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# The fight for a dry night

*Studies on treatment, comorbidity and family  
experience of nocturnal enuresis*

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### **Abstract**

Borgstrom, M. 2025. The fight for a dry night. Studies on treatment, comorbidity and family experience of nocturnal enuresis. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 2211. 91 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-2664-1.

*Aim:* This thesis aimed to understand the importance of constipation therapy, basic bladder advice and/or the enuresis alarm in the first-line therapy of nocturnal enuresis, and how these treatments are experienced. The aim was also to find out whether children with enuresis are more likely to be constipated than others.

*Methods:* To provide more evidence for the efficacy, or non-efficacy, of basic bladder advice in enuresis a randomized controlled study was designed. A comparative study evaluated the antienuretic effect of fecal disimpaction in children with enuresis and concomitant constipation. A qualitative approach was used to study children's and their parents' experiences of labor-intensive procedures in the management of enuresis. Finally constipation in children with enuresis as compared to children without bladder problems were evaluated.

*Results:* No favorable effect of basic bladder advice as first-line treatment of enuresis was found. No significant reduction of wet nights per 14 days was noted with laxative treatment and when comparing to healthy controls, children with enuresis were not more constipated. However, children with enuresis showed indirect signs of overactive bladder since they had smaller voiding volumes than children without bladder related symptoms. For the first time, children with their parents were heard regarding management of the procedures related to enuresis therapy and it was experienced as challenging and difficult. However, strategies for managing and overcoming these difficulties were suggested by the participants.

*Conclusions:* Basic bladder advice lacks therapeutic effect in nocturnal enuresis and treatment of constipation is also, by itself, ineffective to get children dry at night. Overall, we found no support for a major link between constipation and enuresis. And since laxative therapy, bladder advice and the enuresis alarm were all found to be cumbersome by the children and their families we recommend that only the evidence-based procedure – i.e. the enuresis alarm – be used as a standard management of nocturnal enuresis. Furthermore, to adhere to treatment children with enuresis express that they need more support from their parents. The healthcare provider, in collaboration with the parents, needs to find options to suit the individual child.

*Keywords:* Nocturnal Enuresis, Constipation, Treatment, Basic Bladder Advice, Alarm, RCT, Interview

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*This thesis is dedicated to all children suffering from enuresis*



# List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I. Borgström, M., Bergsten, A., Tunebjer, M., Hedin Skogman, B., Nevéus, T. (2022). Daytime urotherapy in nocturnal enuresis: a randomised, controlled trial. *Arch Dis Child*, 107(6), 570-574\*
- II. Borgström, M., Bergsten, A., Tunebjer, M., Hedin Skogman, B., Nevéus, T. (2022). Fecal disimpaction in children with enuresis and constipation does not make them dry at night. *J Pediatr Urol*, 18(4), 446.e441-446.e447\*
- III. Borgström, M., Hjelm, K., Skogman, B. H., Nevéus, T., Tunebjer, M. (2024). Experiences of labor-intensive procedures in the management of nocturnal enuresis – An explorative interview study in children and parents. *PLoS One*, 19(12), e0314623\*
- IV. Borgström, M., Tunebjer, M., Hedin Skogman, B., Neveus, T. Children with enuresis – are they more constipated than others? (*manuscript*)

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# Abbreviations

ADHD	Attention-Deficit Hyperactivity Disorder
BBA	Basic Bladder Advice
DO	Detrusor Overactivity
ICCS	International Children's Continence Society
MNE	Monosymptomatic Nocturnal Enuresis
NMNE	Non-Monosymptomatic Nocturnal Enuresis
PEG	Polyethylene Glycol
RCT	Randomized Controlled Trial

# Prefase

I have always known that I was meant to work with children and started out as a “dagisfröken” (preschool teacher) — back in the days when it was still called “dagis” and we were called “fröken.” Later, as a recently graduated nurse I elbowed my way into the pediatric ward, (avdelning 34) — when it was difficult to get a position straight after graduation. From my very first day, I felt at home at the Pediatric Clinic in Falun. Today, I am a pediatric nurse working in the clinic with my own patients as a urotherapist.

The desire to help children feel better has always been there, and I cannot bear the thought of children suffering, regardless of the cause. My interest in the bladder and bowel began when I assisted with uroflowmetry measurements for physicians’ appointments. It was difficult to obtain accurate curves, and I discovered that most children were constipated, which interfered with the results. During these brief examinations, I quickly realized that children and their families did not know much about the bowel and bladder — and above all, they lacked someone to turn to for questions and guidance. The level of knowledge among the personnel was low both in primary care and at the pediatric clinic. I didn’t have any better knowledge either, but I was eager to learn.

I began reading literature and found a book that became my go-to reference: *Sängvätning och annan inkontinens hos barn* (Bedwetting and Other Incontinence in Children), edited by Sven Mattsson and Tryggve Nevéus. I also found excellent online guidelines for managing children’s bowel and bladder issues, published by the Swedish Enuresis Academy. I would have been astounded if anyone had told me that Tryggve would be my head supervisor, Sven would be my opponent when I would defend this thesis, and that I would eventually be elected as a board member of the Academy!

The most common phrase I’ve heard from parents over the years is: “Why has no one told us this before? Then we would have understood.” This often came from parents whose child had been prescribed constipation treatment without any explanation — leading them to stop the medication because “it didn’t help anyway...” My frustration over children with bladder issues — and especially constipation — not receiving the help they need has driven me to work hard. In the beginning, I saw as many children as I could fit into my schedule, which of course became unsustainable. But the upside was that I

gained a wealth of knowledge about the complex situations children and families face, and the importance of tailoring information, treatments, and follow-ups to everyone individually.

Through my urotherapy education, my knowledge of the bladder and bowel has deepened, and my interest has grown. The interest in science and pedagogy has driven my continued exploration of the subject. As my knowledge increased, so did my desire to educate others — because it became clear that no one had helped these children, even though they had struggled for years. This led to an invitation to write a handbook for the Child Health Care, which I accepted, hoping that children with bowel and bladder issues would receive help at a very early stage.

I was given the opportunity to join this research project, which offered further specialization, and I gladly accepted. The topic itself could have been anything — as long as I also had the chance to study constipation and interview children, which was very important to me.

I have personally met and examined every child in the study, and all data has been generated from these examinations or collected via registrations returned in prepaid envelopes. Some registrations were beautifully decorated by the children, and many bore traces of everyday life — coffee stains (I hope), and crumpled pages. I got to know some children well, as they turned out to be therapy-resistant, and a few are still in treatment today.

On the same day I was offered my doctoral position in Region Dalarna, my first grandchild was born. Ebba is now 7½ years old as my doctoral journey nears its end. My second grandchild Astrid is 5, and a third will be born this coming spring. What an incredible blessing! Throughout my PhD studies, spending time with them has been the perfect way to stay grounded in the present moment, offering deep restoration and energy. It's still unclear how, but I promise all children and parents that I will continue working to ensure they receive the best possible help — at the right time.

# Background

## The child with enuresis

Children who suffer from enuresis may experience a range of emotions and consequences related to their situation and it is common for children to feel shame, guilt, and frustration over their inability to control urination (1). These feelings can affect their self-confidence and social interactions, which can lead to avoidance of social situations, such as sleepovers with friends (2, 3). There are studies published about children with bowel and bladder problems with a focus on quality of life (4), but there is a lack of studies with a qualitative approach. In one qualitative study, performed by Malhotra and colleagues, the emotional responses and coping behaviors in children and adolescents with urinary incontinence (including enuresis), were explored. Feelings revealed were embarrassment, anxiety, annoyance, sadness and shame. The informants expressed experiences of their daily life using behavioral strategies to deal with it; strategies they had learned from parents and providers, were regulating fluid intake, having an extra change of clothes or sheets available as well as accounting for the need to change by waking up earlier. They had strategies to prevent accidents in a socially compromising situation by not participating in that activity, for example sports, or bringing incontinence products and sheets to sleepovers (3). Nothing, however, is written about how children experience the actual treatment of their enuresis, in particular the procedures used at home. From a clinical point of view, it can be assumed that the procedures entail a lot of work and have an impact on everyday life, apart from the disorders *per se*.

## Parents' perspective

Parents may feel helpless and frustrated about their child's enuresis, especially if the child does not seem to care and, in addition, the condition naturally generates a lot of laundry. Parents struggle not to blame their child or themselves. For example, a parent who had enuresis as a child may feel guilty for passing it on to their son or daughter. Parents feel concerned about their child's development and interpersonal relationships and strive to protect their child, resulting in avoiding sleepovers at friends' houses or hotels. In summary, research

shows that enuresis is not only a physical condition but also has significant emotional and psychosocial effects on the family, underlining the need to offer support and interventions that take these aspects into account (5).

## The Convention on the Rights of the Child

In 1989 United Nations made a historic commitment to the world's children when the Convention on the Rights of the Child legally recognized the human rights of all children under 18 years (6). The convention has been elevated to law in Sweden since 2020 (7). Accordingly, children have the right to the best possible healthcare and adequate medical care, and it is important to listen to children and ensure that their voices are heard when it comes to their healthcare and treatment. Providing age-appropriate information enables children to participate in decisions about their care. Furthermore, children have the right to freely express their views on all matters affecting them. This means that, when it comes to treatments and medical decisions, children should be involved in the decision-making process. This will help create a more inclusive and effective healthcare system. This makes sure that their needs and preferences are considered, which not only supports their rights but can also lead to better healthcare results (6).

## Bladder and bowel function

The urinary bladder has mainly two functions: to store the urine and to empty the reservoir completely when convenient. The latter is more important than the former. Up to the age of five it is normal to wet the bed and to have accidents during the day. Bladder functions are classified according to their relation to the storage and/or voiding phase (8). The fullness of the bladder depends on the intake of drinks and fluid-rich food. Emptying of the bladder is governed by our social life and routines that children are taught from their parents (9).

Defecation, or in other terms, bowel movements or passing stools, is the biological process by which waste material is expelled from the gastrointestinal tract. Within the large intestine (colon), water is absorbed from waste material, forming a solid mass of feces. Upon completion of the process in the final section of the large intestine, the rectum is filled with feces. Stretch receptors in the rectal walls send signals to the brain, creating the urge to defecate. The process involves both involuntary and voluntary muscle actions: The internal anal sphincter (which is involuntary) relaxes when the urge to defecate is experienced (10). The external anal sphincter (which is voluntary) can

be contracted to delay defecation until a suitable time and place is available (11). Defecation frequency can vary widely between individuals, with normal patterns ranging from every other day to three times per day (12) and the optimal position for defecating is in a squatting posture (10). Bowel function in children is classified in frequency, consistency and presence of retentive posturing to delay defecation (10).

## Lower urinary tract symptoms

To decrease the risk of confusion, relevant words and expressions need to be properly defined. Definitions used here are thus based on the updated lower urinary tract terminology of the International Children's Continence Society (ICCS) (8).

Storage symptoms include *urinary incontinence*, *frequency*, *urgency* and *nocturia*. Urinary incontinence is subdivided into two subtypes, depending on whether urine leaks constantly or in discrete portions: *continuous* and *intermittent incontinence*. Intermittent incontinence, in turn, is subdivided into *daytime incontinence* and *nocturnal enuresis*. Thus, enuresis denotes the intermittent, involuntary passing of urine that occurs exclusively at night during sleep and should not be used to characterise incontinence while awake. Intermittent incontinence is only clinically relevant from the age of five, whereas continuous incontinence is considered pathological regardless of age and may be associated with congenital malformations (2).

