Evaluation of and Treatment for Monosymptomatic Enuresis: A Standardization Document From the International Children's Continence Society

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Purpose: We provide updated, clinically useful recommendations for treating children with monosymptomatic nocturnal enuresis.

Materials and Methods: Evidence was gathered from the literature and experience was gathered from the authors with priority given to evidence when present. The draft document was circulated among all members of the International Children's Continence Society as well as other relevant expert associations before completion.

Results: Available evidence suggests that children with monosymptomatic nocturnal enuresis could primarily be treated by a primary care physician or an adequately educated nurse. The mainstays of primary evaluation are a proper history and a voiding chart. The mainstays of primary therapy are bladder advice, the enuresis alarm and/or desmopressin. Therapy resistant cases should be handled by a specialist doctor. Among the recommended second line therapies are anticholinergics and in select cases imipramine.

Conclusions: Enuresis in a child older than 5 years is not a trivial condition, and needs proper evaluation and treatment. This requires time but usually does not demand costly or invasive procedures.

Key Words: urinary bladder; nocturnal enuresis; reference standards; societies, medical; child

Abbreviations and Acronyms

ICCS = International Children's Continence Society
MNE = monosymptomatic NE
NE = nocturnal enuresis
NMNE = nonmonosymptomatic NE
UTI = urinary tract infection

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See Editorial on page 425.

SCOPE OF THE DOCUMENT

THIS document represents the ICCS recommendations on treatment in children with MNE. By MNE we mean "enuresis in children without any other lower urinary tract symptoms," in accordance with ICCS terminology.[1] Although the focus of the article is children, we believe that it will also be useful when dealing with adults.

The document is intended to be clinically useful for primary, secondary and tertiary care. We present not only the optimal, recommended strategy but also the minimal requirements for the health care provider with limited resources and time.

The purpose is not to provide detailed discussions on pathogenesis or epidemiology. Likewise management of NMNE is outside the scope of this document. However, there is a large gray zone between MNE and NMNE. After thorough evaluation many chil-

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dren assumed to have MNE are found to have NMNE. Furthermore, the pathogenesis overlaps between the 2 conditions. Thus, evaluation of and treatment for the 2 entities have many similarities.

The text is not a formal systematic review of evidence-based medicine. Evidence in this field of knowledge is quite weak. However, we present what evidence there is.

The document was produced on the initiative of the ICCS Board. Before finalization a draft document was circulated among all ICCS members as well as experts from other relevant associations, including the American Association of Pediatrics Section on Urology and the European Society for Pediatric Urology.

BACKGROUND

Although views are conflicting regarding how many children with enuresis are truly monosymptomatic, we suspect that they represent less than half of all bed wetting children. Modern research has established 3 major pathogenetic mechanisms as crucial, including nocturnal polyuria, detrusor overactivity and an increased arousal threshold. The Aarhus group found in the 1980s that many children with enuresis lack the normal nocturnal increase in vasopressin secretion and, thus, have exaggerated urine production.[2] Later research showed that, although nocturnal polyuria is common in children with MNE,[3] not all of them have polyuria[4] and not all patients with polyuria have vasopressin deficiency.[5] In some bed wetting children nocturnal detrusor overactivity has been detected.[6] Since neither the polyuria mechanism nor nocturnal detrusor overactivity explains why the children do not awaken, sleep mechanisms must also be involved.[7]

Comorbid conditions often have a central role in the pathogenesis and potential therapy resistance of enuresis. Paramount among these conditions are constipation[8] and neuropsychiatric disorders, such as attention deficit hyperactivity disorder.[9] These 2 conditions may decrease the chance of successful therapy.

Although enuresis tends to disappear spontaneously as the child grows, a significant proportion of patients continues to wet the beds into adolescence or adulthood.[10] The impact of enuresis on affected children is mainly psychological and may be severe.[11] This makes treatment not only justified but mandatory.

PRIMARY EVALUATION

General

The first health care professional to meet the child with enuresis may be a general practitioner, a pediatrician, a pediatric urologist, a urotherapist or a school nurse. They are all adequate and what is important is their experience and commitment. A minimal primary evaluation should make the health care provider able to 1) identify the child who has enuresis secondary to underlying medical conditions, 2) identify the child who for other reasons needs further examinations, 3) identify the child with relevant comorbid conditions and 4) start adequate first line treatment after excluding points 1 to 3.

