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Review Article

Management and treatment of nocturnal enuresis—an updated standardization document from the International Children's Continence Society

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Summary

Background
Enuresis is an extremely common condition, which, although somatically benign, poses long-term psychosocial risks if untreated. There are still many misconceptions regarding the proper management of these children.

Aim
A cross-professional team of experts affiliated with the International Children's Continence Society (ICCS) undertook to update the previous guidelines for the evaluation and treatment of children with enuresis.

Methods
The document used the globally accepted ICCS terminology. Evidence-based literature served as the basis, but in areas lacking in primary evidence, expert consensus was used. Before submission, a full draft was made available to all ICCS members for additional comments.

Results
The enuretic child does, in the absence of certain warning signs (i.e., voiding difficulties, excessive thirst), not need blood tests, radiology or urodynamic assessment. Active therapy is recommended from the age of 6 years. The most important comorbid conditions to take into account are psychiatric disorders, constipation, urinary tract infections and snoring or sleep apneas. Constipation and daytime incontinence, if present, should be treated. In nonmonosymptomatic enuresis, it is recommended that basic advice regarding voiding and drinking habits be provided. In monosymptomatic enuresis, or if the above strategy did not make the child dry, the first-line treatment modalities are desmopressin or the enuresis alarm. If both these therapies fail alone or in combination, anticholinergic treatment is a possible next step. If the child is unresponsive to initial therapy, antidepressant treatment may be considered by the expert. Children with concomitant sleep disordered breathing may become dry if the airway obstruction is removed.

Introduction

Background, scope of the document

This article is intended as suggested guidelines for healthcare professionals managing children with enuresis. It has been developed by leading experts within the International Children's Continence Society (ICCS) and represents an update of the previous guidelines [1,2]. Although evidence is given more weight than experience, we have, in the interest of readability, chosen to present the recommendations as a narrative review rather than a formal meta-analysis.

We have chosen to address both MNE and NMNE in one document, since the overlap between these entities is large both concerning pathophysiology and management, and the same professionals usually encounter both groups. The aim is not to provide a complete background regarding pathogenesis, epidemiology and theoretic basis of therapy, but to be clinically useful for the nonexperts.

Classification, definitions

The focus of this article is enuresis, that is, bedwetting. The globally accepted ICCS LUT terminology [3] will be consistently adhered to. Accordingly, incontinence of urine is divided into continuous and intermittent variants, the former of which denotes the small number of children who due to anatomic or neurologic

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reasons have a continuously dribbling loss of urine. Intermittent incontinence refers to children aged 5 years or more who suffer from involuntary wetting in discrete portions. When it is clear from the context that continuous incontinence is not referred to, the word intermittent may be dropped. If (intermittent) incontinence happens at night while asleep, the term nocturnal enuresis, or just enuresis, applies. Thus, all bedwetting children aged five or more suffer from enuresis, regardless of pathogenesis or concomitant daytime symptoms.

Enuresis is subdivided into primary or secondary variants on the basis of whether a previous symptom-free interval of at least 6 months has appeared or not. A clinically more important subdivision is into monosymptomatic and non-monosymptomatic enuresis, the latter term reserved for those children who, in addition to their bedwetting, have any of the following daytime LUT symptoms:

- Daytime incontinence
- Urgency (sudden, unexpected, and imperative urge to void)
- Voiding difficulties—poor stream, hesitancy, need to strain to void
- Abnormally low or high daytime voiding frequency (voiding <4 or >7 times per day)

Children with NMNE can be suspected to have a somewhat different pathogenesis, and need to be managed differently, than those with MNE.

The storage capacity of the bladder, a crucial parameter in the evaluation of these children, is approximated by assessing the *voided volumes* via a voiding chart. From the amount of urine voided at each micturition average and maximum voided volumes are calculated. To compare these values with that of other patients the EBC for the child's age is calculated using the following formula: ([age in years] * 30) + 30 mL. This formula is valid until the early teens when the adult capacity of 400 mL is reached [4].