Enuresis is subdivided with regards to concomitant daytime lower urinary tract symptoms into *non-monosymptomatic nocturnal enuresis* (NMNE) and *monosymptomatic nocturnal enuresis* (MNE), the former term used if the child also has urgency, daytime incontinence, increased/decreased voiding frequency or any other daytime lower urinary tract symptom, while MNE implies bedwetting being the only symptom. The rationale behind this subdivision is that it is reasonable to assume that the pathogenesis and appropriate treatment may differ between NMNE and MNE. Both NMNE and MNE are furthermore subdivided according to their onsets; they are labelled *primary enuresis* when the child never established urinary continence and *secondary enuresis* when occurring after a continent interval of six months or more. The latter necessitates ruling out rare cases of underlying pathology such as diabetes, kidney disease or urogenital malformations. Still, most cases of secondary enuresis share underlying pathogenesis with primary enuresis and should be managed in a similar way (2). The incontinence subtypes are shown in Figure 1 (8). Thicker circle lines denote patients included in the thesis.

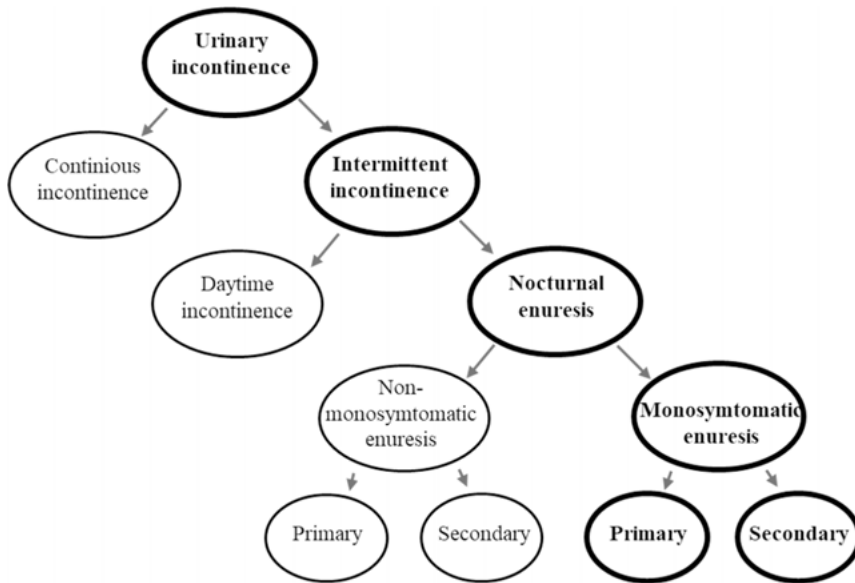


Figure 1. Incontinence and nocturnal enuresis subtypes. Illustration by Tryggve Nevéus.

Furthermore, enuresis is considered frequent if occurring four nights per week or more and infrequent if occurring less than four nights per week. Enuresis frequency has some implications for long-term prognosis, which is worse in frequent enuresis (13). In many studies, children with infrequent enuresis are excluded – a practice that may be questioned since the bother for the individual child may be severe even when the enuresis is sporadic.

*Daytime voiding frequency* is a crucial parameter in the non-invasive urodynamic evaluation of children. The reference interval is quite broad, but a frequency of less than four is considered decreased, and above eight as increased. *Urgency* is defined as a sudden and unexpected imperative urge to void, a symptom which is often indicative of underlying detrusor overactivity (see below). Children who have urgency symptoms are said to suffer from overactive bladder. This condition is often, but by no means necessarily, accompanied by increased voiding frequency and/or daytime incontinence. *Detrusor overactivity* (DO) is the occurrence of involuntary detrusor contractions observed during filling cystometry. This is the presumed underlying mechanism behind most cases of daytime incontinence and/or urgency. Thus, most patients with overactive bladder can be assumed to suffer from DO. However, a child who postpones voiding will sooner or later experience an urge to empty

their bladder, which makes it difficult for an observer to determine the cause of the urgency (8).

Voiding symptoms include *hesitancy* to initiate voiding, *straining* to initiate or uphold voiding, *weak stream* due to low urinary flow, and *intermittency* when urine escapes in several discrete spurts during each voiding. All these symptoms are warning signs that may indicate underlying anatomic obstruction or neurogenic bladder disturbance. Lastly, *dysuria* means pain during voiding. This symptom should raise the suspicion of lower *urinary tract infection* (8).

## Functional constipation

The term functional indicates that no organic cause can be identified. The recommended international standard for diagnosis of functional constipation are the Rome IV criteria (10, 14) explained below. In this thesis, functional constipation will henceforth be referred to as constipation. International studies report constipation rates of 0.7-30%, varying due to different contexts and definitions (15). The exact prevalence of constipation is difficult to ascertain, because patients suffering from the condition not always seek healthcare (16).

For children and adolescents, constipation diagnosis means that at least two of the following criteria have been present during the recent month:

- Two or fewer defecations per week
- At least one episode of fecal incontinence per week
- History of retentive posturing or excessive stool retention
- History of painful or hard bowel movements
- Presence of a large fecal mass in the rectum
- History of large-diameter stool that may obstruct the toilet

Digital rectal examination supports the diagnosis since the presence of formed stool in the rectum in a child who does not sense a present urge to defecate, is strongly indicative of fecal impaction (14).

## Nocturnal enuresis

Nocturnal enuresis is thus the scientific term for bedwetting. The alternative terms “enuresis”, “intermittent nocturnal incontinence” and “enuresis nocturna” can be used interchangeably. Enuresis will be the term used in this thesis. Nocturia is characterised by awakening during the night with a need to urinate. Before five years of age voiding while asleep is considered normal and the term enuresis is not applied (8).

The pooled prevalence of enuresis among children and adolescents is 7.2% (95% CI: 6.2-8.1%) (17). The prevalence in the general population decreases with age from 5-10% of seven-year-olds (18) to 3-5% of ten-year-olds and reaches 0.5-1% in adults (19). For most of the children enuresis will spontaneously resolve and the rate of spontaneous cure after five years of age, although hard to assess due to effective healthcare interventions, is probably around 15% per year (20). Enuresis can be seen as a trivial condition, but only if the child and their family think it is trivial. Otherwise, it should be treated (21).

The understanding of enuresis has during the last decades undergone dramatic improvement. While previously considered primarily a psychiatric disorder, enuresis is now understood to be a more complex condition with several interacting somatic pathogenetic mechanisms, three of which have been found to be crucial, nocturnal polyuria, nocturnal detrusor overactivity (DO) and high sleep arousal thresholds. These mechanisms may, in turn, possibly be explained by a common underlying disturbance on the brainstem level (22).

The genetic component has been implicated in studies of epidemiology, twin studies and formal genetics. Findings in these studies include dominant inheritance patterns, familial aggregation, concordance of enuresis among twins and specific genes associated with the condition (23-25). It is, however, important to point out that the genetic findings explain far from all cases of enuresis. Furthermore, familial enuresis can have different pathogenetic mechanisms among family members. The fact that one individual has inherited the condition from a parent says nothing about the individual's prognosis or response to therapy, i.e. genotype and phenotype are not clearly linked (26, 27).

Since the seminal studies from the Aarhus group in the end of the 1980s, nocturnal polyuria, i.e. excessive urine excretion during the night, has been shown to be common in enuresis. The researchers found that children with enuresis lacked the physiological nocturnal increase in vasopressin secretion and thus produced excessive amounts of urine at night (28). Furthermore, the fact that nocturnal polyuria is indeed causing the enuresis is supported by the observation that children with enuresis, particularly those with nocturnal polyuria, benefit from treatment with the antidiuretic hormone desmopressin (29). The role nocturnal polyuria plays in enuresis is further supported by the observation that enuretic events can be provoked in children without enuresis by excessive fluid intake before sleep (30).

Nocturnal DO is another explanation for enuresis. It has been shown that, especially among children who do not respond to antidiuretic treatment, uninhibited nocturnal detrusor contractions, i.e. DO, are common (31). Further arguments supporting DO as a pathogenetic factor are the large overlap between enuresis and daytime incontinence; a condition usually caused by DO (32);

and the fact that anticholinergic, detrusor relaxant drugs are effective at least in some children with enuresis (33).

In all cases of enuresis, sleep must be a part of the problem, regardless of whether the child has nocturnal polyuria or DO. Both bladder distension and detrusor contractions are recognized as strong arousal stimuli (34), yet these children do not wake up. Thus, sleep, almost by definition, plays a crucial role in the pathogenesis of enuresis. This has also been confirmed by questionnaire studies (35) – parents of children with enuresis almost universally state that their child is difficult to arouse from sleep at night – and a polysomnographic study with objective evaluation of arousal thresholds, in which it was found that children with enuresis were indeed more difficult to arouse from sleep than other children (36). However, this does not necessarily mean that these children’s sleep is of good quality or polysomnographically deep (37, 38). On the contrary, they may because of their enuresis have poor sleep (39). In the same manner, low quality sleep may be caused by DO and upper airway obstruction, both of which may cause enuresis. This claim is substantiated by the therapeutic response of enuresis after successful treatment of upper airway obstruction with adenoidectomy in children with both obstructive sleep apneas and enuresis (40). The pathogenic mechanisms (22) – nocturnal polyuria, DO and high sleep arousal thresholds – are summarized in Figure 2.

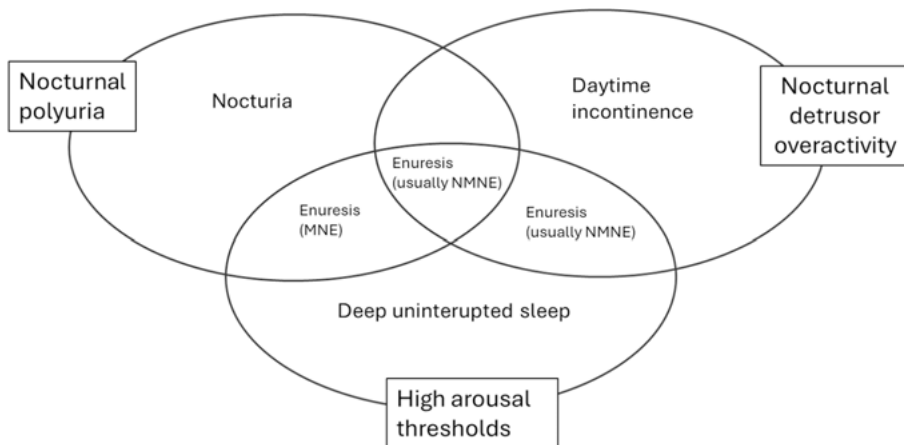


Figure 2. The pathogenic mechanisms – nocturnal polyuria, DO and high sleep arousal thresholds. Illustration by Tryggve Nevéus.

## Comorbidity

### Psychological and psychiatric problems

Social, psychological and psychiatric problems are known to be more prevalent among children suffering from urinary as well as fecal incontinence (41). The evidence for psychiatric mechanisms as *causes* for enuresis is, however, very limited. Only a very weak connection has been observed between enuresis and psychological trauma or neglectful parenting (42). On the other hand; enuresis, with the impracticalities and raised risk of discrimination that it entails, causes low self-esteem (43) and subsequent psychological problems. Furthermore, neurodevelopmental disorders such as Attention-deficit hyperactivity disorder (ADHD) are, for unclear reasons, overrepresented among children with enuresis (44) and may interfere with the treatment, leading to lower adherence, as well as worse outcomes (45). A significantly higher prevalence of ADHD was seen in a tertiary care sample (28%) than in a non-tertiary care sample (10%) reflecting ADHD diagnosis as a risk factor for long-term, persistent enuresis (46). If suspected, a child psychological or psychiatric assessment is recommended (47).