History

A good case history is the cornerstone of the evaluation. No amount of expensive examinations can substitute for a poor history. Much of the history should focus on voiding habits. We must ask specifically about symptoms such as urgency, holding maneuvers (standing on tiptoe, pressing the heel into the perineum etc), interrupted micturition, a weak stream and the need to use abdominal pressure to pass urine. Current or previous daytime incontinence must be asked about and, if present, described. How often does it happen and in which situations? We also must know how often the child voids during normal days but for this the completion of a frequency-volume chart, as described, provides much more reliable data than family recollection. The family should also be asked whether the child has had any UTIs.

Concomitant daytime bladder symptoms means that the child has NMNE, which strictly speaking is not dealt with in this document. It is important to distinguish bed wetters who only have urgency, decreased/increased voiding frequency or moderate intermittent daytime incontinence from those who void with a weak stream, must use abdominal pressure or have continuous incontinence. The latter children must be sent to a specialized center without delay.

We obviously must know more about bed wetting as such. How often does it occur, every night or only sporadically? Has the child always been wetting? Does the child also have nocturia? Frequent bed wetting is a poor prognostic sign[12] but nocturia indicates that the child is not extremely difficult to arouse from sleep. Somatic and psychological comorbid conditions are more common in children who were previously dry than in those with primary MNE.[13,14]

Since bladder and bowel function are closely interrelated, questions on bowel habits should also be posed. If concomitant constipation is not treated first, it may be difficult to get the child dry. If the child has bowel movements every second day or less often, or stool consistency is usually hard, constipation is probable.[15] Fecal incontinence is also com-

mon in constipated children and it should specifically be asked about. Questions should be directed to the child and not just the parent.

Some questions on general health and development are indicated. Has the child lately become tired or lost weight? The main reason for these questions is that children with kidney disease or diabetes must be detected. A good pediatric history also includes prenatal and perinatal data.

An estimation of fluid intake is needed for 2 reasons. Children with polyuria due to diabetes or kidney disease obviously need further investigation and desmopressin therapy may be dangerous in children with habitual polydipsia. The best estimation of fluid intake is made with a bladder diary.

Obviously we must know about which strategies the family has used to treat or cope with enuresis. Do the parents routinely wake the child at night or has evening fluid intake been decreased? If alarm or pharmacological treatment has been tried without success, we must know whether these therapies were used in the correct way, especially the alarm.

To not miss a child with a significant psychiatric comorbidity at least some general questions on the behavior of the child must be asked. An alternative is to provide the parents with a screening questionnaire.[16] It is also useful to ask the child whether he or she considers the bed wetting a big problem. We must estimate the motivation of the child and the caregivers. The child with concomitant attention deficit hyperactivity disorder may need psychiatric treatment in parallel with anti-enuretic therapy but the child who does not feel bothered by bed wetting may not comply with treatment. When there is secondary enuresis, we may also ask the parents whether the recurrence of wetting coincided with any major family event.

The presence or absence of heavy snoring and/or nocturnal sleep apnea in a bed wetter can be relevant information since some become dry after upper airway obstruction is relieved.[17]

So far it is clear that the initial consultation may take some time. However, it is time well spent and followup visits may then be much shorter. We realize that some health care providers will never have so much time. For their benefit we provide a simplified scheme on the ICCS website (http://www.i-c-c-s.org).

Physical Examination and Other Primary Examinations

Physical examination in a child with MNE is usually normal. On the other hand, alarming symptoms such as a weak stream or severe/continuous incontinence definitely call for a thorough somatic examination. Opinions differ on the feasibility of rectal/genital examination. It should only be done when the child and family are comfortable with the procedures. If the history is suspicious for constipation, rectal palpation is useful since formed feces in the rectal ampulla strongly support the diagnosis. At least rapid examination of the back and external genitals is mandatory in all children with a history of UTI or NMNE.

The sole obligatory laboratory test in children with MNE is a urine dipstick test. Glycosuria means that diabetes mellitus must be immediately excluded and proteinuria in repeat samples should prompt investigations for kidney disease.

