Current management of nocturnal enuresis
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Purpose of review
Nocturnal enuresis is an especially common problem with the potential to have an appreciable negative impact on the emotional health of a child.
Recent findings
Our understanding of the pathogenesis continues to improve. A disorder of sleep arousal, a low nocturnal bladder capacity, and nocturnal polyuria are the three factors that interrelate to cause nocturnal enuresis. Constipation is a very common and often unrecognized factor that appreciably affects bladder function.
Summary
Successful treatment involves interventions that simultaneously improve these factors. Self-esteem improves with any form of therapy and dryness is possible for the majority of children.

Keywords
bedwetting alarm, behavioral therapy, bladder capacity, constipation, desmopressin, nocturnal enuresis, polyuria, sleep arousal

Introduction
Nocturnal enuresis has a very high prevalence in the preschool population and the prevalence slowly falls during childhood such that only 1–2% of adults continue to experience the problem [1–7,8•]. Treatment is important to minimize the negative impact on the emotional health of the child [9–11]. Treatment should not be deferred simply because the problem will likely resolve over time. Modern therapy results in resolution of the wetting in the majority of children, and a cure or effective control can be achieved in most children regardless of the age when treatment is initiated [1].

Definition
The International Children's Continence Society (ICCS) has published standards of terminology and definitions for the symptoms, investigative tools, diagnoses, and treatments pertinent to children with nocturnal enuresis and other forms of voiding dysfunction [12].

Nocturnal enuresis is traditionally subdivided into primary (PNE) and secondary (SNE) forms [13]. In a prospective study of 170 children with nocturnal enuresis assessed at a tertiary care pediatric center, the presentations of the patients with PNE and SNE were remarkably similar, which suggests that for the majority of patients with SNE, the pathogenesis is no different than that for PNE [14].

Nocturnal enuresis is also divided into monosymptomatic (MNE) and non-MNE forms. MNE is defined as present when the child does not have any associated daytime voiding symptoms such as frequency, urgency, or daytime incontinence [1,12,15,16]. When a meticulous history is obtained, the majority of children with nocturnal enuresis have at least subtle daytime voiding symptoms [14]. Therefore, according to how strictly a clinician defines daytime voiding symptoms, MNE is variably less common than non-MNE.

Prevalence
Bedwetting is a common problem throughout the world [2–7,8•]. Butler and Heron [8•] reported recent prevalence data based on the Avon Longitudinal Study of Parents and Children (ALSPAC). The ALSPAC is an ongoing study of 13 973 infants with an estimated date of delivery between 1 April 1991 and 31 December 1992. Questionnaires were obtained from the parents at 15, 24, 38, 54, 65, 78, 91, and 115 months of age. The authors reported on data obtained from questionnaires obtained at the latter five ages. Based on the Diagnostic and Statistical Manual of Mental Disorders (DMS)-IV definition of nocturnal enuresis as wetting at least twice a week, the age-related prevalence of bedwetting was 8.4, 6.0, 4.0, 2.6, and 1.5%, respectively. For infrequent bedwetting, which Butler and Heron defined as less than twice a week, the prevalence was 21.6, 16.2, 15.6, 12.8, and 8.2%, respectively. Infrequent bedwetting is therefore present

in about one in seven children in grade one, and in about one in 12 children in grade 4. In a grade one class of 25 children, there will be at least three children who wet the bed and in a similar-sized grade 4 class, there will be about two children.

Pathogenesis of nocturnal enuresis

The conventional paradigm for bedwetting presumes that three factors participate in the pathogenesis of nocturnal enuresis [1,15,16]. A disorder of sleep arousal is invariably present. The children do not wake up to the sensation of a full or contracting bladder. Nocturnal polyuria and a reduced nocturnal bladder capacity are the other two factors. Various clinical studies have tried to clarify the prevalence of these latter two factors in children with bedwetting [1,15,16]. A practical perspective is to presume that both factors are operative, and that at the moment of wetting, the amount of urine produced by the kidney was greater than the nocturnal bladder capacity.

