

REVIEW ARTICLE

Practical recommendations of the EAU-ESPU guidelines committee for monosymptomatic enuresis—Bedwetting

Guy Bogaert MD, PhD¹  | Raimund Stein MD, PhD²  | Shabnam Undre MD³ |
 Rien J. M. Nijman MD, PhD⁴ | Josine Quadackers MD⁴ | Lisette 't Hoen MD⁵ |
 Radim Kocvara MD, PhD⁶ | Selcuk Silay MD⁷  | Serdar Tekgul MD, PhD⁸  |
 Christian Radmayr MD, PhD⁹ | Hasan Serkan Dogan MD⁸ 

¹Department of Urology, University of Leuven, Leuven, Belgium

²Department of Pediatric, Adolescent and Reconstructive Urology, Medical Faculty Mannheim, University of Medical Center Mannheim, Heidelberg University, Mannheim, Germany

³Department of Pediatric and Adult Urology, East and North Herts NHS Trust, Stevenage, UK

⁴Department of Urology and Pediatric Urology, University Medical Centre Groningen, Groningen, The Netherlands

⁵Department of Urology, Erasmus University Medical Center, Rotterdam, The Netherlands

⁶Department of Urology, First Faculty of Medicine in Praha, General Teaching Hospital, Charles University, Prague, Czech Republic

⁷Division of Pediatric Urology, Department of Urology, Istanbul Medeniyet University, Istanbul, Turkey

⁸Division of Pediatric Urology, Department of Urology, Hacettepe University, Ankara, Turkey

⁹Department of Urology, Medical University of Innsbruck, Innsbruck, Austria

Correspondence

Guy Bogaert, MD, PhD, Department of Urology, University of Leuven, KU Leuven, 49 Herestraat, B-3000 Leuven, Belgium.

Email: guy.bogaert@uzleuven.be

Abstract

Background and Aims: The objective of this update of the EAU-ESPU guidelines recommendations for nocturnal enuresis was to review the recent published literature of studies, reviews, guidelines regarding the etiology, diagnosis and treatment options of nocturnal enuresis and transform the information into a practical recommendation strategy for the general practitioner, pediatrician, pediatric urologist and urologist.

Material and Methods: Since 2012 a monthly literature search using Scopus® was performed and the relevant literature was reviewed and prospectively registered on the European Urology bedwetting enuresis resource center (<http://bedwetting.europeanurology.com/>). In addition, guideline papers and statements of the European Society for Paediatric Urology (ESPU), the European Association of Urology (EAU), the National Institute for Health and Care Excellence (NICE) and the International Children Continence Society (ICCS) were used to update the knowledge and evidence resulting in this practical recommendation strategy. Recommendations have been discussed and agreed within the working group of the EAU-ESPU guidelines committee members.

Results: The recommendations focus to place the child and his family in a control position. Pragmatic analysis is made of the bedwetting problem by collecting voiding and drinking habits during the day, measuring nighttime urine production and identification of possible risk factors such as high-volume evening drinking, nighttime overactive bladder, behavioral or psychological problems or sleep disordered breathing. A questionnaire will help to identify those risk factors.

Conclusion: Motivation of the child is important for success. Continuous involvement of the child and the family in the treatment will improve treatment compliance, success and patient satisfaction.

KEYWORDS

bedwetting, guidelines, monosymptomatic enuresis, practical recommendations

Abbreviations: EAU, the European Association of Urology; ESPU, European Society for Paediatric Urology; UTI, urinary tract infections.

1 | INTRODUCTION

Monosymptomatic nocturnal enuresis (NE) is involuntary voiding of urine during sleep, in children over 5 years of age in the absence of congenital or acquired defects of the urological or central nervous system and without day-time voiding symptoms. Nonmonosymptomatic NE is defined as NE with day-time lower urinary tract symptoms, recurrent urinary tract infections (UTIs), and/or bowel dysfunction.¹ The term “secondary nocturnal enuresis” is used when a child or adult begins wetting again after having stayed dry for more than 6 months (this time period is opinion based).

Higher than normal night-time arousal is mandatory in NE.²⁻⁴ Other important factors are either a high night-time urine output or a low night-time bladder capacity or increased night-time overactive bladder, or a combination.