Enuresis per se is not an indication for blood tests. Likewise routine ultrasound of the kidneys and upper urinary tract is not warranted. However, at centers where there is experience with ultrasound measurement of bladder wall thickness this parameter can be assessed at this stage to provide a useful prognostic indicator.[18]

Completion of a frequency-volume chart or bladder diary is recommended for several reasons. 1) It provides objective data that may support the history. 2) It helps detect children with NMNE. 3) It provides prognostic information. 4) It detects children who require extra evaluation. 5) It detects children with polydipsia. 6) It detects families with low adherence to instructions from health care providers. In a good frequency-volume chart fluid intake and voided volume should be measured for at least 2 days, and enuresis, daytime incontinence, other bladder related symptoms and bowel movements should be noted for at least 1 week.

At many centers nocturnal urine production is also assessed at this early stage by weighing diapers since nocturnal polyuria indicates that desmopressin treatment would probably be successful.[3] Two frequency-volume charts are provided at the ICCS website.

TREATMENT

While general advice should be given to all bed wetting children, active treatment should usually not be started before age 6 years. Moderate learning disability is no contraindication to treatment.

General Lifestyle Advice

Evidence for the beneficial effects of general advice is experience based (grade IV evidence) unless otherwise stated. The family should be instructed on normal bladder function and the pathogenesis of enuresis. An individualized program with a series of realistic goals between appointments and monthly followup to sustain motivation improves the outcome.

It may be wise to instruct the family to keep a calendar of dry and wet nights. This provides a

baseline to judge the effect of therapeutic interventions and has an independent therapeutic effect (grade Ib evidence).[19]

Children with NE should be counseled to void regularly during the day, and always at bedtime and on awakening. It is usually prudent to ask the child to void in the morning, at least twice during the school day, after school, at dinner time and just before turning out the lights and going to sleep. Children who prefer to sit to void should be counseled on the optimal posture to relax the pelvic floor muscles.

Nocturnal polyuria should be treated with an approach that minimizes evening fluid and solute intake but is flexible enough to allow participation in social and sports activities. Liberal water and solute intake during the day is recommended, especially during the morning and early afternoon hours.

If there is any sign of constipation, this should be treated. The goal is to have a soft movement passed without discomfort every day, preferably after breakfast. The need to choose foods that soften the stool should be discussed. A stool softener such as polyethylene glycol helps children optimally empty the bowel (grade Ia evidence).[20] Physical activity should be encouraged.

If the parents have the habit of waking the child at night to go to the toilet, they should be informed that this is allowed but not needed and would only help for that specific night, if at all.

All families must know that the bed wetting is the fault of neither the child nor the parents. The physician or nurse should encourage the child to lead a normal life despite the condition and promise the child that we will not give up until he or she is dry. The child also must know that enuresis is a common condition.

The Alarm

Alarm therapy results in dryness in about two-thirds of children (grade Ia evidence).[21] It is presumed to cure NE due to conditioning effects on arousal[22] and/or by increasing nocturnal bladder reservoir function.[23] Alarm therapy should be considered in every child with NE but especially in those with well motivated parents. Moderate intellectual impairment is not a contraindication.

We believe that parental assistance is important for successful alarm therapy. The child should awaken to the alarm, void in the toilet and reattach the alarm. A parent or caregiver should attend the child each time to ensure that the child does not merely turn the alarm off and fall back asleep. Consistency is crucial and the alarm should be used every night.

We recommend an appointment on the day that the alarm is started to review technical aspects and then early followup after 2 to 3 weeks with at least a telephone call to provide encouragement. The therapy requires a minimum 2 to 3-month trial. If after this time no positive effect is seen, treatment should be stopped. Otherwise it should be continued until at least 14 consecutive dry nights are achieved.

Relapses occur after successful therapy but often respond to another course of alarm therapy. Overlearning can help a child decrease the risk of relapse (grade Ib evidence). After a child attains dryness, he or she is instructed to drink a modest extra amount of water an hour before bed. If the child remains dry after a month of overlearning, the alarm may be discontinued.[24] The combination of alarm treatment and desmopressin is often advocated but evidence is conflicting.[25,26]

Desmopressin

The antidiuretic vasopressin analogue desmopressin is also an evidence-based therapy (grade Ia evidence).[27] As an estimate, 30% of children with enuresis are full responders and 40% have a partial response. The curative potential is low. Desmopressin is available as oral tablets, a rapidly melting oral lyophilisate that is not yet available in the United States and a nasal spray but use of the latter is discouraged.