Nocturnal polyuria, which is a crucial pathogenetic mechanism, is currently defined as a nocturnal urine production (weight of urine in sheet covers or diapers plus first morning void), on a night with enuresis, of at least 130% of the EBC for the child's age. This definition may, awaiting ongoing research, be modified.

Epidemiology, pathogenesis, consequences

Enuresis is common. Approximately 5—10% of 7-year-olds suffer from the condition. The prevalence in teenagers is around 3% whereas 0.5—1% of adults still wet their beds [5,6]. An annual spontaneous remission rate of 15% is often quoted [7], but the chance of becoming dry without treatment is markedly lower if enuresis is frequent [8].

Enuresis is often inherited [9] but a mismatch between genotype and phenotype means that the presence or absence of enuresis in the individual patient's family history gives limited clinical information [10]. Although the old view of enuresis as a primarily psychiatric condition has not been supported by evidence this misconception still lingers both among parents and healthcare providers [11]. A detailed description of the pathogenesis lies outside the scope of this document, but a valid summary of the current understanding is that enuresis is regarded to be due to a mismatch between nocturnal urine production, nocturnal bladder storage capacity and the ability to arouse from sleep [12—14]. Underlying these mechanisms are possibly disorders of central nervous system signal processing and the default mode network [15—17]. The increased arousal thresholds do not, however, mean that these children sleep well; in fact, sleep quality of enuretic children is often poor [18,19].

Nocturnal polyuria may be assumed to be more common in MNE, whereas it is logical to assume that NMNE is more linked to decreased bladder storage capacity [20], but the overlap is great and both mechanisms may be relevant in the same child.

Enuresis is not a trivial condition. If left untreated, it may result in poor self-esteem [21], avoidance of social activities like camps and sleep-overs as well as parental stress [22]. Furthermore, there are data suggesting that enuresis is linked to chronically disturbed sleep and treatment may, via amelioration of sleep disturbance, have favorable effects on daytime behavior and executive function [23]. Finally, as mentioned above, not all enuretic children will "grow out of" their condition [24].

Comorbidity

Several conditions may coexist with enuresis and need to be taken into account since they may influence prognosis and/or response to therapy. All comorbid conditions mentioned below except sleep-disordered breathing can be expected to be more common in NMNE than in MNE.

Although previous notions of enuresis as a primarily psychiatric disorder have not stood the test of time behavioral issues are still relevant in the enuretic population. First, as mentioned above, enuresis may lead to chronic low self-esteem. Second, enuresis is overrepresented among children with various psychiatric conditions such as ADHD [25]. Treatment of such co-occurring conditions may not by itself make the child dry but may sometimes be necessary in order for the child to be able to comply with antienuretic therapies that demand a high degree of collaboration. In a child with enuresis and bothersome psychiatric issues both conditions can and should be treated in parallel.

While constipation is extremely common in children with daytime incontinence, it is also clearly overrepresented in NMNE and probably in MNE as well [26,27], since constipation and detrusor overactivity are strongly interrelated [28]. The child with bladder dysfunction may often have concomitant fecal impaction with or without overt gastrointestinal symptoms. At least in NMNE, treatment of the enuresis should not be started before constipation has been ruled out or successfully treated. For more in-depth information regarding diagnosis and management of childhood constipation and its links to bladder problems, as well as how to manage constipated children, please consult the relevant ICCS documents [29,30].

Although it is clear that urinary tract infection (UTI) may have incontinence as a symptom, most enuretic children do not have bacteriuria as a cause for their bedwetting. It should be kept in mind that asymptomatic bacteriuria (ABU) —a benign condition that should not prompt antibiotic

treatment—is common in all ages and more common in children with bladder dysfunction [31]. ABU should be suspected in all children with positive urine cultures but no unexplained fever and no daytime bladder symptoms of recent onset.