### Daytime incontinence

As mentioned, DO is recognized as an underlying pathogenetic mechanism in both daytime incontinence and enuresis. Daytime incontinence is more common among girls (18). Children with enuresis have been found to have small voided volumes but frequent micturition when filling out voiding charts (48, 49). Children with overactive bladder (and thus, presumably, underlying DO) tend to void more frequently and with smaller volumes than other children (50, 51). Unsurprisingly, daytime incontinence is common among children suffering from enuresis (32).

### The bladder and bowel interrelationship

Concomitant disturbances of the bladder and the bowel have been labeled bladder and bowel dysfunction (8) and are overrepresented in children with urinary tract infections or urologic conditions such as vesicoureteral reflux and hydronephrosis (52). The nerves of the bladder and the bowel share origin and the intimate anatomical proximity of the two organs may also explain why they influence each other. The distended rectum of the constipated child will deform the bladder from behind (53). And the causality may go in both directions: when a child with DO tries to control the bladder by holding maneuvers functional constipation may be the result. Constipation is quite prevalent, with

a 6.8 times higher risk among daytime incontinent children (54), and also among children with enuresis (55), although the latter link is less clear (56). It has been found that mainly the subgroup of children with enuresis with overactive bladder are more frequently constipated (57). Still, it should be kept in mind that sometimes the co-occurrence of bowel and bladder problems may be just coincidental. Laxative treatment of constipation in children with daytime incontinence will probably help for the bladder problems as well (58), but to what magnitude treatment of constipation helps in the treatment of enuresis has not been studied (55).

## Management of children with nocturnal enuresis

### Initial evaluation

A nurse or physician can evaluate enuresis and initiate treatment, as long she or he has the knowledge and competence to do so (2). A basic history should be acquired, with focus on general health, bladder and bowel habits and psychological factors such as neurodevelopmental disorders. The child should be specifically asked about daytime symptoms such as incontinence (present or previous), urgency and voiding difficulties. The frequency of enuresis needs to be evaluated, as well as the presence of dry periods. Constipation symptoms according to Rome IV criteria are asked for. It is also important to explore the child's views on their enuresis. The child's growth and general wellbeing is to be investigated, as well as if there is excessive thirst or whether the child has had recurring urinary tract infections or symptoms of upper airway obstruction. If the history does not give rise to any suspicion of underlying conditions such as diabetes, polyuric renal failure or neurogenic bladder, no physical examination is needed and no laboratory tests other than a urinary dipstick analysis is required (21). Collection of data concerning bladder and bowel habits is useful in the evaluation of the child with enuresis (2).

### Expected bladder capacity

To calculate urine volume is difficult, and possibly even more in children, due to their age and the fact that the bladder does not always fill to a certain level but empties in varying volumes and at varying intervals. Therefore, the methods used to calculate the expected bladder capacity explained should be seen as more indicative of bladder function and micturition habits than of anatomy.

When a child is born the urinary bladder holds approximately 30 mL. As the child grows the bladder reservoir function increases with 30 mL per year until the age of 12-13 years when the adult bladder capacity is reached. The

expected bladder capacity, a standard for comparison when evaluating bladder storage function, is expressed in mL and calculated using the formula  $[30 + (\text{age in years} \times 30)]$ , applicable up to the adult capacity of approximately 400 mL is reached (55, 59, 60). Expected bladder capacity, albeit by no means a perfect tool, is easy to use and clinically helpful. The child's maximum daytime voided volume is considered small or large if less than 65% or greater than 150% of expected bladder capacity, respectively. A small average or maximum voided volume is often considered indirect evidence for underlying DO (61). Nocturnal polyuria refers to a urine production during sleep (including the first morning void) exceeding 130% of expected bladder capacity (8).

### Voiding chart and bladder/bowel diary

The voiding chart and bladder/bowel diary are crucial tools in the non-invasive evaluation of lower urinary tract function in children. In the voiding chart, the child or their guardian records voided volumes at each micturition during a few days. Daytime micturition frequency as well as average and maximal voided volumes are the central data extracted from the voiding chart. The family is also asked to record the weight of diapers or sheet covers before and after the night so that enuresis volumes and nocturnal urine production can be assessed, by adding enuresis volume plus the first void in the subsequent morning. These parameters are all valuable in the management of children with enuresis. Both daytime voided volumes, enuresis volumes and nocturnal urine production need to be expressed as a percentages of expected bladder capacity, thus taking the child's age into account (59, 60). A bladder/bowel diary is the objective recording and documentation of frequencies of enuresis, nocturia and bowel movements during a period of 14 days (2).

### Transabdominal ultrasound

When diagnosing constipation, the discomfort of rectal examinations has led to the utilization of transabdominal ultrasound measurements of rectal diameter behind the bladder as an alternative diagnostic tool, for children aged 4 or older, with 30 mm as the cut-off limit (62-64). This is a useful, safe and reproducible point-of-care tool that allows treatment responses to be monitored over time (65). In the clinical context, this is a pedagogical tool and a great help when parents and children with a lower urinary tract disorder need to be convinced that constipation may need to be addressed (65). Figure 3 A presents the image of a normal rectum in a non-constipated individual, whereas

Figure 3 B shows the bladder and rectum of a constipated patient with the bladder base compressed by fecal mass (fecal impaction).

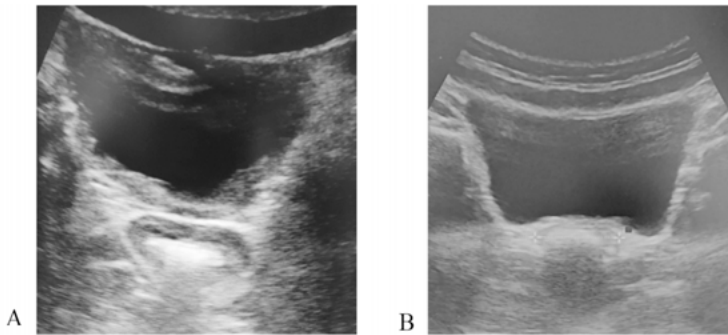


Figure 3. Transverse view of transabdominal ultrasound.  
A – normal rectum. B – bladder compressed by a distended rectum.  
Photo by Malin Borgström

## Therapies

According to the ICCS guidelines, three treatment modalities have been recommended as first-line therapies in enuresis. At first basic bladder advice (BBA), internationally named standard urotherapy, for 8-12 weeks were recommended and if the child still wet the bed, next treatment alternatives were alarm treatment or desmopressin, as presented in Figure 4.

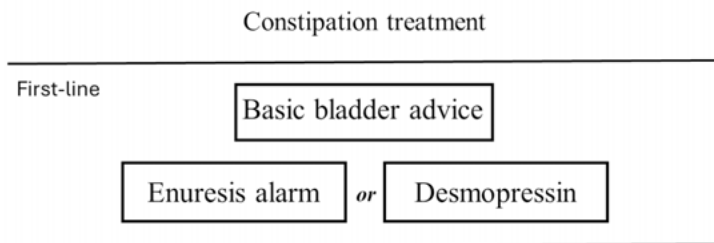


Figure 4. First line treatment for enuresis.

If alarm treatment yields no response, desmopressin should be tried, and vice versa (66). The role of BBA as a recommendation has thereafter been limited to NMNE, due to insufficient evidence to support the method in MNE (2, 67). Importantly, urotherapy in this context does not refer to more advanced urotherapy with components such as cognitive behavioral therapy or biofeedback. Even though terms such as “standard urotherapy”, “daytime urotherapy” or

“basic urotherapy” have been used in papers I-IV they all refer to the same therapy, BBA, as described.

### Basic bladder advice and constipation treatment

The cornerstones of BBA, as advocated for children with lower urinary tract dysfunction or enuresis, are the following (68):

- education/demystification; explanation about normal lower urinary tract function and how the child deviates from the normal
- institution of regular voiding habits according to a schedule, with micturition approximately every second hour and just before going to bed
- regular drinking habits, with fluid intake spread evenly during the day and avoidance of excess fluid intake in the evenings
- correct voiding posture, squatting with support for the thighs and feet
- documentation of symptoms and voiding habits via repeated completion of voiding diaries
- regular support, encouragement and feedback from the healthcare provider.

The case for BBA as an antienuretic therapy rests on its noninvasive nature and established effect on daytime incontinence due to DO, which, as mentioned, is also common in enuresis (69). Constipation therapy or bowel management, by disimpaction and bulk laxatives, can be considered as a part of BBA and is widely recommended (70).

When constipation is treated it includes a 4-step approach (71) of:

- education: demystification and explanation of bowel function
- disimpaction, achieved by rectal enemas or oral agents such as polyethylene glycol (PEG) in high dosage
- prevention of reaccumulation, achieved with maintenance treatment with bulk laxatives such as PEG.
- if needed, increased fluid intake and dietary interventions, changes in behavior such as increased physical activity and the avoidance of postponing defecation
- follow-up.

## Alarm treatment

The most curative therapy for enuresis available is alarm treatment, consisting of a urine detector linked to an apparatus emitting a strong, usually acoustic, arousal stimulus (72). The antienuretic mechanism of the alarm is somewhat unclear but can be assumed to address the high arousal threshold found among most children with enuresis. The evidence for the efficacy of alarm treatment is well established (73); between 50 and 80% of children are cured after using the alarm continuously for 1-2 months (74). It is important to point out that nonresponse to alarm therapy can in some instances be due to technical malfunction of the device, inability of the family to adhere to the instructions given or incorrect instructions given by the caregiver. Not much is known regarding predictive factors for alarm treatment response but infrequent enuresis is considered a negative predictor and family motivation can be assumed to indicate a higher chance of success (75).

If the alarm is chosen, the device is demonstrated for the child and parents, and the following instructions are given (2):

- the parent is required to sleep in the same room as the child to help them to get up immediately when the alarm goes off, since the child with enuresis most often is a heavy sleeper
- when the alarm has sounded, the child is instructed to complete the voiding in the toilet after which the sheets are changed, and the child goes to bed again
- alarm therapy needs to be continuous, every night, with no “alarm holidays”, for at least 6 weeks.

The healthcare provider needs to contact the family after approximately two weeks of treatment to provide encouragement, answer questions and solve technical problems (2). Alarm therapy can be challenging for families to manage without the support of a caregiver, indicating the labor-intensity of the treatment (76). If a favorable effect has been observed within 6-8 weeks, the treatment should continue until 14 consecutive dry nights have been achieved. If there has been no sign of success after 6-8 weeks, therapy is interrupted and a follow-up appointment with the healthcare provider is made (2).