Monosymptomatic NE has a high prevalence in children, 5% to 10% at 7 years, and 1% to 2% in adolescents with a spontaneous yearly resolution rate of 15% in all ages.^{5,6} There is a clear hereditary factor in NE.² The incidence of NE is around 15% if none of the parents or their immediate relatives have suffered from NE, around 44%, if one of the parents or their immediate relatives have suffered from NE and could be up to 77% if both parents have a positive history. There is also a gender difference: male to female ratio of 2:1 at any age.⁷

NE has secondary stressful consequences for the child and their parents or caretakers, such as feelings of embarrassment, shame, guilt, loss of self-esteem, and it could create a sense of helplessness. It is important to identify associated comorbid problems (such as attention deficit hyperactivity disorder), to inform the children and their parents about possible treatments for these issues and advise them accordingly depending on the child's mental status, the family expectations, eventual social issues, and cultural background. It is known that the quality of life of mothers will improve after successful treatment of their child.⁸

The present manuscript aimed to develop a structured practical approach to this common and multifactorial condition with the help of available evidence in the literature.

2 | METHODOLOGY, LITERATURE SEARCH, CREATION OF RECOMMENDATIONS, AND SYNTHESIS

Since 2012, a monthly literature search using Scopus was performed by one of the authors. The relevant literature was reviewed and prospectively registered on the European Urology bedwetting enuresis

resource center (<http://bedwetting.europeanurology.com/>). In addition, guideline papers and statements of the European Society for Paediatric Urology, the European Association of Urology, the National Institute for Health and Care Excellence, and the International Children Continence Society were used to update the knowledge and evidence resulting in this practical recommendation strategy.

3 | DIAGNOSTIC EVALUATION

When children and their parents present with the symptom of NE, it is important to gain an objective view from a focused checklist, a 2-whole-day voiding and drinking diary as well as a 2-weeks measurement of the night-time urine production.

A checklist (Table 1) consisting of simple questions for parents has been developed to differentiate between monosymptomatic and nonmonosymptomatic NE. Questions focus on the history of UTIs, drinking and voiding habits such as urgency and frequency during the day. It also includes questions that investigate the motivation of the child and the social pressure of the condition. Any “yes” answer in this group of questions would direct us to evaluate the day-time incontinence conditions. Two questions will try to identify comorbidities such as sleep-disordered breathing or behavioral and psychiatric problems.

It is important for the child and their parents, as well as for the doctor to have objectively assessed the drinking and voiding habits of the child. This simple tool can diagnose aberrant drinking behaviors and correlate this with urine production. Urgency, frequency of voiding as well as voided volumes should be recorded. This information will help to educate the child and the family about renal and bladder physiology. It is known that the compliance of children or their parents to complete a drinking and voiding diary can be challenging. A minimum of 2 days has been shown to be sufficient to evaluate the average voiding volumes as well as the drinking habits.⁹

For a representative diagnostic view on night-time urine production, it is recommended to collect information for 2 weeks. Differences may be expected between the different days of the week due to social or sports activities. To improve compliance and accuracy parents can be asked to weigh the diapers, since this is easier than completing a voiding diary during the day.¹⁰ The first voided volume in the morning may differ from the average day time-voided volumes and needs to be added to the diaper weight for the complete night-time urine production. Diaper weight

TABLE 1 Pragmatic checklist allowing the doctor to differentiate monosymptomatic from nonmonosymptomatic nocturnal enuresis

	Yes	No
Social and motivation		
Did the child ask for medical help for the bedwetting problem?		
Has the child been bullied or punished because the bedwetting problem?		
Did the parents ask for medical help for the bedwetting problem?		
Monosymptomatic vs nonmonosymptomatic enuresis		
Does the child wet clothing during the day?		
Did the child have one or more proven UTI?		
Does the child void <3 times per day?		
Does the child void >8 times per day?		
Does the child have a prolonged voiding time or need to strain?		
Comorbidity		
Does the child have bowel problems (constipation or soiling)?		
Does the child drink a lot?		
Does the child snore or have sleep-disordered breathing?		
Does the child have behavioral or psychiatric problems at school or socially?		

Note: Checklist to measure motivation and social pressure, to differentiate between monosymptomatic vs nonmonosymptomatic NE, as well as to identify comorbid factors.