Finally, there is a link between enuresis and heavy snoring or sleep apneas in a subgroup of enuretic children. Approximately 50% of enuretic children with sleep-disordered breathing will become dry by undergoing adenotonsillectomy [32]. The reason for this link may be either that the child with constant arousal stimuli from the airways will become paradoxically difficult to arouse from sleep or that the increased negative intrathoracic pressure caused by inefficient breathing efforts will increase atrial natriuretic polypeptide secretion and thus urine production [33].

Initial evaluation

Warning signs

The initial evaluation should make the clinician able to react, without delay, to the following important warning signs (see Table 1).

History

The medical history is the most important—and sometimes the only necessary—part of the evaluation of the enuretic child. The purpose is to 1) find out if extra evaluation is needed and 2) to gather enough information to be able to choose first-line therapy, together with the child and family. During history taking the clinician needs to make sure to talk with the child and not just the parent—it's the child's problem that needs to be addressed and the child needs to be involved in the therapeutic process. The history should focus on at least the following items:

General health. Has growth and development been normal? Weight loss? Nausea? Excessive thirst with a need to drink at night? (diabetes?)

The enuresis. Is every night wet or does the enuresis occur less frequently? Has there been prolonged dry periods?

Daytime micturition habits. Is there daytime incontinence, and if so how often and when? Does the child experience urgency? Are there voiding difficulties, that is, weak stream or a need to strain to void? Squatting or other holding maneuvers?

Has there been *previous UTIs*?

Bowel habits. According to the Rome IV criteria [34], at least two of the following criteria should be present for at least 4 weeks to meet the definition of constipation. Note that the first 5 criteria can be evaluated by history alone whereas the last criterion, if assessed, requires either digital rectal examination or measurement of transverse rectal diameter by ultrasound (see below):

- Two or fewer defecations per week
- History of excessive stool retention
- History of painful or hard bowel movements
- History of large-diameter stools that may obstruct the toilet
- Fecal incontinence at least once per week
- Presence of a large fecal mass in the rectum (this criterion need only be assessed when there is diagnostic doubt).

Sleep problems. Is there consistent heavy snoring or sleep apneas? daytime sleepiness?

Behavioral issues. Are there problems regarding concentration or social interactions at home or in school? A screening tool may be used [35]. Is the bedwetting a big problem for the child, and if so why?

Previous treatment. Which therapies and strategies have been used? Why did they not work?

The ICCS has produced clinical guidelines which can function as a checklist for the clinician [36].

Examinations

The *physical examination* of the enuretic child usually comes out completely normal or gives findings unrelated to the enuresis. Thus, in the absence of warning signs in the history (see above) the child could be managed initially without being examined by a physician. In case of doubt, however, a general physical examination, focusing on general health and signs of occult spinal dysraphism (lower back findings, leg and anal cleft asymmetries, abnormal neurology of the lower limb) is needed.

The *voiding chart*, as described by the ICCS [3] is recommended in the initial evaluation of all enuretic children, and mandatory if there are any indications from the history that the enuresis is of the nonmonosymptomatic kind, that is, if there are any daytime LUT symptoms. The benefits of the voiding charts are many fold: relevant data regarding renal and LUT function, as well as contraindications to therapy, are gathered; the child is made aware of his/her bladder function; and information regarding the family's

Table 1 Warning signs in the initial assessment of the child with enuresis.

Warning sign	Action
Weight loss, growth retardation and/or nausea	Check creatinine and urine glucose. Physical examination.
Excessive thirst with a need to drink at night	Check urine glucose. Complete a fluid intake list. Consider creatinine and morning urine osmolality. Physical examination.
Voiding difficulties—weak stream, need to strain to void	Check uroflow and residual urine. Physical examination.
Secondary nocturnal enuresis with recent debut	Check urine glucose. Physical examination.
Heavy snoring or sleep apneas	Contact otorhinolaryngologist. Physical examination.