## Desmopressin

The nocturnal polyuria of enuresis is addressed by desmopressin. By mimicking the actions of physiological vasopressin, desmopressin inhibits urine pro-

duction and may thus prevent the bladder from becoming full during the sleeping hours if taken in the evening (77, 78). Approximately one third of children given desmopressin will be reliably dry at night as long as the drug is given (77). Desmopressin, in contrast to the alarm, does not demand hard work from the parents (or healthcare personnel). However, fluid intake must be restricted during the evening and night to eliminate the risk for water intoxication. Positive predictors of desmopressin response are age >8 years, infrequent enuresis, monosymptomatic enuresis and, especially, nocturnal polyuria (79, 80). Desmopressin is offered to alarm non-responders and to those not sufficiently motivated or unable to adhere to alarm instructions. The beneficial effects will be apparent immediately. If therapeutic response is achieved, medication can thereafter be administered every night or alternatively only when needed (*e.g.* during trips or sleepovers) at the discretion of the family. If therapeutic response is absent for 1-2 weeks, treatment will be ineffective and should be stopped (21).

## Management of the therapy-resistant child

After the first-line therapies have been performed, it can be assumed that approximately 25% of children with enuresis remain (81). These are to undergo a general physical examination by a specialist, in search for rare underlying conditions such as spinal dysraphism. A bladder/bowel diary, if not already completed, is to be filled out. Further, the physician should check if alarm treatment has been carried out correctly, since incorrect instructions are commonly given or correct ones misunderstood. Non-invasive urodynamic assessment is made by and ultrasonographical post-void residual urine measurement. Radiological imaging or invasive examinations such as cystometry may be needed for children with enuresis in whom malformations or if neurogenic bladder disturbance is suspected, but this is rare (82).

Anticholinergic treatment is the established second-line therapy. The subgroup of children with enuresis most likely to benefit from anticholinergic treatment are probably those with signs of DO, *i.e.* urgency and/or low daytime voided volumes (33). For children with enuresis who snore heavily, or experience nocturnal apneas, tonsillectomy and/or adenoidectomy may be considered in consultation with an otorhinolaryngologist. Referral to a psychologist or child psychiatrist may be appropriate if neurodevelopmental disorders are severe or suspected to make adherence to antienuretic therapy difficult. If dryness at night is still not achieved, the cautious use of tricyclic antidepressant therapy is warranted. This is to be handled by specialists only. Throughout these alternatives, alarm treatment can be tried yet one more time (66).

## Rationale of the studies

The actual effects of BBA on enuresis have not been properly scientifically assessed by prospective randomized controlled trials (RCT). However, based on its noninvasive nature and established effect on daytime incontinence due to DO (69) as well as clinical experience, BBA has been kept in the ICCS guidelines. Studies in which, directly or indirectly, the effects of BBA is evaluated as a treatment of enuresis, have so far been of limited value for several reasons: drop-out rates were often high or not reported (83-85), children were awakened at night by their parents (84, 86, 87) or other therapies such as desmopressin or the alarm were also given (83). The overall therapeutic effect of BBA in these studies was modest or absent. The efficacy of the method was questioned by the results of the first randomized controlled study on BBA's effect on enuresis published by our group in 2010 (88). On the other hand, urotherapy's effect on daytime incontinence is reasonably well documented (68) and it is thus not far-fetched to assume that it may be effective at least in a subgroup of children with enuresis. The reasons mentioned can also be assumed to be the reason for recommending constipation treatment to children with enuresis, but more studies are needed regarding this as well. Also, we do not know if children with enuresis are more constipated and how they differ from children without bladder-related problems.

Children have the right to the best possible healthcare and adequate medical care and therefore it is essential to make sure their voices are heard (6). This means that we need to know more about children's experiences of the various therapies given to manage enuresis and constipation, especially labor-intensive ones and those intruding on the child's integrity. Moreover, the children's experiences of managing the procedures at home have not previously been explored. Overall, qualitative research in this research field has been relatively scarce and only focused on the burden of the condition (5), not the therapy. This makes it particularly important to highlight their challenges and success factors to increase their influence in the fight for a dry night.

# Aims

## Overall aim

The overall aim of this thesis was to better understand the importance of constipation therapy, BBA and/or the enuresis alarm in the first-line therapy of enuresis, and how these treatments are experienced. The aim was also to find out whether children with enuresis are more likely to be constipated than others.

## Specific aims

The specific aims were:

### Study I

To provide more evidence for the efficacy, or non-efficacy, of basic bladder advice in enuresis in a randomized controlled study.

### Study II

To evaluate the antienuretic effect of fecal disimpaction in children with enuresis and concomitant constipation.

### Study III

To explore children's and their parents' experiences of labor-intensive procedures in the management of enuresis.

### Study IV

To evaluate the prevalence of constipation in children with enuresis as compared to children without bladder problems.

# Methods

## Design

Study I, II and IV are quantitative studies. Study III is a qualitative study. Study I was registered in [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT03812094). An overview of the study designs is presented in Table 1.

Table 1. Overview and descriptions of studies I-IV.

Study	I	II	III	IV
Design	Randomized controlled	Prospective comparative	Qualitative explorative	Case-control
Data collection	Voiding parameters Rome IV criteria Rectal diameter Bladder/bowel diary	Voiding parameters Rome IV criteria Rectal diameter Bladder/bowel diary	Semistructured interviews	Voiding parameters Rome IV criteria Rectal diameter Bladder/bowel diary
Participants	60 children with enuresis	66 children with enuresis	14 children with enuresis, together with a parent	66 children with enuresis 58 controls without bladder problems
Primary outcome measure	Reduction of wet nights	Reduction of wet nights	-	Constipation according to Rome IV criteria Rectal diameter
Data analysis	Between-subjects ANOVA or Kruskal-Wallis tests. T-tests, Mann-Whitney U and Chi <sup>2</sup> tests.	Paired t-tests or Wilcoxon signed rank tests. T-tests, Mann-Whitney U or Chi <sup>2</sup> tests	Inductive with qualitative content analysis	Independent t-tests and Chi <sup>2</sup> tests

## Settings

Children with enuresis who had been referred by their general practitioner or school nurse to the pediatric outpatient ward in the regional hospital in Dalarna County, central Sweden, were invited to participate in study I-IV. It should be

noted that the eligible subjects constituted a primary care population of children who had previously not sought help for their enuresis, and that both a high and a low enuresis frequency was accepted for inclusion if the patients were bothered by their bedwetting. The control group was recruited from the general population through a combination of mass media advertisements and word-of-mouth referrals within the same geographic area as the children with enuresis. The lead researcher, a specialist pediatric nurse and qualified urotherapist (MB), collected relevant historical data and examined all the participants.

## Participants

### Patients with enuresis (Study I-IV)

Inclusion criteria were:

- children aged 6-11 years who sought help for enuresis.

Exclusion criteria were:

- daytime incontinence
- previous BBA
- previous treatment with the enuresis alarm or second-line antiu-  
retic therapy
- voiding dysfunction or suspected lower urinary tract malformation
- concomitant disorders affecting endocrine, renal, urological or neu-  
rological function
- inability of the family to adhere to instructions or give informed  
consent.

The children included needed not be strictly monosymptomatic, since urgency symptoms or increased/decreased voiding frequency were not exclusion criteria. This was in line with the current ICCS guidelines (2). The intention was to include all children with enuresis who would usually, at the time of inclusion, be considered appropriate candidates for BBA. Neurodevelopmental disorders were no exclusion criteria if the family was expected to be able to adhere to therapies given.

Children were divided into two groups, with and without constipation. Children were considered constipated either because they fulfilled the Rome IV criteria or had a distended rectum (i.e. rectal diameter >30 mm).

From the whole group of patients with enuresis, that completed study I and II, a sample of children was selected purposively to the interview study (III) with the intention to include all genders and ages as well as varied experiences of managing the labor-intensive procedures in the former studies. Since enuresis is more common in 6–7-year-old children, most of the interviewed children were in that age. The children were invited together with a parent, and before the interview it was clarified that the child was the main character and the parent's participation was aimed mostly to provide a context to the child's story. The interview took place in a child-friendly room at a pediatric outpatient ward familiar to the child. The children could choose whether they wanted to sit in a chair or on a rocking toy or move freely about the room.

### Participants without any bladder symptoms (Study IV)

The children with enuresis from study II were in study IV compared to healthy control participants who had no bladder-related symptoms day or night. Exclusion criteria were the same as for children with enuresis. Concomitant bowel-related problems were neither inclusion nor exclusion criteria.

### Measures (Study I, II, IV)

The primary outcome variable in the RCT (Study I) was the reduction of wet nights per two weeks before and after the intervention period, as well as the difference in treatment in this reduction between the three treatment arms. In a similar way, the central outcome variable of study II was the reduction in the number of wet nights due to constipation treatment, i.e. the difference (if not reduction) in number of wet nights between baseline and after constipation treatment among constipated children with enuresis. Therapeutic response to a therapy was defined by the reduction of wet nights per two weeks; non-response is <50%, partial response is 50-99%, and full response is 100% reduction (2), and thereafter dichotomized into responders and non-responders, with the cutoff point put at 50% reduction of enuresis frequency.

Constipation diagnosis was set with the help of Rome IV criteria (page 17). The questions were directed to the child and the parent filled in the medical history if needed. Abdominal ultrasound was performed with the patient supine, and the 7.5 MHz probe was applied on the abdominal skin approximately 2 cm above the symphysis. Measurements were made with a moderately filled bladder at an angle of about 15 degrees downward from the transverse plane. The measurement was performed two times, and the mean transverse rectal diameter was considered the correct transverse rectal diameter (89). Outcome

value of the measurements were in mm or dichotomized into no rectal distension ( $\leq 30$  mm) or rectal distension ( $>30$  mm) (90).

Bowel movements were registered prospectively in a diary, i.e. the family recorded every time the child passed stools for 14 days. Baseline variables were used when comparing constipated and non-constipated children with enuresis (Study II), and constipated children with and without enuresis (study IV). When looking for predictive factors to therapeutic response (study II), factors were of two basic types: 1) anamnestic data (age, weight and rectal diameter in mm) gathered by the urotherapist (MB) at the first appointment, and 2) data gathered from the bladder/bowel diary and voiding chart. All urine volume variables were expressed as percentages of expected bladder capacity according to the child's age.

## Power calculation and sample size

Based on earlier studies by Dr Nevéus' group, sample size was approximated for the main outcome number of wet nights in a 14-day period (88, 91). Given a mean difference of 11.5 (standard deviation: 2.7) wet nights between two independent groups, 15 children were needed to attain 90% power at a two-sided alpha of 5%. Assuming 25% dropout rate, 20 children were recruited in each treatment arm.

## Interventions

### Interventions in the randomized controlled trial (Study I)

All children who completed the baseline investigations and still suffered from enuresis, including those who had been given treatment for constipation (in Study II), were invited to take part in the randomized study. Regardless of group, all children were given information about lower urinary tract function and enuresis pathogenesis, and all ongoing laxative therapy was continued.

The randomized allocation was generated using the virtual sealed envelope service of [www.Random.org](http://www.Random.org) in blocks of 3 and 6 and was blinded to everyone involved until the allocation was revealed by the study nurse to the individual family. Given the nature of therapies given, it was not possible for the allocation to be blinded during the eight weeks of treatment (or non-treatment).

The children were randomly consigned into the following three groups:

- Group A) BBA was given for 8 weeks in accordance with ICCS guidelines, as described in page 24. Instructions were given by a qualified pediatric nurse and urotherapist. Follow-up contact by phone was made after 2 and 6 weeks.
- Group B) Alarm therapy was given for 8 weeks in accordance with ICCS guidelines, as described in page 25. Instructions were given by a qualified pediatric nurse and urotherapist. Follow-up contact by phone was made after 2 and 6 weeks.
- Group C) controls group. For eight weeks no active treatment was given to these children.