Abbreviations: NE, nocturnal enuresis; UTI, urinary tract infection.

over 130% of the age expected bladder capacity may be indicative of high night-time production vs a night-time overactive bladder. The expected bladder capacity is calculated as $(\text{age in years} + 1) \times 30 \text{ mL}$.¹¹ There are also other formulas, but this one has been the most recommended one. It should be emphasized that the expected bladder capacity is only a number and is different from voided volumes, that are recorded on the voiding charts. A child may not necessarily void when his or her bladder has reached full capacity. The severity of NE in number of wet nights per week has also been associated with lower and later spontaneous resolution.¹²

A physical examination should be performed with special attention to the external genitalia and surrounding skin as well as to the condition of the clothes (wet underwear or encopresis). Examination of the sacral skin and spine region for any sign of neurologic disorders must not be forgotten. Testing the grasp function of the toes is a simple neurological test for an intact S1 to S3 innervation.¹³ Measuring body height and body weight, calculation of the body mass index may detect any issue regarding failure to thrive, growth retardation, or the presence of obesity. There is no evidence to suggest obesity is associated with NE, however, obese children have a higher risk of sleep-disordered breathing and overactive bladder.^{14,15}

Urine analysis, dip stick, and microscopy is indicated if there is a sudden onset of NE, a suspicion or history of UTIs, or inexplicable polydipsia as in the sudden onset of diabetes mellitus type I. Uroflowmetry and renal ultrasound are only indicated if there is a sign of nonmonosymptomatic NE, such as a history of

previous urethral or bladder surgery, straining while voiding, interrupted voiding, an abnormally weak or strong stream or a voiding time of more than 20 seconds, or an inconclusive voiding diary.¹⁶ When readily available, a renal and bladder ultrasound is a noninvasive extension of the physical exam, and it may be used to exclude an anatomical problem of the kidneys, a thick bladder wall or distended rectum.

Due to higher than normal night-time arousal, the child with NE is able to continue to sleep in a wet bed, making this a unique feature. Recent studies have shown chronobiology of micturition in which the existence of a circadian clock in the kidney, brain, and bladder is suggested.¹⁷ A higher incidence of comorbidity and correlation between nocturnal urine production and sleep-disordered breathing, such as obstructive sleep apnea, has been found and investigated.¹⁸ Symptoms such as habitual snoring, apneas, excessive sweating at night, and mouth breathing in the history or via sleep questionnaires can lead to the diagnosis of adenotonsillar hypertrophy. However, looking at enuretic and nonenuretic children, the incidence of sleep-disordered breathing between both groups seems not to be different.¹⁹ If sleep-disordered breathing occurs, a referral to an ear-nose-throat specialist should be advised. It should be pointed out that, even if sleep-disordered breathing is diagnosed and treated, NE may persist and require additional treatment.²⁰

Mental health, behavioral or psychiatric problems are important comorbidity factors in NE.¹⁶ If there are additional comorbid factors of developmental, attention or learning difficulties, family problems, parental

distress, and possible punishment of the child, a referral to a psychologist could be advised and followed-up.^{21,22} It should be explained that in the event of behavioral or psychiatric problems, the success rate will be lower and the relapse rate higher so that the child and their family have realistic expectations of the treatment.² Adolescents and young adults with NE have a higher incidence of anxiety, depression, chronic fatigue, and lower self-esteem.²³ It is unknown if these conditions result from NE or make it worse.

4 | MANAGEMENT

Before introducing any form of treatment, it is important to educate the family and child, demystify the pathophysiology of NE, emphasize that a higher than normal night-time arousal is an elementary cause, and thereby clear any form of guilt. Also, highlight the fact that there are no simple solutions (Figure 1).^{24,25} Furthermore, elucidate that there certainly are options for the NE problem, but these will require an intense collaboration from the child, the family, and the doctor.²⁶ The decrease in prevalence is pronounced around 5 years of age and it is therefore advised to treat a child with NE from the age of 6 to 7 years onwards,^{27,28} especially if the child has the wish to become dry.