ability to adhere to instructions is gained. Finally, the completion of voiding charts can be regarded as part of the therapy, at least in the presence of daytime symptoms. The standard voiding chart should include assessment of incontinence (night or day) for at least 1 week and daytime voided volumes as well as fluid intake for at least two days. Please note that the diagnostic value of maximum voided volumes in enuretic children is limited by the fact that this is usually the first morning void, but only if the preceding night has been free from enuresis or nocturia. If measurement of nocturnal urine production on "wet nights," via the weighing of diapers or sheet covers and adding the first morning void, are added the detection of nocturnal polyuria (as defined above) will also be made possible, which is of great value. This variable should preferably be measured during 1 week.

A *urine dipstick*—detecting glucosuria and leukocytes—is a necessary part of initial evaluation if enuresis is secondary, if there are any daytime LUT symptoms, or if there are any relevant warning signs (see above) in the history. Glucosuria, obviously, means that diabetes mellitus immediately needs to be excluded. Leukocyturia, or a positive nitrite test, should prompt a urine culture, provided there is a clinical suspicion of UTI supported by day-time symptoms such as daytime incontinence, urgency or dysuria. The likelihood of cystitis needing treatment in an enuretic child with a positive urine culture ranges on a spectrum from highly unlikely in the case of primary MNE to quite possible in the child with secondary NMNE of recent debut with dysuria as one of the daytime symptoms.

Blood samples are only indicated if there is glucosuria or general warning signs suggesting polyuric renal failure. Neither are *urodynamic investigations* needed in the absence of voiding difficulties. Finally, the only *imaging* that may sometimes be indicated at this early stage is an ultrasonographic examination of the bladder and rectum to confirm a suspicion of constipation unrecognized by the family. A transversal rectal diameter behind the bladder in excess of 30 mm is suggestive of rectal impaction and is a very common Rome IV criterion in children with constipation [37,38].

Initial treatment

Who should see the child? Which child should be treated?

The main reasons to treat children with enuresis are psychological and social, not somatic. The children need help to become dry before their self-esteem and social interactions become adversely affected. Thus, the "wait and see-attitude" is not adequate in the management of the child who is old enough to be bothered by his/her condition. This usually means that by the age of six the child needs both general advice and active treatment. Note, however, that this age limit is not absolute—some children (and their parents) may be much bothered at the age of five and some may have learned to live with bedwetting without noticeable problems at the age of seven. Also, daytime incontinence may need to be treated at an earlier age—this is dealt with in separate ICCS documents [39,40]. The first healthcare provider to see the enuretic child may be a nurse, a urotherapist, a general practitioner, a pediatrician or a pediatric urologist; the profession is of minor importance as long as he/she knows what to look for and which questions to ask.

General advice

Regardless of the child's age and the later choice of therapy, some information needs to be given to all families. First, the child needs to know that this is not his or her fault. Many families still believe that enuresis is caused by poor parenting skills or psychological factors [11], and this misconception needs to be removed. We should also tell the family that help is available and that we will not give up until we succeed.

Various, often unsuccessful, strategies that the family have used may need to be addressed. Parents who regularly wake the child at night need to know that this strategy is neither medically motivated nor curative [41]—if it helps then it usually only helps for that specific night. Parents who restrict the child's fluid intake in the evenings should be dissuaded from this practice unless they see a clear benefit (regarding fluid restriction during desmopressin therapy, see below). The advice to give extra fluid during daytime to keep him/her well hydrated is often given, but the evidence base is scant (evidence level IV). Furthermore, the child should have a say regarding the choice of incontinence products—diapers or sheet covers. Many school-age children do not want to wear diapers.

The value of basic bladder advice or urotherapy in nocturnal enuresis (as opposed to daytime incontinence) is unclear, due to lack of randomized, controlled studies. In children without daytime symptoms the provision of such instructions is not supported by the evidence [41,42], whereas it is logical to assume that these are indeed useful in NMNE (evidence level IV), given the prominent role of urotherapy in daytime incontinence due to detrusor overactivity [40].