Obviously the antidiuretic activity of desmopressin can be suspected to be a cause of its beneficial effect in enuresis cases and indeed nocturnal polyuria is a positive predictor of the therapeutic response.[3] Central nervous system effects may be an additional anti-enuretic mechanism.[28]

Desmopressin is most efficient in children with nocturnal polyuria (nocturnal urine production greater than 130% of expected bladder capacity for age) and normal bladder reservoir function (maximum voided volume greater than 70% of expected bladder capacity for age).[3,29] Other children who are likely candidates for desmopressin treatment are those in whom alarm therapy has failed or those considered unlikely to comply with alarm therapy.

Overall desmopressin is a safe drug with few side effects and low risks even when used for several years. There is a single safety concern. If combined with an excessive fluid intake, desmopressin can cause water intoxication with hyponatremia and convulsions. Recent reports suggest that the risk of this complication is higher when the nasal spray is used.[30] Consequently the enuresis indication has been removed for the nasal spray in many countries. Thus, oral formulations are preferred and polydipsia is a contraindication to desmopressin treatment. If the family needs a general recommendation about fluid intake, a good rule of thumb is that an evening intake of 200 ml (6 ounces) or less and then no drinking until morning is well on the safe side.

Desmopressin tablets should be taken at least 1 hour before going to sleep since the maximum renal concentrating effect and minimal diuresis is attained after 1 to 2 hours.[31] Oral melt tablets should be taken 30 to 60 minutes before bedtime. The ordinary dose of the tablets and the melt formulation is 0.2 to 0.4 mg and 120 to 240 μg, respectively. This dose is not influenced by body weight or age, and the prescribing physician may choose to start with the higher dose and taper down in cases of good effect or use the opposite strategy. The anti-enuretic effect is seen immediately. If there is a positive effect, it is up to the family to choose between daily medication or desmopressin administration before important nights only. If the family chooses the former strategy, it is important to have regular short drug holidays to assess whether medication is still needed.

Anticholinergics

The anticholinergic drugs with reasonable documentation of efficacy and safety in childhood are oxybutynin, tolterodine and propiverine. Not all of them are available in all countries. None can as yet be considered evidence-based first line therapy for nocturnal enuresis but they suppress detrusor overactivity, which may be present even in children with MNE.[6] Several open, nonrandomized studies indicated beneficial effects in therapy resistant children with enuresis,[32,33] which has now been corroborated by a recent, randomized, placebo controlled study (grade Ib evidence).[34]

Several things should be taken into account before considering anticholinergic treatment. 1) Since the purpose of medication is to decrease detrusor overactivity, nonpharmacological methods to attain this goal should be tried first, ie the institution of sound, regular voiding habits. 2) Exclude or treat constipation. 3) Exclude post-void residual urine, dysfunctional voiding or low voiding frequency. This means that a frequency-volume chart must be completed and uroflowmetry with ultrasound measurement of post-void residual urine must be performed.

Anticholinergics are only indicated in children with enuresis in whom standard treatment has failed. Our experience is that the drugs are useful in approximately 40% of these children and often combination treatment with desmopressin at a standard dose is needed.[32] The usual dose is 2 mg tolterodine, 5 mg oxybutynin or 0.4 mg/kg propiverine at bedtime but this dose may need to be doubled. The anti-enuretic effect should appear within a maximum of 2 months and sometimes much earlier.

The most bothersome side effect is constipation, which may be heralded by a slowly decreasing anti-enuretic effect, while the greatest danger is that post-void residual urine may cause UTIs. Thus, the child must maintain sound voiding habits and the family must react if the child has dysuria or unexplained fever. There is also the risk of mood changes but this side effect seems to be uncommon when alternatives other than oxybutynin are chosen.[35] Furthermore, since anticholinergic drugs decrease saliva secretion, the child should be instructed to maintain good oral hygiene. If there is a good therapeutic response, we recommend that drug withdrawal be attempted regularly, approximately every 3 months.