There may be several goals in the management of NE. It is important to identify the expectation of the family, to manage the perception of treatment outcome with regard to the reduction in number of wet nights. A reduction in wet nights may be a measurable

effect of the treatment. However, if a child is still wetting once a week, his or her perception would be they are still not dry. Sinha et al²⁹ have proposed a stepwise approach in the management: reduce the guilt, encourage hope, avoid a punitive response, raise awareness in the child, include the cooperation of the child to decrease the nocturnal urine ;production.²⁹

In Table 2 we have proposed a structured approach in the work-up of a child and his family with an NE problem. We have focused on the fact that the family is well informed, and the child is involved in the choice of eventual treatment choice. They should know that they can be guided throughout the treatment process until success is reached and that they can change their choice of treatment at any time, depending on their motivation.

4.1 | Supportive treatment measures

Initially, empathy along with an explanation about normal and regular eating, drinking, and voiding habits is necessary, stressing normal, not increased, fluid intake during the day and reducing fluid intake in the hours before sleep. From the Dortmund Nutritional and Anthropometric Longitudinal Designed study it was shown that a fluid intake to achieve an euhydration status is dependent on the energy used per 24 hours.³⁰ The mean 24 hours of water intake should range from 0.9 to 0.96 mL/kcal. Boys, aged between 4 and 7 years consume 1500 kcal/24 hours, boys between 7 and 10 years 1800 kcal/24 hours. Girls between 4 and 7 years consume 1300 kcal/24 hours and girls between 7 and 10 years 1650 kcal/24 hours. It is very difficult to impose children to drink more than they want. A recent review on water intake and hydration state in children, worldwide, has found that 60% of all children would not drink enough, which was assessed based on urine osmolality greater than 800 mmol/kg.³¹ In practice, this reflects a drinking volume of 30 to 40 mL/kg body weight and is considered average (normal). Basic bladder advice, combined with keeping a chart depicting wet and dry nights has not been shown to be successful in the early treatment for NE and this, therefore, is not encouraged as a form of treatment.^{32,33}

4.2 | Conservative wait and see approach

A “wait and see” approach can be chosen, when the child and the family are unable to comply with treatment, if the treatment options are not possible for

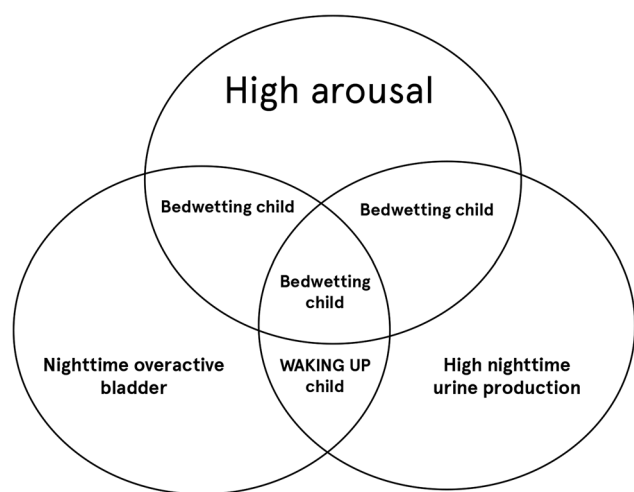
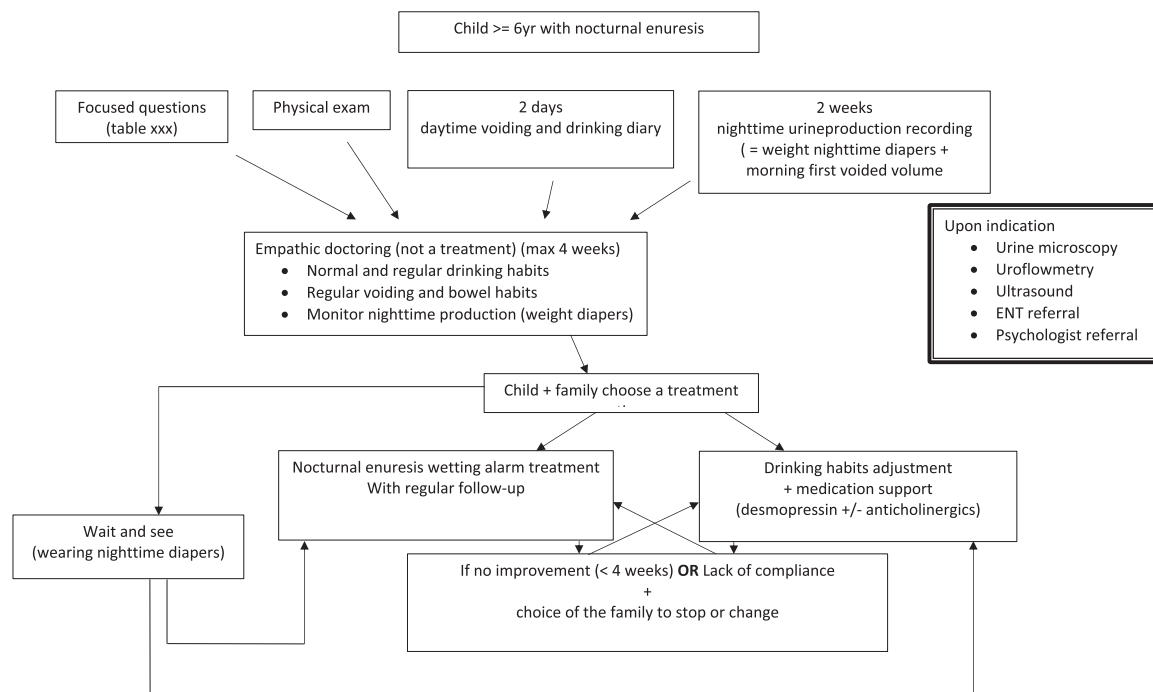