Nonmonosymptomatic nocturnal enuresis—initial treatment

The fact that there are concomitant daytime LUT symptoms indicate 1) that uninhibited detrusor contractions are likely to play a role as a pathogenetic factor, which will influence choice of therapy and, 2) comorbidity—somatic or psychiatric—is extra common and may need to be addressed. These children need to complete a voiding chart and the initial evaluation should include a urine dipstick.

Constipation is more common in this group, and should be treated on the slightest suspicion (evidence level IV for effect against enuresis). For the diagnosis and management of constipation see the appropriate ICCS document [29]. Likewise, the increased prevalence of behavioral issues in this group should be kept in mind. Sometimes the help of a psychologist or psychiatrist may be needed to increase the compliance to instructions given [43].

Although the evidence base is weak, the consensus is that bothersome daytime LUT symptoms should be treated before the nocturnal enuresis is addressed (evidence level

IV). Thus, the child with NMNE should be instructed to 1) establish regular voiding habits with micturition approximately 6 times per day, 2) drink adequately especially in the morning and at lunch, and 3) adopt a good voiding posture with the thighs well supported. That said, there is no evidence-supported reason to delay specific antienuretic therapy in the child whose daytime symptoms are minor and not a cause of concern for the family—that is, some urgency, marginal incontinence episodes and/or high/low voiding frequency. On the other hand, if daytime incontinence is a major problem this should be managed first (evidence level IV)—the reader is advised to consult the relevant documents [39,40].

Monosymptomatic nocturnal enuresis—initial treatment

There are two established first-line therapies in MNE: the enuresis alarm (evidence level Ia) and desmopressin (evidence level Ia). Regardless of the therapy chosen, the role of the parents is crucial.

The *enuresis alarm* is a device which gives a strong arousal stimulus, usually acoustic, to the child and family at the moment when urine activates a detector located in the child's bed or clothing. The success rate is between 50 and 70 per cent [44] and a large proportion of those successfully treated will become cured [45].

Favorable prognostic indicators for alarm therapy are frequent enuresis and a motivated child and family [46,47]. Obviously, if the parents have sleep problems or if the child shares a room with siblings, compliance with alarm treatment may be difficult. Concomitant ADHD can also decrease success rate. Likewise, the alarm would not be the first choice for a child whose enuresis is infrequent or periodic. Finally, in the child who wets more than once per night the alarm, as monotherapy, may not be the first choice. If alarm therapy is chosen it is imperative that the following practicalities are adhered to:

- The alarm should only be used by well-motivated, well-informed families
- The device should be thoroughly demonstrated for both child and parents
- The alarm needs to be used continuously, every night without interruption
- The parents need to be prepared to wake the child immediately when the signal is heard, since very often during the first weeks of treatment the child itself will not wake up by the signal
- The healthcare provider should contact the family after 1—3 weeks to give encouragement and solve technical problems during this crucial period
- If there is no sign of progress after 6 weeks therapy should be stopped
- If there is progress (smaller wet spot, occasional dry nights) then therapy should be continued until 14 consecutive dry nights have been achieved

Desmopressin was developed as an analogue to the antidiuretic human hormone vasopressin, or antidiuretic hormone. Its antienuretic effect is best explained by decreasing nocturnal urine production to a level which can be accommodated within the bladder. Approximately one-third of enuretic children will be reliably dry as long as they take the drug, whereas one-third will have no benefit and one-third will have an intermediate response [48].

Desmopressin can be used long-term without substantial risks, and side-effects are rare. The only contraindication is habitual polydipsia and the only risk that both prescriber and patient need to be aware of is that if medication is combined with excessive fluid intake water intoxication with hyponatremia may ensue [49]. The chance of response is highest in children with MNE who have nocturnal polyuria and normal daytime voided volumes [50,51].