In all groups, bladder/bowel diaries were again registered during week 7 and 8. After the intervention, the children were offered to continue or try another treatment for their enuresis just as they normally would in the clinical setting (2).

### Intervention in the comparative study (Study II)

In children with enuresis and concomitant constipation, the latter condition was also demystified and explained with illustrations (Figure 5 ), focusing of the distended rectum that compresses the bladder from behind and bladder relief if the bowel was emptied regularly (53, 70).

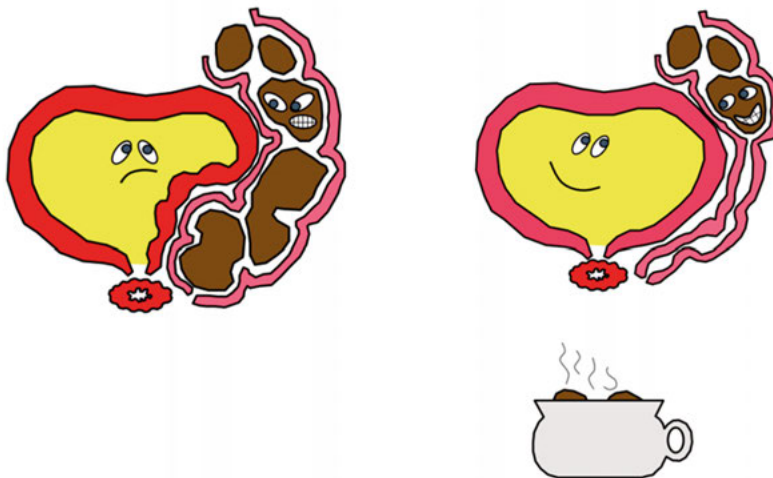


Figure 5. Distended rectum that compresses the bladder from behind and bladder relief if the bowel was emptied regularly. Illustration by Tryggve Nevéus

Laxative treatment was prescribed with mini enemas and PEG, according to international guidelines (71). Thus, the child was prescribed mini enemas for three days followed by every other day for one week. After the initial disimpaction, the child was instructed to empty their bowel every day or at least every second day. If the child did not have bowel movements the second day, additional mini enemas would be given. Adherence to treatment was encouraged and evaluated via telephone contacts. Constipation treatment was further continued for at least eight weeks during the RCT study.

## Data collection

### Baseline examinations

Examinations included uroflowmetry and ultrasonographical assessment of post-void residual urine volume and rectal diameter. A checklist (see appendix I, Checklista) was completed with information gathered during the initial appointment. In addition to assessment of exclusion/inclusion criteria and inquiry after possible warning signs indicating severe underlying pathology, the crucial history data gathered were the following:

- enuresis subtype – primary/secondary, MNE/NMNE
- family history of enuresis
- presence of urgency
- previous daytime incontinence
- subjective arousal thresholds
- constipation according to Rome IV criteria.

Upon fulfilling criteria for inclusion, the child and their guardian were offered to proceed with the study.

### Bladder and bowel registrations

The child and parent were instructed to complete a bladder/bowel diary for a period of 14 days. During a weekend within these 14 days the more elaborate voiding chart (see Appendix II Kiss och bajsdagbok) was filled out. The guardians were instructed to return the bladder/bowel diary and voiding chart after completing them. In the bladder/bowel diary bowel movements as well as enuretic and nocturic events were documented. From the registrations the following variables were obtained:

- Enuresis frequency (number of wet nights per 14 days)
- Bowel movement frequency (14 days)
- Daytime micturition frequency (two days)
- Maximum and average daytime voided volumes (two days)
- Enuresis volumes (three nights)
- Nocturnal urine production during nights with enuresis (*i.e.* sum of enuresis volume and first morning void in  $\leq$  three nights)
- 24 h urine production (48 hours)

Daytime voided volumes, enuresis volume and nocturnal urine production were all recalculated as percentages of expected bladder capacity according to the patient's age. Voided volumes with and without the first morning void was registered separately. That is because the first morning void usually, in children without enuresis, represents a full bladder, whereas the situation is different for children with enuresis after a wet night. After these examinations were completed a new appointment to the study research nurse (MB) was given.

For children with constipation the same registrations were made after two weeks of constipation treatment before entering the RCT study, provided they still suffered from enuresis. During the last two weeks of the eight-week treatment (or observation) period wet and dry nights were again registered. The design of study I and II is illustrated graphically in Figure 6.

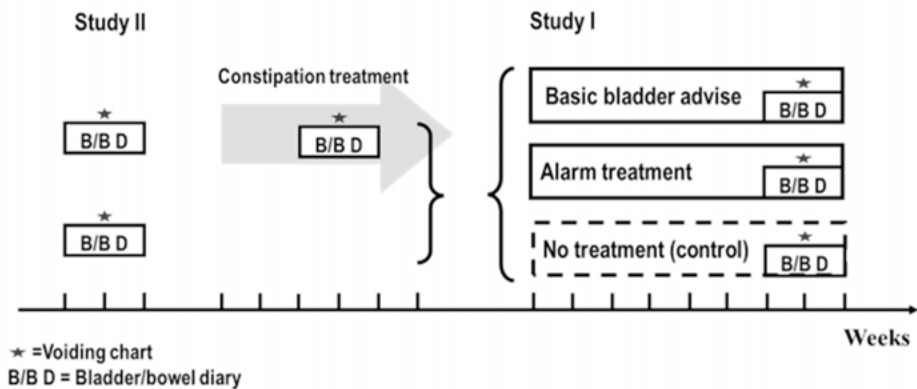


Figure 6. Overview of study I and II

The control group consisting of healthy children without any bladder-related symptoms underwent the same baseline examinations and registrations of bladder/bowel diary and voiding chart.

## Qualitative interview data

The researchers developed a guide for the interviews with semi-structured, open-ended questions based on their professional experience with urinary tract problems, pediatrics, and talking to children. This ensured that the questions were age-appropriate and understandable to the children. The short interview protocol (Appendix III, Intervjuguide) focused on the child's description of performing the procedures at home. A pilot study revealed that it was difficult for them ( $n = 3$ ) to recall and describe their experiences, even though the interviews were conducted no later than two weeks after the end of treatment. Additionally, the interviews were conducted online due to the pandemic, which made it challenging for the children to focus. Consequently, the interviews were thereafter held in a child-friendly room at a children's ward, and a revised interview technique was used. This technique involved showing the children actual objects (props) with which they were familiar when managing the study treatment (Figure 7). The potentially labor-intensive procedures that were explored, and the objects used, were as follows:

- voiding chart and bladder/bowel diary - paper lists for registration and measure-cup
- constipation treatment - mini-enema, PEG and a catheter
- basic bladder advice – 8-week toilet diary with stickers, water bottle and a footstool
- alarm treatment - alarm device, sensor and fixation to underwear (sanitary pads)



Figure 7. Props used during interviews (Photos by Malin Borgström)

The use of actual objects resulted in richer statements. Still, the interviews in the pilot study turned out to provide information fit to be included in the analysis. The interviews continued until an overall picture emerged and no new information was acquired (92).

This method of using props is inspired by other research fields, such as criminology, where it is important and common to interview younger children. Children can recall and provide richer answers when props are used to prompt them (93, 94). Thus, the children were asked to pick up and talk about one object at a time. This way, the child chose the order of the conversation by describing and talking about their experience. Additional questions were asked to encourage the children to elaborate on their experiences. The interviewer redirected the child's conversation when it wandered off topic, gently guiding the discussion back to the main topic. During the interview, the parent had an opportunity to share experiences from their perspective.

## Analyses

### Study I

The primary outcome measure in the RCT was therapy response, defined as the reduction of the number of wet nights per 14 days at the end of therapy (or no treatment), compared with before the intervention. The therapy response in the three groups was classified as response, partial response or non-response to therapy according to ICCS (8). Thereafter, therapeutic response was dichotomized into responders and non-responders, with the cutoff point put at 50% reduction of enuresis frequency. The therapy response in the three groups was compared using between-subjects ANOVA or Kruskal-Wallis tests. Possible predictive factors influencing therapy response were explored among all data gathered at baseline using t-tests, Mann-Whitney U tests or Chi<sup>2</sup> tests depending on the type and distribution of the variables.

### Study II

When analyzing the treatment of constipation in children with enuresis, the number of wet nights per two weeks was compared between baseline and after laxative therapy, using paired t-tests or Wilcoxon signed rank tests. As described in study I, the children were also in this study classified according to treatment response (8). Possible predictive factors indicating an antienuretic effect of fecal disimpaction were examined among all baseline data, and baseline data were also compared between children with and without constipation.

Variables were compared using t-tests, Mann-Whitney U tests or Chi<sup>2</sup> tests depending on the type and distribution of the variables.

### Study III

The qualitative data were analysed inductively with content analysis according to Patton [20] and the intention was to adhere closely to the interviewee's own words. Since children's experiences of enuresis management at home was previously not explored, it was regarded as very important to describe their views and not to interpret what was said. All interviews were audio recorded and professionally transcribed verbatim. In total, the interviews produced a transcript material of 268 A4 pages in font size 12 with double line spacing. The transcripts were read through to ensure that the material corresponded to the tape-recorded interviews. By reading the text several times a sense of the content was obtained. Meaning-bearing units were identified and coded close to the text. Codes with similar patterns were grouped together, resulting in subcategories, and finally sorted into categories, presented according to the method used, in Table 2.

Table 2. Example of categorization.

Category	Sub-category	Meaning unit
Managing procedures made it complicated	Awkward situations	<i>"I started laughing at myself and started joking about it and then, well, I was kind of afraid that my friends would notice that I had a box of sanitary pads in my room."</i>

### Study IV

We investigated parameters related to constipation in children with or without enuresis, specifically focusing on rectal diameter, constipation diagnosis according to Rome IV criteria and the frequency of bowel movements over a period of two weeks. A comparative analysis between the two groups was conducted. Comparisons were made using the statistical methods described for study I and II. Further analysis was conducted using bladder diaries to evaluate voiding patterns and volumes over two consecutive days. These data were compared between children with or without enuresis.

## Ethical considerations

The research included in this thesis was conducted in accordance with the principles of the Declaration of Helsinki and the Convention on the Rights of the Child. The Regional Ethical Review Board in Uppsala approved the full project (dnr 2018-004, 2019-04670). The Ethics Review Authority in Uppsala also approved our subsequent request to recruit control children via advertisements (dnr 2019-00254). Upon entering the study, all children and parents were given written and oral information and gave written consent to participate (Appendix IV Studieinformation barn, Appendix V Studieinformation förälder). Furthermore, participants were informed that participation was voluntary and that they could cease participation at any given time if they so decided, with or without explanation. Lastly, the children and parents were assured that discontinuation would not affect the care they received. All participating children were rewarded with two cinema tickets, and those who were interviewed also received a ticket to a play centre.

### Patients with enuresis (study I, II, III).

Although enuresis can generally be perceived as a sensitive subject, the children who were recruited were actively seeking help and aware that “intimate” questions about enuresis and toilet habits would be asked, meaning they were therefore unlikely to be offensive to the child or parents. No painful, risky or offensive examinations or treatment procedures were included. Trans-abdominal ultrasound examinations and uroflow measurements were, and are, established methods in the evaluation of daytime incontinence or therapy-resistant enuresis even outside the research setting. The treatments in the studies – constipation therapy, BBA or alarm treatment – were all standard at the time. Children who were randomized to no treatment could possibly have found this problematic. However, these children still had an advantage in participating, as they otherwise would have had to wait 12 weeks for a regular appointment at the pediatric clinic. After the eight-week period all children who still suffered from wet nights were immediately offered treatment.