FIGURE 1 Elementary causes in the pathophysiology of nocturnal enuresis, in a child with a nocturnal enuresis problem

TABLE 2 Structured approach in the work-up of a child and his family with a nocturnal enuresis problem

Abbreviation: ENT, ear-nose-throat.

the family situation, and if there is no social pressure. However, the child should wear diapers at night to ensure a normal quality of sleep.³⁴ In addition, it is important to empathize with the child and the family that the quality of life of the parents with an enuretic child that is impaired and that it will improve if the child becomes dry.²²

4.3 | NE wetting alarm treatment

The night-time wetting alarm (the device that cause an acoustic sound or vibrating when becoming wet) treatment is a form of sleep conditioning. It attempts to influence the cycle of light sleep, deep sleep, and rapid eye movement sleep to change the arousal situation around the night-time voiding.³⁵ However, the change in arousal is not the only change that has been observed, as some studies have shown an increase in nocturnal functional bladder capacity, increase in vasopressin production as well as a positive behavioral effect, due to the use of the night-time alarm and waking up.⁵ The method of action is to modify the awakening, reform high arousal to low arousal, specifically when the status of a full bladder is reached. It is of utmost importance that the child is able and willing to collaborate. Initial success rates of 80% are realistic, with low relapse rates,

especially when night-time diuresis is not too high and bladder capacity is not too low.³⁶ Regular follow-up accompanying the progression of the treatment will improve the success.³⁷

Few studies have focused on the effect of the environmental temperature or the seasonal effects, however, it has been suggested that the winter season is associated with a lower success rate of the alarm treatment for NE.³⁸

It is important that the child and the family understand the method of action of the night-time wetting alarm treatment and that they choose this method of treatment themselves.⁵ On questioning the child and the family, it is unsurprising that 10% to 30% of the children withdraw or will fail to comply if this form of treatment was imposed rather than selected.³⁹ In addition, adults who used a night-time wetting alarm during their childhood report that this was the worst time of their lives, even if they were cured by the alarm.⁴⁰

4.4 | Adjustment of drinking habits in combination with medication support

The cornerstone in the medical management option is the children adjusting their drinking habits. The child

should be able to drink sufficient in the morning and during the day and being able to reduce the intake in the early evenings, especially when considering prescription of desmopressin, a synthetic antidiuretic agent.⁴¹ The child should be able to understand the balance between drinking and making urine and should be motivated to make an effort themselves.²⁶ The effect of the pragmatic approach of fluid restriction and on avoiding caffeinated beverages has never been studied.⁴²

Supervision of this compliance should be performed by continuously monitoring the weight of the diapers and the first morning-voided volume until success is achieved. In the case of high night-time diuresis, success rates of 70% can be obtained with additional antidiuretic medication such as desmopressin, D-amino D-arginine vasopressin (DDAVP), either as tablets (200-400 µg), or as sublingual DDAVP oral lyophilisate (120-240 µg). A nasal spray is no longer recommended due to the increased risk of overdose.⁴³ Relapse rates can be high after desmopressin (DDAVP) discontinuation, however, a recent meta-analysis study has shown that structured withdrawal results in better relapse-free rates.⁴⁴ Specifically, a dose-dependent structured withdrawal strategy has shown improved success rates.