Desmopressin is given in the evening, 60 min before bedtime. The globally most common formulations are oral tablets and oral quick-melting lyophilizate. For reasons of pharmacokinetics and patient preference, the latter formulation is usually preferable [52], although it has not been approved in many countries, including the United States. Standard dosage is 0.2—0.4 mg for the tablets and 120—240 ug for the lyophilizate. The prescriber may either start with the full dose and titrate down after a week or so in case of good treatment effect, or use the opposite strategy. In either case, the efficacy (or lack thereof) will be immediately evident and there is no justification for prolonged medication more than 1—2 weeks in a child who has no beneficial effects of the therapy.

Various strategies can be used to ensure that desmopressin is not combined with excessive fluid intake. One safe instruction may be to allow maximum 200 mL during the last hour before bedtime and then no drinks during the night. Children who are dehydrated or thirsty due to intense exercise or sweating can quench their thirst with water and still take desmopressin.

If the child is dry on therapy then the family and child decide whether to use the drug every evening or just on "important nights." If the former strategy is used then recurring drug holidays are needed to see whether treatment is still needed. Although the curative effect of desmopressin is low and treatment may be needed for several years, there is some evidence to suggest that the chance of continued dryness after therapy is slightly higher if the drug is discontinued gradually, by decreasing dosage during a couple of weeks or months before stopping [53,54]. However, other studies have been unable to confirm this [55].

The choice of first-line therapy can be made in two ways (A or B), depending on whether to put most emphasis on the prognostic indicators for desmopressin (A) or the alarm (B).

Strategy A means that the family has completed a voiding chart including measurements of nocturnal urine production. If this shows that the child has nocturnal polyuria and normal daytime voided volumes then desmopressin is tried first, and if nocturnal urine output is normal and MVV are low the alarm is provided. If both nocturnal polyuria and reduced MVV—below 65—70% of EBC—is present combination therapy with desmopressin and alarm can be considered.

Strategy B means that the family chooses which therapy to use first after being informed about the pros and cons of both alternatives. This means that the families most motivated for the alarm will choose the alarm.

Regardless of which strategy (A or B) is used, if the first choice of therapy (alarm or desmopressin) did not make the child dry then the other alternative should be offered. If both fails as monotherapy a combination of the two can be considered.

Management of therapy-resistant children

Evaluation

The child with enuresis who has neither responded to desmopressin nor alarm therapy needs to be examined by a physician, usually a pediatrician or a pediatric urologist. The case history will—in addition to the items mentioned above—have extra focus on comorbidities and possible reasons for failure of first-line therapy. Thus, questions need to be asked regarding Rome IV criteria for constipation; possible behavior issues need to be enquired about and the family will be asked to describe how the unsuccessful therapies were given. Often it will be found that the alarm was incorrectly used—that is, the parents were not instructed to help the child to wake up immediately or the device was not used consistently every night. In some cases a high evening salt and/or protein intake may be suspected to influence negatively desmopressin response.

The child needs to be physically examined, with focus on signs of spinal dysraphism as described above.

A voiding chart including nocturnal urine production assessment needs to be completed. A central benefit of the voiding chart in this situation is that the presence of nocturnal polyuria means that desmopressin should be considered as part of a combination treatment. Furthermore, therapy-resistant children should undergo noninvasive urodynamic investigation with flowmetry and residual urine measurement. The reason for this is that the finding of pathological curves or post-void residual urine on repeated measurements means that a) anatomic obstruction or neurogenic bladder needs to be excluded and b) anticholinergic treatment is contraindicated. Therapy-resistance *per se* constitutes no indication for blood tests, radiology or invasive urodynamics.

Many of the therapy-resistant children will need to be treated for constipation *ex juvantibus* (evidence level IV) according to the ICCS guidelines [29] and some will need the assistance of a child psychologist or psychiatrist (evidence level IV) [43]. There is also a subgroup that may need surgical treatment for sleep-disordered breathing (evidence level III).