### Healthy controls - children without enuresis (study IV)

As just described (for patients with enuresis) no painful, risky or offensive examinations were included. However, for children in the control group it could be more sensitive to talk about their toilet habits and consent to examinations like transabdominal ultrasound. Therefore, even though information about the study, emphasizing that participation was entirely voluntary and

could be terminated at any time, had already been given, this was repeated if any hesitation was shown during the baseline visit. The families had all volunteered to participate in a study on the pediatric lower urinary tract so intimate questions about pee and poo could not come as a surprise.

# Results

A total of 98 children with enuresis were invited to participate in the study. Of these, 18 declined, and seven were found not to fulfil the inclusion criteria. Following the initial nurse visit, one child withdrew from the study, three became spontaneously dry, and one failed to return the bladder/bowel registrations, resulting in 66 children with enuresis. There were 58 children without any bladder related problems recruited as healthy controls to study IV, resulting in 124 children in total. Figure 8 graphically describes the patient flow through the studies.

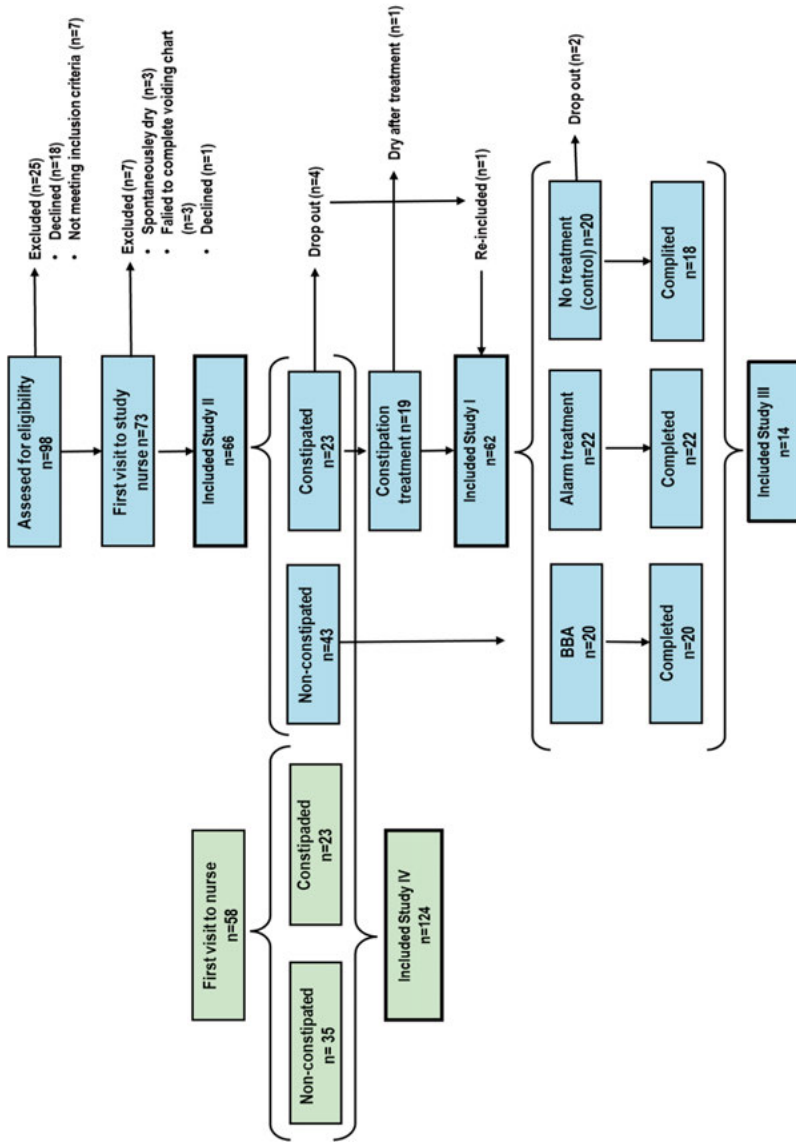


Figure 8. Patient flow chart through the studies, green representing children without any bladder related problems and blue representing children with enuresis.

## Study I

In the randomized controlled trial 62 children were randomized into three groups: BBA (n = 20), alarm treatment (n = 22) and controls (n = 20). Unfortunately, two children in the control group dropped out of the study because they were not motivated to complete the diary entries, resulting in 44 boys and 16 girls completing the study. History and voiding chart data of all participating is presented in Table 3 and 4, respectively.

Table 3. History data, all participating children (n=60).

	Proportion (%)
Heredity (parents or siblings)	28/60 (47)
Urgency	41/60 (68)
Previous daytime incontinence	30/60 (50)
High arousal thresholds	53/60 (88)
Constipation	19/60 (32)

Table 4. Table 4 Voiding chart data, all participating children (n=60).

	N	Mean ± 1 SD	Median (range)
Wet nights per two weeks	60	10.1 ± 4.3	12 (13)
Daytime micturition frequency	60	5.6 ± 1.9	5.5 (10.5)
Enuresis volume*	53	67 ± 51	63 (345)
Urine production per 24 h/kg	50	29 ± 12	25 (47)
Nocturnal urine production, wet nights*	46	117 ± 58	114 (332)
Maximum voided volume, morning void excluded*	59	78 ± 31	78 (120)
Maximum voided volume, morning void included*	59	86 ± 33	75 (139)
Average voided volume, morning void excluded*	59	46 ± 19	41 (92)
Average voided volume, morning void included*	59	48 ± 17	44 (73)

\* All volumes expressed as percentages of expected bladder capacity for the child's age, according to the Koff-Hjälms formula (59, 60).

The sex distributions in the three groups were as follows: BBA, 5 girls and 15 boys (25/75%); alarm treatment, 6 girls and 16 boys (27/73%); observation, 5 girls and 13 boys (28/72 %)  $p = 0.98$ . The children's ages and body mass index indices also did not differ between the three groups ( $p = 0.70$  and  $p = 0.59$ , respectively). As can be seen, there were no significant differences between the groups. Some families were unable to provide full data for all the variables based on registration at home. The categorical and continuous baseline variables for each group are listed in Table 5.

Table 5. History and voiding chart data, at baseline, comparison between study groups (n=60).

	BBA (n = 20)	Alarm (n = 22)	Controls (n = 18)	p- value
Heredity (parents or siblings)	12/20 (60)	10/22 (46)	6/18 (33)	0.26
Urgency	16/20 (80)	15/22 (68)	10/18 (56)	0.27
Previous daytime incontinence	7/20 (30)	11/22 (50)	12/18 (67)	0.15
High arousal thresholds	16/20 (80)	21/22 (96)	16/18 (89)	0.30
Constipation	8/20 (40)	3/22 (14)	8/18 (44)	0.07
Wet nights per two weeks before intervention	10.3 ± 4.6	9.7 ± 4.1	10.4 ± 4.4	0.86
Daytime micturition frequency	3.5 ± 5.4	5.7 ± 1.5	5.5 ± 2.6	0.87
Enuresis volume*	65 ± 37	71 ± 72	72 ± 36	0.91
Urine production per 24 h/kg	30 ± 13	28 ± 12	27 ± 11	0.80
Nocturnal urine production, wet nights*	109 ± 51	118 ± 72	121 ± 48	0.85
Maximum voided volume, morning void excluded*	76 ± 35	74 ± 29	84 ± 31	0.58
Maximum voided volume, morning void included*	82 ± 34	85 ± 37	92 ± 26	0.63
Average voided volume, morning void excluded*	51 ± 25	44 ± 16	47 ± 16	0.53
Average voided volume, morning void included*	50 ± 22	47 ± 16	49 ± 14	0.85

Data shown are either proportions (%) or mean ±SD.

\* All volumes expressed as percentages of expected bladder capacity for the child's age, according to the Koff-Hjälms formula (59, 60).

## Treatment results (Study I)

As can be seen in Table 6 only the alarm significantly reduced the number of wet nights.

Table 6. Number of wet nights per 14 days before and after the intervention.

	Before the intervention*	After the intervention*	Reduction of wet nights*	p value
BBA	12.5 (1.0–14)	11.5 (0–14),	0 (–4.9–7.9)	0.44
Alarm	11.0 (1.2–14)	3.5 (0–13)	4.5 (0–13.9)	<0.001
Control	12.5 (1.0–14)	12 (0–14)	0 (–4–0.3)	0.55

\*Number of wet nights, median (with range) per 14 days.

Pairwise comparisons with Bonferroni corrections revealed no significant difference between the BBA and control groups ( $p = 1$ ), but the alarm group differed significantly from both the BBA group ( $p = 0.016$ ) and the no-treatment group ( $p = 0.004$ ). The result is illustrated graphically in figure 9.

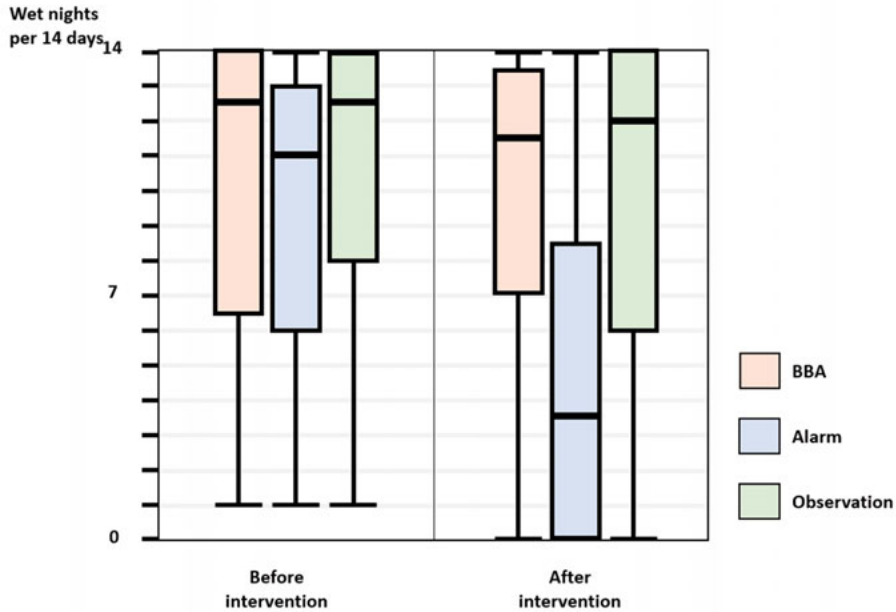


Figure 9. Nights with enuresis before and after the intervention (n=60, BBA 20, alarm 22, control 18).

The proportion of full responders, intermediate responders and non-responders, according to the ICCS terminology,<sup>10</sup> was 10%, 5% and 85% for the BBA group, 27%, 23% and 50% for the alarm group and 11%, 11% and 78% for the control group.

### Predictive factors (Study I)

Potential predictive factors were sought within all the treatment groups. It was found that neither age, sex nor any other baseline variable provided any predictive information. Although the number of children becoming dry during BBA (n=2) was too small for proper evaluation, it should be noted that these children had a baseline enuresis frequency of less than 50% of the nights. The situation for the children in the BBA group is highlighted in Figure 10.