Few studies have examined the eventual positive predictive factors for a desmopressin treatment predicting a higher success rate, however, it seems that older children, fewer number of wet nights per week, and nocturnal polyuria would be associated with a higher desmopressin response.⁴⁵ A higher (relative to the day time) night-time plasma copeptin level would predict a better desmopressin treatment outcome.⁴⁶

In the event of insufficient desmopressin response or if a night-time overactive bladder is suspected, as calculated from the 2-week measurement of the night-time urine production by weighing the diapers and added with the first time morning-voided volume, combination treatment with desmopressin and an anticholinergic medication will result in a higher success rate.⁴⁷⁻⁴⁹ Imipramine; a tricyclic antidepressive drug, has been used in the past extensively as a possible treatment for NE. A recent Cochrane review has concluded that imipramine is effective in reducing the number of wet nights per week, however, there is a lack of sustained effect after stopping the medication.⁵⁰ In addition, it was found that the night-time alarm treatment, compared with imipramine, had better short- and long-term effects.

Oxybutynin, as anticholinergic medication, in monotherapy has the same effect as placebo and is therefore not indicated as a single treatment in children with monosymptomatic NE.⁵¹

4.5 | Alternative treatment options for NE

A prospective, placebo-controlled randomized trial has shown that neurostimulation in the form of transcutaneous electrical nerve stimulation in children with monosymptomatic NE has no antienuretic effect and therefore the night-time urine production and the maximum voided volume remained unchanged.⁵²

Acupuncture, needle or laser, has been proposed in the treatment of NE, however, the conclusion from a Cochrane review and a recent systematic review and meta-analysis is that it is a safe but inefficient treatment.^{53,54} Hypnosis, chiropractic treatment, and medicinal herbs have been reported, however, the studies have always been single small trials, some even of dubious methodology and none in comparison with the established and recognized treatments using desmopressin or the alarm.⁵⁴

4.6 | Specific suggestions for adolescents and young adults with NE

In general, the same identical approach and treatment options are given to adolescents and young adults, however, specific lifestyle adjustments, such as the avoidance of caffeine and sedative use are emphasized upon as this can influence the sleep cycle.²³ In addition, if obesity is one of the comorbidities, this could cause sleep apnea episodes during the night resulting in a higher night-time urine production.

5 | CONCLUSIONS

We have provided a pragmatic evidence-based approach to the diagnosis and management of NE (Table 2). This algorithm focuses on collecting day-time voiding and drinking habits, measuring night-time urine production, and identification of possible risk factors such as high-volume evening drinking, night-time overactive bladder, behavioral or psychological problems, or sleep-disordered breathing. Using this information when managing the patient and parent, as well as emphasizing the importance of continuous cooperation and motivation to ensure successful outcomes, is essential. Patient and parent expectations need to be managed and treatment tailored to each child based on the multimodality assessment and findings. The proposed focused questions (Table 1) can be asked at the time of intake clinical visit and will help to have an indication

for motivation, distinguish monosymptomatic from nonsymptomatic NE, and detection of possible comorbid factors. In addition, once the child and his family have chosen a specific treatment, regardless if it is an adjustment of drinking habits supported with medication or the night-time alarm treatment, a regular follow-up is required to maintain their motivation and increase the chance of a successful treatment outcome.³⁷

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ORCID

Guy Bogaert  <http://orcid.org/0000-0002-5989-1253>
 Raimund Stein  <http://orcid.org/0000-0002-3217-5089>
 Selcuk Silay  <http://orcid.org/0000-0001-5091-9654>
 Serdar Tekgul  <http://orcid.org/0000-0002-3708-459X>
 Hasan Serkan Dogan  <http://orcid.org/0000-0002-1145-7343>

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