Anticholinergic treatment

Provided that there is no residual urine and that constipation is excluded or successfully treated anticholinergics can be considered as second-line antienuretic therapy, often in combination with desmopressin (evidence level Ib). The rationale for this is that detrusor overactivity is a crucial pathogenetic mechanism in enuresis, especially in NMNE or enuresis nonresponsive to desmopressin therapy [56]. Furthermore, there is now modest evidence from randomized controlled studies that anticholinergic drugs are effective in enuresis, at least as an add-on to desmopressin [57].

There are no serious risks associated with these drugs, and many side-effects that are often seen in adults are rare in children. The most clinically relevant side-effects in the pediatric population are constipation (which may in turn influence LUT function), postvoid residual urine (with risk for UTIs), and dry mouth (which may lead to caries) [58]. Psychiatric side-effects such as mood swings are sometimes seen with oxybutynin [59]. All side-effects wane as medication is discontinued.

There are several anticholinergic drugs available, but it needs to be emphasized that only oxybutynin is available for label use in children. The reasons that we chose to mention other alternatives in this review are that 1) the side-effect profile is more favorable in the off-label alternatives [60,61] and 2) other alternatives can be expected to become available for label prescription in the near future.

Before considering anticholinergic treatment, constipation and residual urine need to be excluded or successfully treated. If treatment of constipation is needed this should continue as long as anticholinergics are given. The family needs to ensure that the child voids regularly and that oral hygiene is good.

Medication is taken in the evening 1 h before bedtime and should be started with a dose in the lower interval mentioned in Table 2. The favorable effect, if any, may not be immediately apparent, so the therapy should be evaluated after 1—2 months. If then there is an insufficient reduction of wet nights but no side-effects desmopressin may be added (in standard dosage) and anticholinergic dose increased. There is insufficient evidence to provide recommendations whether to increase anticholinergic dosage or add desmopressin first, so this will have to be decided on an individual basis. Another strategy is to start with combination therapy and then try and discontinue desmopressin. If a satisfactory situation is reached and the child is dry at night then the family should be instructed to make regular attempts to gradually discontinue medication approximately every third month.

The risk for the accumulation of postvoid residual urine during anticholinergic treatment of enuresis is difficult to assess. We suggest that residual urine is measured once after 3—6 months or earlier in every child and that regular new measurements are made if there is a history of previous UTIs or if the drug, due to concomitant daytime incontinence, is given twice daily. More important still is that the family is instructed to seek medical attention if the child develops UTI symptoms such as dysuria or unexplained fever. A child who has a UTI while on anticholinergic treatment should be checked for residual urine and the drug should be discontinued at least temporarily.

If initial therapeutic response is good but the wet nights then start to reappear constipation should be suspected. Temporary discontinuation of anticholinergic medication for a couple of weeks while the constipation is addressed often leads to dryness when the drug is reintroduced.

The noradrenergic drug mirabegron has recently proved to be an efficient and safe addition or alternative to anticholinergics in adults with detrusor overactivity [62]. Future research will determine its possible role in children with enuresis [63].

Antidepressant treatment

The tricyclic antidepressant imipramine is an evidence-based antienuretic therapy [64] (evidence level Ia) that can be used by specialists as a third-line alternative if desmopressin, the alarm and anticholinergics have all been unsuccessfully tried and/or are contraindicated. The mode of action in enuresis is unclear but the beneficial effect may be due to a combination of noradrenergic, serotoninergic and anticholinergic action on the bladder, urine production and arousal mechanisms [65—67]. Among therapy-resistant enuretic children, 30—50% may be expected to benefit from imipramine [68—70], and this proportion increases if desmopressin is added [66]. There are no known clear prognostic indicators for imipramine therapy and it is not known whether children with MNE or NMNE are most likely to respond.