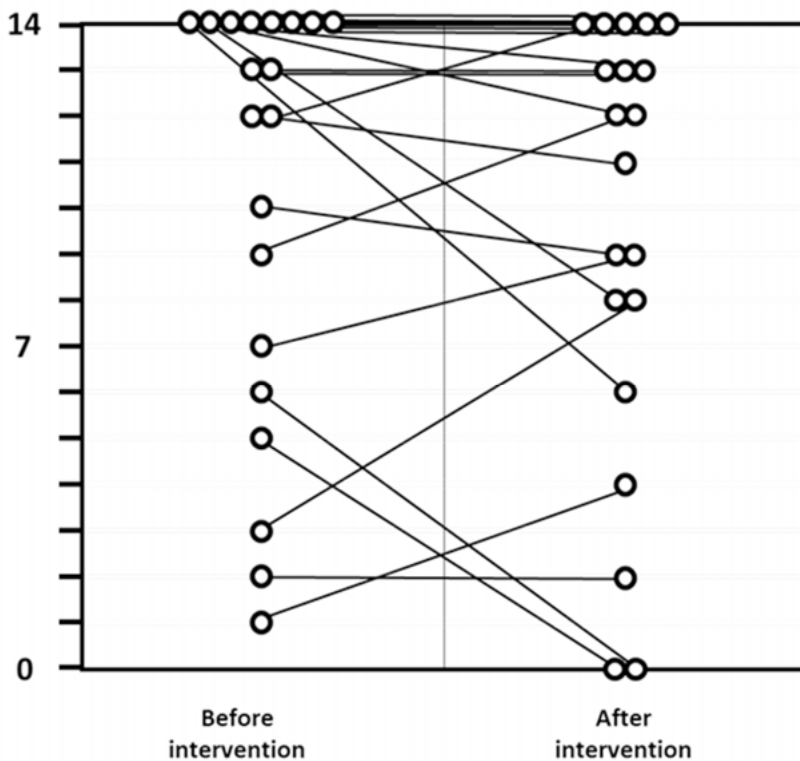


Table 6 Voiding chart data at baseline, all participating children with enuresis.

	n	Mean ± 1 SD	Median (range)
Wet nights per two weeks	66	9.9 ± 4.1	11 (1-14)
Daytime micturition frequency	63	5.4 ± 1.9	5.3 (2.5-13)
Enuresis volume*	57	67 ± 50	63 (4-349)
Urine production per 24 h/kg (mL/kg)	55	27 ± 12	26 (4-57)
Nocturnal urine production, wet nights*	48	117 ± 56	112 (35-365)
Maximum voided volume, morning void excluded*	65	79 ± 31	71 (28-148)
Maximum voided volume, morning void included*	65	87 ± 31	76 (28-167)
Average voided volume, morning void excluded*	65	48 ± 19	41 (15-107)
Average voided volume, morning void included*	65	49 ± 17	46 (20-93)

\* All volumes expressed as percentages of expected bladder capacity for the child's age according to the Koff-Hjälms formula (59, 60).

The distribution of age ( $p = 0.87$ ), sex ( $p = 0.45$ ) and body mass index ( $p = 0.53$ ) for the two groups did not differ. Moreover, as can be seen from the further analyses of children with enuresis (Table 7), no statistically significant difference was found between the constipated and non-constipated children. In the constipated children 20/23 (87%) were rectally distended, i.e. rectal diameter above 30 mm. Baseline data were compared between children with and without rectal distension as well, but no significant differences between the groups were found (data not shown). Three subjects dropped out after baseline evaluation due to social circumstances. Baseline data in these children collected before dropout did not differ from those of other subjects.

Table 7: History and voiding chart data at baseline, constipated and non-constipated children.

	Constipated (n = 23)	Non-constipated (n = 43)	p-value
Heredity	13/23 (57%)	18/43 (42%)	0.26
Urgency	15/23 (65%)	28/43 (65%)	0.99
Previous daytime incontinence	9/23 (39%)	22/43 (51%)	0.35
High arousal thresholds	18/23 (78%)	38/43 (88%)	0.47
Wet nights per two weeks	9.9 ± 4.1	9.9 ± 4.1	0.93
Daytime micturition frequency	5.1 ± 1.7	5.6 ± 1.9	0.30
Enuresis volume*	72 ± 37	64 ± 57	0.56
Urine production per 24 h/kg	29 ± 12	27 ± 11	0.47
Nocturnal urine production, wet nights*	124 ± 44	113 ± 62	0.53
Maximum voided volume, morning void excluded*	80 ± 34	77 ± 29	0.71
Maximum voided volume, morning void included*	90 ± 33	85 ± 31	0.57
Average voided volume, morning void excluded*	49 ± 17	47 ± 19	0.74
Average voided volume, morning void included*	50 ± 16	49 ± 18	0.76

Data shown are either proportions (%) or mean ± SD.

\*All volumes expressed as percentages of expected bladder capacity for the child's age, according to the Koff-Hjälms formula (59, 60).

## Treatment result (Study II)

Of the children in the constipation group (n = 23), three did not complete the follow-up, leaving 20 children for analysis of the antienuretic effect of fecal disimpaction. The median number of wet nights at baseline was 11 (range 2-14, mean  $9.8 \pm 4.1$ ) and after at least two weeks of treatment 10 (range 1-14, mean  $9.3 \pm 5.1$ ). This effect was not statistically significant ( $p = 0.43$ ). The same lack of antienuretic effect of constipation treatment was seen when looking specifically at children with rectal distension (data not shown). However, we do not know whether the rectal distension or the Rome IV status changed by treatment of constipation, since it was not reassessed.

There were three children who were partial responders to constipation therapy i.e. reduced their enuresis frequency by more than 50%. Baseline enuresis frequency was lower in this group than in the nonresponding majority, ( $4.3 \pm 2.5$  versus  $10.7 \pm 3.6$ ;  $p = 0.011$ ). No other factor had any predictive value. However, there was one interesting effect: while given laxative treatment the children's voided volumes tended to increase and the maximum voided volume (morning void excluded) came out significant  $p = 0.006$ , ( $82 \pm 36$  before



Table 7. Description of participating children, Study III (n=14).

Children in pair with a parent	n
Boys	9
Girls	5
Age	
6	4
7	6
8	1
9	3
Experience of procedure/treatment*	
Bladder/bowel diary voiding charts	14
Constipation treatment	7
BBA	8
Alarm treatment	5
Outcome of enuresis treatment (n)	
Completely dry at night	1
Partial response, $\geq 50\%$ reduction of wet nights	4
Nonresponse, less than 50% reduction of wet nights	9

\*Several participants had experience of more than one procedure.

The experiences of children and parents revealed success factors and challenges in labor-intensive management at home due to enuresis and constipation. In summary, managing the treatment of enuresis at home can be challenging for children and their parents. There were procedures that children did not like, and routines were difficult to remember, leaving them in a complicated situation. However, favorable strategies in how to manage and overcome these difficulties, and the increased knowledge gained, was also reported.

The results were sorted in four categories; 1) experiences of how to manage; 2) managing procedures was a favorable experience; 3) managing procedures made it complicated; 4) problematic to remember. In the presentation of the qualitative results BBA is named Standard Urotherapy. The categories, with subsequent subcategories, are summarized in figure 12.

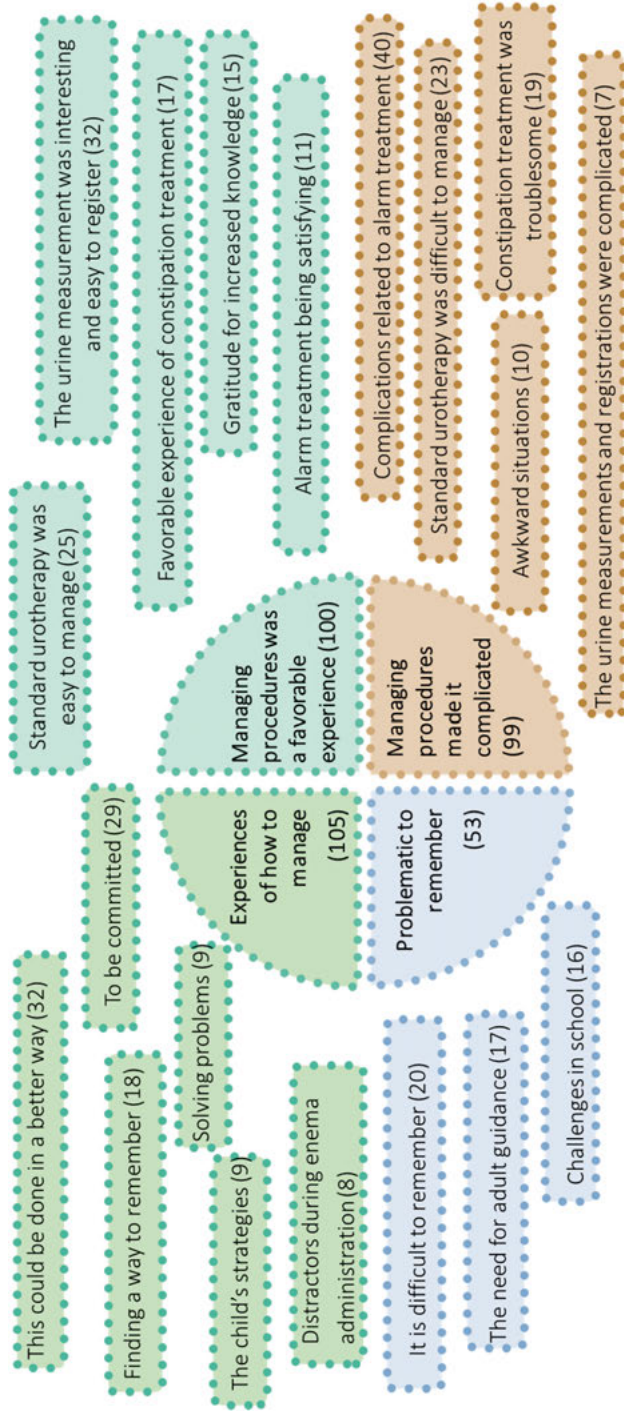


Figure 12. Results in categories and subcategories (number of citations)

## Experiences of how to manage procedures

Children expressed that interventions **could be done in a better way** and managing technicalities of the alarm were unsatisfying. Several children wanted the alarm to be designed differently, with, for instance, bespoke signals. One suggestion for improvement, by many parents and some children, was a mobile phone app that could provide information, motivation and reminders. A few parents saw potential for improvement in the healthcare system. They expressed that the child's constipation was discovered too late, resulting in delayed treatment of enuresis.

