcomes and quality of life for these individuals. Educating patients and their caregivers about enuresis, ADHD and their comorbidity can help improve treatment adherence and reduce the stigma associated with both of these conditions. Vitally important situations when psychological therapy should be considered as part of the treatment plan are as follows:

- **Emotional distress and low self-esteem.** The child may feel embarrassment, shame or guilt related to bedwetting, leading to social withdrawal and low self-worth.
- **Anxiety and depression.** The child displays symptoms of anxiety or depression, such as excessive worry, ongoing sadness, irritability, or changes in sleep and appetite.
- **Trauma or significant life stressors.** Enuresis can reoccur following a significant life event, such as losing a loved one, parental divorce, or moving to a new school or home. The child may have also experienced emotional or physical trauma.
- **Behavioural issues.** The child exhibits behavioural issues such as aggression, defiance or attention difficulties, which may be linked to or worsened by the stress of enuresis.
- **Family dynamics and parental stress.** The family may show signs of strain, such as parental frustration, sibling teasing, or misunderstandings about the condition, leading to conflict or lack of communication regarding the child's enuresis.
- **Resistance to conventional treatments.** The child does not respond to conventional treatments, such as alarm therapy or medication, or the enuresis persists despite these efforts.
- **Adolescent enuresis.** Enuresis persists into adolescence, where peer relationships and social acceptance become increasingly important, and the adolescent may experience intense embarrassment or social isolation as a result of the condition.

When there is suspected ADHD, psychological interventions, such as cognitive-behavioural therapy, can be highly effective in addressing the emotional aspects of enuresis. When the parent is more stressed than the child in cases of enuresis, it is essential to address the parent's emotional needs as part of the treatment plan. By addressing the psychological aspects alongside the physiological ones, healthcare providers can offer more comprehensive care,

helping children overcome the symptoms of enuresis and the emotional challenges accompanying it. Empathy, education and appropriate interventions can mitigate the psychological burden of enuresis, allowing children to regain their confidence and improving their overall quality of life.

Enuresis and adenotonsillar hypertrophy

Obstructive sleep disorders, characterised by snoring and increased respiratory effort due to upper airway obstruction (UAO), are prevalent in paediatric populations. UAO is a common concern, affecting ~27% of children, and is often attributed to nasal or oropharyngeal pathologies.[78] Adenotonsillar hypertrophy is the most frequent cause of UAO, while other contributors encompass craniofacial malformations, septal deviation and allergic rhinitis.[79,80] In this context, obstructive sleep apnoea (OSA) emerges as a common presentation in children with adenotonsillar hypertrophy, further complicating the clinical landscape.[81,82]

Enuresis and OSA are prevalent sleep-related problems in children, sparking significant interest in exploring their potential relationship. Studies have illuminated the association between OSA and NE, with both conditions sharing an underlying sleep disturbance marked by altered arousal responses and fragmented sleep patterns.[82] This interplay is rooted in the pathophysiological mechanisms operating, ultimately leading to increased intra-abdominal pressure and altered blood pressure, which in turn induce natriuresis and polyuria by affecting levels of ADH and atrial and brain natriuretic peptides.[83]

Sans Capdevila *et al*.[84] conducted a study involving 17 646 children, revealing that habitual snorers, constituting 26.9% of the sample, had an increased prevalence of enuresis, predominantly among boys. In contrast, non-snorers displayed a lower prevalence of enuresis at 11.6%. Additionally, children with enuresis exhibited elevated brain natriuretic peptide levels, with marginal increases observed among children with OSA. Although evidence suggests that OSA may influence ANP levels and renal function, potentially leading to increased urine output, further research is necessary to understand these mechanisms fully.[85]

Additional investigations

Ultrasound is recommended as the first line in the investigation of enuresis in this update.

In cases resistant to treatment, additional investigations are recommended to exclude SMSE and help guide management.[86] Some of the investigations already done in the initial assessment, such as a detailed volume voided chart over 48 hours, may need to be repeated. The weight of night-time nappies should be added to the volume voided.[86] Night-time urine production should be recorded over ~2 weeks to differentiate between high-volume urine production and night-time OAB.[86]

Uroflowmetry is indicated if there is a history of previous bladder/urethral surgery. Uroflowmetry and post-void residuals are useful in the work-up of NMSE. Rectal wall distension can be measured on ultrasound to assess constipation, and this is useful in the initial assessment. A course of laxatives may also be given as a trial to investigate the possible role of a distended colon as a cause.[87] Functional MRI has not been shown to be helpful; the main concern is that the MRI is done when the child is awake, and enuresis happens during sleep.[88] While routine urodynamics are not indicated, these tests may help guide treatment by potentially adding anticholinergics to the treatment regimen, or biofeedback may be helpful to the child.[89] Telemedicine, with closer follow-up, should be considered, as this helped in the investigation and treatment of MSE during the COVID-19 pandemic.[90]