Sleep arousal disorder

Parents are the first to suggest that this factor is fundamental to the wetting in their children and clinical studies support this perspective [17].

Nocturnal polyuria

The four factors that might contribute to nocturnal polyuria include the evening fluid intake, the evening solute intake, the daytime fluid and solute intake, and the nocturnal secretion of antidiuretic hormone (ADH) [1,15,16,18].

The evening fluid intake of a child is a basic and often poorly controlled factor. Many parents experiment with fluid restriction and when the wetting does not resolve, these parents presume fluid intake is not a factor, and allow surprisingly large fluid intakes in their child.

The evening solute intake is another factor. Many elementary aged children eat dinner within a few hours of an early bed time. Many children have a bedtime snack. Overnight, the kidney is obliged to process the evening solute intake and the excess solute will result in urine production.

Children with nocturnal enuresis might have an abnormal circadian rhythm with increased water and solute retention during the day and the reverse by night [19••,20,21••]. Many children with nocturnal enuresis do not drink appreciable amounts of fluid during the morning and afternoon, especially on school days.

A low nocturnal secretion of ADH is recognized as a possible cause of nocturnal polyuria [18].

The longer a child sleeps and the smaller the functional bladder capacity, the more likely that the nocturnal urine production will exceed the bladder capacity. A six-year-old child sleeps an average of about 10.75 h and has an expected functional bladder capacity of only 7 oz [1]. In lieu of the long sleep duration, small nocturnal bladder capacity, and propensity of kindergarten and elementary school-aged children to drink and snack in the evenings; it is remarkable that nocturnal enuresis is not even more prevalent.

Reduced nocturnal bladder capacity

The expected functional nocturnal bladder capacity increases from 6 oz at the age of 5 years to 11 oz at the age of 10 years [1,22]. Even a normal functional bladder capacity is therefore a limitation to dryness in kindergarten and early elementary-aged children. Any condition that further reduces bladder capacity would appreciably enhance the prevalence of bedwetting. The two most common conditions that reduce the expected functional bladder capacity are cystitis and constipation [23–26,27•]. Cystitis is more common in girls and relatively straightforward to identify with a urinalysis and urine culture. Constipation, however, is subtle and appreciably under-recognized as a factor. Many children with nocturnal enuresis have a bowel pattern that places them at risk for nocturnal enuresis but that does not conform to current definitions of constipation. When a liberal definition was used, abnormal bowel health was present in 75% of children with PNE and 58% of children with SNE [14].

O'Regan et al. [24] reported the association of constipation with bedwetting over 20 years ago. Loening-Baucke [27•] recently reported a retrospective review of 482, 4 to 17-year old children who attended a primary pediatric clinic. The prevalence rate of constipation was 22.6%. Urinary incontinence was significantly more commonly observed in the children with constipation. In an earlier study, Loening-Baucke [26] reported that relief of constipation resulted in disappearance of nocturnal enuresis in 63% of 41 patients.

Studies have not clarified precisely how constipation causes nocturnal enuresis. Presumably the physical presence of stool has a direct impact on the bladder capacity. The pelvic bones form a funnel and the bladder is located in the narrowest dependant portion. The volume of a child pelvis is small and the bladder cannot escape the impact of stool. Another theoretical possibility is that nocturnal colonic movement might stimulate a detrusor contraction.

Once a child leaves home in the morning to attend kindergarten or elementary school, a parent often loses touch with the bowel health of their child. McGrath et al. [28••] reported a prospective cross-sectional study of 277 children with nocturnal enuresis who were assessed

at a tertiary care pediatric service. These authors compared parental reporting of constipation with a clinician-based assessment. The prevalence reported by parents was 14.1% compared with a prevalence of 36.1% based on a clinical assessment. Direct questioning of the child offers better insight into bowel health than the observations of most parents. A stool calendar should be kept for 2–4 weeks to determine if bowel health is a factor.