Tricyclic Antidepressants

The tricyclic antidepressant imipramine was previously frequently used for enuresis and many randomized studies show that it is better than placebo (grade Ia evidence).[36] Approximately 50% of unselected children with enuresis respond to the drug and the response rate seems to be the same in children with therapy resistant enuresis.[37]

Due to safety concerns and side effects imipramine is only relevant as third line therapy at tertiary care facilities. Another situation in which imipramine may be used is in children in whom the alarm has failed and whose families cannot afford desmopressin. The anti-enuretic dose is 25 to 50 mg at bedtime with the larger dose given to children older than 9 years. The effect is evaluated after 1 month. When there is a partial response desmopressin at the standard dose may be added, provided that the fluid intake of the child is restricted during the evening and night.[37] If treatment is successful, the family should taper to the lowest effective dose and ensure that regular drug holidays of at least 2 weeks are interspersed every third month or so to decrease the risk of tolerance, which otherwise is quite high.[37] The purpose of drug holidays for imipramine is different than that for desmopressin.

The central problem with imipramine is that it is potentially cardiotoxic and an overdose may prove fatal.[38] The drug should be kept securely locked and out of reach of smaller siblings. If there is any history of palpitations or syncope in the child, or any sudden cardiac death or unstable arrhythmia in the family, long QT syndrome must be excluded by prolonged electrocardiogram recording before imipramine treatment is considered.

Although other side effects are not dangerous, they are also problematic, including mood changes, nausea or insomnia.[36] These problems often appear earlier than the beneficial effects. Moderate side effects often gradually disappear even if treatment is continued.

Other Therapies

In 1 or a few studies numerous other therapies have shown positive effects but many of these trials were done in poorly selected or poorly defined patient groups. If more evidence is gathered, the therapies

that may find a place among recommended treatment modalities are acupuncture (grade IIb evidence),[39,40] urotherapy (grade III evidence),[41,42] diet treatment for hypercalciuria (grade IV evidence),[43] combined diuretic-antidiuretic treatment (grade IV evidence)[44] and noncardiotoxic alternatives to imipramine (grade IV evidence).[45]

RECOMMENDED TREATMENT STRATEGY

Therapy in Uncomplicated Cases

Besides general advice, there are currently 2 valid first line therapies, including the enuresis alarm and desmopressin. They are fairly efficient but patients and families differ on which should be tried first. The alarm is best for well motivated families and for children without polyuria but with low voided volume. Desmopressin is best suited for children with nocturnal polyuria and normal bladder reservoir function,[3] and for families in whom alarm treatment has failed or who have refused alarm treatment.

Thus, we may chose between 2 strategies, including 1) present the pros and cons of the alarm and desmopressin, and let the family chose between them or 2) have the family complete a frequency-volume chart with diurnal/nocturnal urine measurements, recommend desmopressin in children with nocturnal polyuria and normal voided volume, and provide the other families with an enuresis alarm. Children in whom 1 first line alternative has failed should be offered the other and vice versa.

Evaluation and Treatment in Therapy Resistant Children

Children with enuresis who are nonresponders to the 2 first line therapies deserve further evaluation. Many of these children have NMNE due to increased voiding frequency, daytime incontinence, urgency or other symptoms and, thus, they are outside the scope of this document. However, some of them are certainly monosymptomatic. Some therapy resistant children may not have used the first line therapy correctly. Therefore, it is important to ask the family about how the alarm was used.

In therapy resistant children the completion of a frequency-volume chart is mandatory if it has not already been done. We also recommend that nocturnal/diurnal urine production be measured and occult constipation be excluded. It is also prudent to perform ultrasound since increased bladder wall thickness indicates probable underlying detrusor overactivity and rectal distention is obviously a sign of constipation.[18] It should also be kept in mind that the reason for therapy resistance may be concomitant psychiatric disorders so that many of these children need psychological screening.

Pending further research the next therapeutic attempt in these children should be anticholinergics, provided that constipation is excluded or treated and no contraindications apply. The drug may need to be combined with desmopressin. If this is not successful, imipramine treatment may be warranted, provided that all safety issues are addressed.

It should be kept in mind that therapy resistant children benefit from regular new attempts with the enuresis alarm. The fact that it did not work 2 years ago does not mean that it will not work now. When new alarm treatment attempts are made, adding desmopressin may be beneficial, at least if the child has nocturnal polyuria.[46]

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