The crucial factor that has limited the use of tricyclics in enuresis is cardiotoxicity. If the drug is overdosed or given to a child with unstable arrhythmia (long QT-syndrome) fatal reactions may occur [71,72]. Thus, the drug should not be given without prior long-time electrocardiographic evaluation if there is any history of unclear syncope or palpitations in the child or a positive family history of sudden cardiac death. Obviously, the recommended dosage should never be exceeded and the family needs to ensure that the pills are kept securely locked.

The most common and limiting side-effects in clinical practice are mood swings and nausea [73]. These side-effects, if mild, may gradually disappear even during continued medication. Furthermore, there is a clear tendency for tolerance, that is, an initially good antienuretic effect may fade as the weeks and months progress [66].

Imipramine should be given approximately 1 h before bedtime. The dosage is 25—50 mg, the larger dose given to children older than 9 years of age or if the lower dose is ineffective and free of side-effects. Therapeutic response is evaluated after 1 month, and desmopressin may be added if the effect is incomplete. As with anticholinergics, an alternative strategy is to start with desmopressin combination therapy. If treatment is successful then it is imperative that regular drug-free periods are interspersed to decrease the risk for tolerance. One suggested strategy is that a drug holiday of 2 weeks is given every third month, but this may have to be individualized. Whenever discontinuing imipramine therapy, this should be done gradually, with dosage halved for 1—2 weeks, to decrease the risk for side-effects on discontinuation [66].

New attempts with the enuresis alarm

Many families will feel uncomfortable using potent drugs such as antidepressants for enuresis. These children, and those who have not responded to second- and/or third-line therapy, should be encouraged to try the enuresis alarm again. Children who are dry on medication may also wish to be able to find a therapy that gives them a chance to stay dry without taking drugs.

Regardless of the background, it is a sensible strategy to encourage children to make fresh attempts with alarm therapy every 2 years or so. Before making a new alarm attempt, it is recommended that the family complete a voiding chart including measurements of nocturnal urine production. If there is nocturnal polyuria the addition of desmopressin—even if it did not work as monotherapy—may increase the likelihood of alarm response [74].

In children who have previously responded to enuresis alarm therapy but then have relapsed, there is some evidence that "overlearning" methods could improve the chance of cure during the next alarm attempt [75]. One such strategy is to instruct the child, after 14 consecutive dry nights have been achieved, to drink 1—2 extra glasses of water every evening (desmopressin is then contraindicated, of course). When 14 consecutive dry nights have reappeared in spite of the extra fluid then the chance for long-term remission or cure can be assumed to have increased.

Table 2 Proposed dosage of anticholinergics in nocturnal enuresis.

Drug	Proposed dosage[a]
Oxybutynin	2.5—5 mg
Tolterodine[b]	2—4 mg
Fesoterodine[b]	4—8 mg
Solifenacin[b]	5—10 mg

[a] All doses are oral tablets given 1 h before bedtime.
[b] Not yet approved for label use in children.

Extra therapy-resistant children

There will always remain a group of children who wet their beds despite correctly using all available first-, second-, and third-line therapies. There are no securely evidence-supported therapies in this group but some experience-based suggestions may be made.

First, and most importantly, a first-line therapy that did not work previously may function after an interval of a few years. The relative importance of the various pathogenetic mechanisms may change over time. This is especially true for the enuresis alarm, which, sooner or later, can be expected to make the child dry.

Second, nocturnal polyuria that is unresponsive to desmopressin may respond to salt reduction or combined diuretics in the morning and desmopressin in the evening (evidence level III) [76,77].

Third, specialists in the field may opt for individualized combination therapies including components such as desmopressin, the enuresis alarm, anticholinergics, mirabegron, or antidepressants. Also, alternatives to imipramine such as atomoxetine or reboxetine have been shown to have antienuretic effects (evidence level Ib) [78,79].

Fourth, severely therapy-resistant enuresis may at the discretion of the specialist become an indication for peripheral electrical stimulation or botulinum toxin injections into the detrusor (evidence level IV). These choices can be assumed to be most relevant if the enuresis is nonmonosymptomatic.

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