Treatment

There is no one universally successful treatment for nocturnal enuresis. Successful treatment of nocturnal enuresis requires therapy directed simultaneously at each of the three pathophysiological causes of bedwetting [1,15,16].

Behavioral therapy

Behavioral therapy offers the potential to cure nocturnal enuresis without the need for a medication [29]. The fundamentals of behavioral therapy include achievement of good bladder and bowel health, improved arousal, and an optimal circadian rhythm of urine production. Successful behavioral therapy requires a supportive parent, a motivated child, patience, and an average of about 6 months of therapy. Compliance improves when parents and children have a good enough understanding of the problem such that the suggested behavioral modifications make sense. A program with personalized calendars of bladder and bowel parameters, a series of realistic goals between appointments, and monthly follow up to sustain motivation improves the outcome [29]. Behavioral therapy should be offered to every child with nocturnal enuresis. Behavioral therapy will increase the success rate of bedwetting alarm therapy or pharmacological therapy with desmopressin.

Good bladder health recommendations

Children with nocturnal enuresis benefit from counseling on good bladder health [29]. Children should be counseled to void regularly enough to avoid urgency and urgency incontinence. Children who void infrequently should be counseled to void at least once every 1.5–2 h. Many children do not void at all during school hours. A good rule is that children should void two or three times during school hours. Girls and boys who prefer to sit to void should be counseled on the optimal posture to relax the pelvic floor muscles to facilitate good emptying. Boys who stand to void should be counseled to pull their zipper or their pants down such that the penis is not bent during voiding.

Treatment of nocturnal polyuria

Nocturnal polyuria should be treated with a common sense approach that minimizes evening fluid and solute intake but is flexible enough to allow participation in social and sports activities. A liberal water intake during the day, especially during the morning and early afternoon hours at school, is recommended. On days when the ambient temperature is high the water intake should be increased to compensate for enhanced insensible water losses.

Desmopressin acetate reduces nocturnal polyuria and results in total dryness in up to 48% of children, but this therapy offers only a control rather than a cure of the nocturnal enuresis [30–34]. Desmopressin acetate is available in a new lyophylisate preparation as well as a tablet and an intranasal spray [35]. The new lyophylisate preparation is ideal for children who have difficulties swallowing a tablet and in a study by Lottman *et al.* [36•] was favored over the tablet by children under the age of 12 years. The only serious reported adverse event with desmopressin is water intoxication [37,38••]. This rare adverse event can be avoided by parent and patient education not to overdo fluids on the nights that the medication is taken. On evenings when desmopressin is taken, children should be instructed not to drink for the 2 h prior to bed. Dehoorne *et al.* [39] reported water intoxication due to a prolonged half life of desmopressin in patients treated with the intranasal formulation. A comparison of the reports of water intoxication in patients treated with the intranasal versus the oral preparations of desmopressin revealed that the spray is responsible for the majority of reported adverse events [38••]. As such, the intranasal formulation should not be prescribed [38••]. Vande Walle *et al.* [35] reported that the new lyophylisate (melt) has a shorter duration of pharmacodynamic action that approximates the typical amount of sleep for an elementary school-aged child, and as such is therefore a safer alternative. Desmopressin unresponsiveness suggests that the limiting factor might be a reduced nocturnal bladder capacity [40]. Raes *et al.* [41••], however, reported that persistent nocturnal polyuria is present in some children who do not respond to desmopressin. Increased nocturnal solute excretion is a possible factor [42]. Some patients initially respond to desmopressin but then fail to respond after variable periods of time. One theoretical explanation for this observation is the presence of an as yet unrecognized factor that overrides the action of ADH to prevent water intoxication [43].

Treatment of a reduced functional bladder capacity

Children with recurrent cystitis benefit from hygiene efforts to minimize colonization with enteric bacteria in the genital area. Children with persistently recurrent cystitis might benefit from short courses of preventive antibiotic therapy.