Definitions of treatment outcome

As per guidelines outlined by the International Children's Continence Society (ICCS), treatment with an enuresis alarm should be discontinued if no positive effects are observed within 6 - 8 weeks. In the event of progress during this time frame, the treatment should be discontinued when the child achieves a stretch of 14 consecutive dry nights. If the child fails to reach this milestone after 16 weeks, the treatment can be deemed partially successful if there is a reduction of ≥50% in the frequency of wet nights per week compared with the baseline measurements. Treatment can be tried again after 12 months. Otherwise, treatment is classified as unsuccessful if failure persists.[91]

The ICCS has also developed standardised definitions for initial and long-term enuresis medical treatment outcomes for research purposes; for clinical purposes, treatment success is determined by the child and the family.[20]

Initial response:

- no response – <50% reduction in baseline symptom frequency
- partial response – 50 - 99% reduction in baseline symptom frequency
- complete response – 100% reduction in baseline symptom frequency.

Long-term outcomes:

- relapse – more than one symptom recurrence per month
- continued success – no relapse within 6 months after interruption of treatment
- complete success – no relapse within 2 years after interruption of treatment.

Refractory enuresis and treatment of relapse

Refractory enuresis is defined as no response to DDAVP therapy and alarm therapy.[92] Factors that should be explored on history and referred appropriately are listed in Table 1.

A history should always be taken and examination performed prior to investigations. Bladder capacity and voiding pattern may be assessed using uroflow studies and post-void ultrasonography to guide the following line of therapy.

Conclusion

NE, particularly MSE, significantly affects the quality of life of affected children, with a prevalence of 14.4% in SA. An updated guideline is proposed, expanding on the previous comprehensive 2017 guideline.[1]

Recommended links

http://i-c-c-s.org/
http://bedwetting.elsevierresource.com/
http://www.espu.org/
http://www.bapu.org.uk/
http://www.eric.org.uk/
https://www.continence.org.au/information-incontinence-english/bedwetting-in-childhood
https://www.rch.org.au/clinicalguide/guideline_index/Enuresis_-_Bed_wetting_and_Monosymptomatic_Enuresis/
http://www.gosh.nhs.uk
https://cps.ca/en/documents/position/evaluation-and-management-of-enuresis-in-the-general-paediatric-setting
https://www.aafp.org/pubs/afp/issues/2003/0401/p1499.html
https://www.uptodate.com/contents/nocturnal-enuresis-in-children-management
https://www.worldbedwettingweek.com/
https://www.bladderandbowel.org/bladder/bladder-conditions-and-symptoms/nocturnal-enuresis/

Table 1. Tabulated approach to treatment failure

Enquire about …	Possible causes	Investigations
Adherence to DDAVP and/or alarm therapy	Caregiver fatigue Slow response Adverse effects	History
Toilet indoors/outdoors Night light	Fear to use the toilet	History
Family history of enuresis	Delayed maturation	History
Fluid intake at night	Excessive urine production	History
Constipation	Compression on bladder Bladder and bowel dysfunction	History
Frequency	Urinary tract infection OAB Small-capacity bladder	Urine dipstick Bladder diary Refer nephrology/urology
Daytime incontinence	CAKUT Bladder capacity	Sonar, KUB VCU may be indicated Refer urology
Constant dribbling of urine	Female epispadias Ectopic ureter (female) Vesicovaginal fistula	Sonar, KUB VCU may be indicated Refer urology/nephrology
Secondary enuresis	Psychosocial stressor home or school	Refer psychology
Snoring	Obstructive sleep apnoea	Refer otorhinolaryngology
Polydipsia, polyuria	Diabetes mellitus Diabetes insipidus Renal tubulopathy	Urine dipstick Haemoglucotest Serum sodium Urine osmolality Refer nephrology
Neurodevelopmental disorders	Delayed maturation Neurogenic bladder	Neurological examination Refer neurodevelopmental specialist[93]
Weight loss or poor growth	Chronic kidney disease	Blood pressure Serum creatinine Refer nephrology

DDAVP = desmopressin; OAB = overactive bladder; CAKUT = congenital anomalies of kidney and urogenital tract; KUB = kidney ureter bladder X-ray; VCU = voiding cystourethrogram.

Declaration. This publication is for educational and medical purposes only. The recommendations are based on scientific evidence and author consensus. Adherence is voluntary and does not replace physician judgement. The recommendations do not prescribe specific diagnostic or treatment protocols or serve as the sole standard of care.

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