Constipation should be presumed present until a stool calendar confirms that the child has daily soft movements. Some children have daily movements but do not empty optimally and the retained stool can have a

negative impact on bladder capacity. The goal of therapy is good bowel health, which might be defined as a soft movement, with a diameter less than 2 or 3 cm, passed without discomfort every morning after breakfast and before the child leaves for school. Encouraging a movement before the child leaves for school prevents withholding during school hours. The need to drink a liberal amount of water, to avoid foods known to cause hard stool, and to choose foods that soften the stool, should be discussed. A stool softener such as polyethylene glycol will help children pick up on the signal of the need to defecate and to optimally empty [44]. The stool calendar should be maintained to follow the progress. Strategies to improve bowel emptying are important and include optimal posture to relax the pelvic floor muscles. Smaller children require an over-the-toilet seat and a footstool. Children should be counseled not to rush or push.

Pharmacological options to improve bladder capacity include antimuscarinic medications such as oxybutynin and tolteridine [45–48]. Behavioral therapy obviates the need for these medications in a substantial majority of children. These medications should not be prescribed without close and regular follow up to screen for constipation and increased postvoid residual volume, adverse events that will worsen nocturnal enuresis.

Bedwetting alarm therapy is reported to increase nocturnal bladder capacity [49–52].

Van Hoeck *et al.* [53[•]] reported that bladder holding exercises ('stretching') do not increase the response rate in children with monosymptomatic nocturnal enuresis. This therapy continues to be prescribed without any good evidence of efficacy in children and is not recommended.

Treatment of the disorder in sleep arousal
Alarm therapy is presumed to cure nocturnal enuresis courtesy of conditioning effects on arousal [54[•],55]. About a third of children successfully treated with alarm therapy substitute a pattern of nocturia for the wetting [56]. In this situation, presumably the disorder in sleep arousal is improved but the children still have a reduced nocturnal bladder capacity. About two-thirds of children successfully treated with alarm therapy sleep dry and do not have nocturia [56]. In this situation, one theoretical explanation is that these children might respond to the alarm with an arousal that is too brief to be recollected but sufficient to inhibit a detrusor contraction and prevent the wetting. Another explanation is that the improvement is related to an increase in bladder capacity and not to an effect on arousal.

Alarm therapy should be considered in every child with nocturnal enuresis. Success with alarm therapy is related to the motivation of the child and to the motivation of the parent who must participate in the therapy [54[•]]. A Cochrane review of 56 trials [57[•]] concluded that alarm therapy resulted in dryness in about two-thirds of children. Alarm therapy requires a minimum 3-month trial. The relapse rate is reported to vary from 4 to 55% [54[•]]. Relapse can be minimized with behavioral therapy prior to alarm therapy, by close follow up during therapy, and by 'overlearning', which involves slowly increasing the evening fluid intake in successfully treated patients while continuing to wear the alarm.

Treatment of children with attention deficit hyperactivity disorder and other learning or behavioral problems
Nocturnal enuresis is more common in children with attention deficit hyperactivity disorder and other learning and behavior problems [58–60]. Behavioral therapy is a greater challenge in some of these children but treatment success is possible with patience and regular follow up to provide encouragement [60].

Conclusion
Nocturnal enuresis is very common and has the potential for an appreciable negative emotional impact on affected children. Studies show improvement in self-esteem with all forms of treatment. Simultaneous strategies to improve arousal, to reduce nocturnal polyuria, and to increase functional bladder capacity can result in the resolution of nocturnal enuresis. Constipation is present in the majority of children with nocturnal enuresis and requires therapy. Behavioral therapy should be offered to all children with bedwetting. Bedwetting alarm therapy can cure nocturnal enuresis and should be considered in all children with the disorder. Desmopressin acetate offers an effective control of nocturnal enuresis and is now available in a melt preparation that offers an improved safety profile.

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