...perhaps you can start thinking about it [constipation] earlier because they have to...be 6-7 years old before you can seek help [for bed-wetting]...then you might start thinking...'Well, could my child be constipated' (parent 2)

**To be committed** was described as important to a few children, who explained that they did what they were supposed to do and did not miss a thing, even if it sometimes was hard. In the beginning they needed reminders from a parent, but after a while they managed by themselves. Parents usually stressed the importance of rigorously following the instructions given, even if this was challenging: "I didn't forget at all [standard urotherapy]. I took care of myself and did everything I was supposed to do" (child 6)

Some children and parents reported strategies **to finding a way to remember** registrations in bladder/bowel diaries, voiding charts and/or standard urotherapy. The strategies were to have objects functioning as visual cues to what they were supposed to do, or to link the new procedures to already existing routines: "...it's much easier when you're at school...then you know when to do everything [standard urotherapy]" (child 6)

When describing **the child's strategies** a few children experienced that their own individual strategies made management easier. Self-made toilet and drinking schedules worked well for some children. One child explained that "you have to face the situation and just do it", whereas some children explained that they realized that if they went to the toilet immediately when the body signalled the need for a bowel movement, they could skip the enema: "...go as soon as I need to...then I don't have to take the horrible thing [enema]!" (child 9)

When families expressed how they were **solving problems**, they explained that minor problems may arise during the treatment, problems that some families solved on their own, for example kitchen utensils for urine measurements when not being at home. With adjustments, things worked better for the child

and treatment could continue, such as adjustments included flavoring the medicine (PEG) with different juices or finding alternatives: "...you can mix strawberry juice. And raspberry juice. And pear juice. I usually have strawberry or raspberry...those are the ones I usually have the most" (child 2)

After the experience of receiving an enema, most of the children and parents found this to be troublesome. However, with **distractors** during **enema administration** they did also discover that the child could be encouraged by a reward or distracted with a mobile phone or tablet (an effective way to make the procedure acceptable for the child): "...you take your mobile phone and can play a bit while you're at it. When using the enema. Because then you think about something else." (child 2)

### Managing procedures was a favorable experience

**The urine measurements were interesting and easy to register** for most of the children and parents. Most of the parents experienced that the measurements were straightforward to perform and registration in the voiding charts with a pencil was considered an easy method. Most of the children observed that the amount of urine in the bladder differed from time to time, and several children tried to break a personal record regarding how much urine they could produce (which, it should be added, was not in accordance with the instructions given). A few children continued measuring urine after the three-day registration, just for fun.

It's fun to measure, especially when you really need to pee...because then you know...if you've been holding it in for quite a while. If you have forgotten, then it is a lot. It has worked quite well to measure it and it was fun too! (child 11)

**Standard urotherapy was easy to manage** and many of the children liked having a toilet schedule with stickers to mark when they had urinated. Most of the children and parents expressed a favorable attitude towards standard urotherapy, since it coincided with already existing routines for the child. "Easy, I just remembered!" (child 12)

Regarding the treatment of constipation, the children **expressed favorable experiences of constipation treatment**. PEG was considered easy to drink and facilitated bowel movements for all the children. Some children knew that the enema treatment was just for a limited time. As the constipation treatment continued, some children felt better and understood that the enemas were good for them. Some parents experienced an improvement in the child's well-being after the start of enema treatment; the child felt better, had less fecal incontinence and

better appetite: “I sat all evening in the bathroom and then I really pooped...it felt nice because sometimes I’d kept it [poop] in for a whole day.” (child 11)

Expressing their **gratitude for increased knowledge**, some parents explained that when they initially received basic information about the child’s condition and treatment, they became calmer and gained a more confident attitude towards the treatment. For example, the knowledge about why the enemas were needed made them more motivated to carry out the recommended procedures at home.

...didn’t really know how this worked, why you wet yourself...so it’s been interesting to learn...I hadn’t thought about him being constipated because he usually went to the toilet anyway...and then you thought ‘yes, but what a good thing, he’s been to the toilet’ like...they start to wipe themselves and so on. Yes. It was, interesting...I think a lot of people don’t know that (parent 2)

Some children and parents expressed **alarm treatment being satisfying**. They expressed that the treatment worked well and resulted in dry nights. Even though children found the treatment somewhat difficult in the beginning, they soon were used to it and thought it was worth the effort to continue: “...I feel satisfied with the treatment...it was at the beginning. Then you were very tired and you usually slept very deeply and all night.” (child 5)

### Managing procedures made it complicated

Many children experienced **complications related to alarm treatment** and explained the enuresis alarm as troublesome since it was difficult for them to wake up at night, and when they did wake up, they were confused and could neither turn off the device nor understand the need to go to the toilet. The morning after, they remembered nothing. The alarm sensor in the underwear was sometimes described as uncomfortable and difficult to attach. A couple of children became afraid of the alarm and thereafter had difficulties falling asleep in the evenings. For several families, alarm treatment was complicated by excessive sensitivity of the sensor, causing false alarms.

That one was difficult too...sometimes it beeped when I was sleeping even though there hadn’t been any pee in the bed, so it beeped anyway and it was a real nuisance. That was what was difficult, it only went off sometimes [the alarm] and then it was very difficult...I went to the bathroom. Yes. Although I hadn’t peed in the bed. (child 14)

Many children expressed that the **standard urotherapy was difficult to manage** and some stated that eight weeks was too long. Some children considered

it difficult to drink without being thirsty and some children said that the scheduled toilet visits interrupted their activities. A few children liked the toilet diary with stickers, but this was only motivating and fun in the beginning. Several children explained that they did not use the footstool (provided to optimize toilet position) since they did not see any benefit and associated it with babies.

This one wasn't very helpful...It feels like when I was so sad I couldn't reach the toilet lid; I used one just like this to reach up, so this feels like my stool when I was a baby ... I can do very well without this (child 9)

**Constipation treatment was troublesome**, and PEG and enemas was difficult to manage. A few children made the reflection that it helped for bowel movements but not the bedwetting. The citrus fruit taste of the PEG was hard to accept for some children, but the enema was described as even worse for some children. It was difficult for most of the children to relax during the rectal administration of the enemas and the emptying phase was usually described as uncomfortable, or even painful. Most of the parents expressed that they suffered with their child. Several children experienced the enema treatment so unpleasant that they never wanted to go through it again: "This is the worst I have ever gotten! I wouldn't want that again...I never want [the enema] again!" (child 9)

When managing the procedures children experienced **awkward situations** since treatment of enuresis entails the use of specific objects such as measurecups for urine, alarm devices and water bottles. Children described these objects as posing a risk of being revealed as a bedwetter if friends visit and see them. The water bottle was described as bothersome when no one else in school uses one. Children said that they were embarrassed and that they needed to come up with strategies to explain why they have an object associated with enuresis or constipation treatment.

...the night I peed [for the registration] ...I had friends at home...I didn't want to say that I measure my pee. So I lied to them a bit then. For example, 'I have to make a list for something.' So, I didn't say 'I measure my pee because I pee in my bed'. (child 8)

**The urine measurements and registrations were complicated** for a few children who found them troublesome because they wanted to do something fun instead, or they considered them unpleasant to handle. A minority of the parents explained that if urine measurements were scheduled during a weekend and something unplanned happened, everything had to be done all over again, another weekend.

“... and it was a bit difficult. We started the routine and thought ‘now we’ll do it this weekend’ and then it turned out that we went to some friends and then we got out of sync a bit and had to change and do it all again the next weekend and so. So, it was mostly because it was quite technical, to remember and when there is a panic ‘I have to go and pee’ and then you have to run first and get the measuring thing and then.”  
(parent 3)

## Problematic to remember

After having experienced standard urotherapy most of the parents expressed that **it was difficult**, even for them, **to remember** such things as registration, regular water intake and toilet routines. Some of the children and parents explained that in the beginning everything went well, but as everyday life went on, they forgot more and more about the instructions. Some children explained that they have other things such as play on their minds. A few parents expressed that since they did not manage to remind the child as they should the child did not comply with the treatment: “At first you remember very well and then in the end, you think about something else and then you forget a little.”  
(child 12)

Both children and adults were aware of the child’s **need for adult guidance** and being reminded by parents. Children expressed that it was difficult if they were not reminded and, therefore, did not comply with the treatment.

...sometimes I forgot to take it [PEG] and once at my father’s place, I forgot to take it...because he didn’t put it on the table... [at my mother’s] then it was in the bag, so sometimes I forget about it if she doesn’t remind me. (child 11)

During standard urotherapy, most children divulged several difficulties and **challenges at school**. The children could not rely on an adult at school to help them to remember the new routines and that made it difficult to follow the instructions. They described that even though they tried hard, it was problematic to adhere to new routines such as regular toilet visits and water intake during school hours. Some children were not allowed to go to the toilet during lessons and many children were not allowed to bring the water bottle into the classroom. Mostly, parents were aware of the complicated situation in school and due to their limited involvement, they had to rely on the child’s own resources.

*Parent:* ... we had written to the teacher, so she knew, twice, or maybe three times.

*Child:* But she didn’t remind me.

*Parent:* No, I think you've had to remember a lot yourself; you've done this very well; you've tried to remember yourself to go to the bathroom. (child and parent 12)

## Study IV

In the study comparing the prevalence of constipation in children with enuresis and healthy controls the age range of all study participants was between 6 to 11 years, with a mean age of 7.3 years ( $\pm 1.3$ ) and 50 (40%) of them were girls. There was a difference in sex distribution between children with enuresis and controls with more girls in the control group ( $p < 0.001$ ). To account for potential confounding factors such as gender and age, logistic regression analyses were performed. However, none of the relevant bladder and bowel variables differed between the sexes so this imbalance did not affect the comparisons between patients and controls. All the children taking part in the study had confirmed uroflow curves and none had any residual urine.

As expected, children with enuresis had a higher genetic predisposition for enuresis (heredity) and were more difficult to wake up (higher arousal thresholds) than healthy controls. But both groups had a similar prevalence of constipation and there was no difference in rectal diameter. Looking at specific items of the Rome IV criteria the only criterion that differed between groups was retentive posturing ( $p = 0.022$ ) which was more prevalent in the controls. Children with enuresis had a slightly lower defecation frequency ( $p = 0.024$ ) although this difference did not make them more prone to be constipated according to the Rome IV criteria.

Further analysis was conducted using bladder registrations to evaluate voiding patterns. The dropout rate consisted of two control children who did not record voided volumes, and the missing data for children with enuresis consisted of micturitions that were noted as 'X' rather than volumes. The results showed that children with enuresis had smaller voided volumes in comparison to the control group, regardless of whether the average or maximum values were used and if the first morning void was included or not. These differences were highly statistically significant ( $p < 0.001$ ), indicating a clear discrepancy in bladder function between the two groups.

## Summary of the main findings

In the RCT (Study I), no favorable effect of BBA as first-line treatment of enuresis was found. Instead, the enuresis alarm was (again) found to be effective. Study II addressed the laxative treatment results in children with enuresis

and concomitant constipation. No significant reduction of wet nights per 14 days was noted, and when comparing to healthy controls in study IV, children with enuresis were not more constipated. However, children with enuresis showed indirect signs of overactive bladder since they had smaller voiding volumes than children without bladder related symptoms. For the first time, children with their parents were heard regarding management of the procedures related to enuresis therapy (Study III). The management were experienced as challenging and there were procedures that the children did not like, as well as new routines that were difficult to remember, However, strategies for managing and overcoming these difficulties were suggested in the study.

# Discussion

The main findings of this thesis are important for children with enuresis and their parents as well as for the healthcare providers, since first-line treatments for enuresis such as BBA or laxatives are poorly supported by evidence. Study I was the first RCT with three arms to investigate if BBA for 8 weeks reduced enuresis frequency, but no such effect was found. The sample is a representative of treatment-naïve children with enuresis in a non-selective, real-life setting. In the same setting alarm therapy was evaluated and the results of 50 % responding (partial or fully) to the treatment can probably be more realistic and kept in mind when introducing the method to a family. BBA is recommended for enuresis based on how to manage daytime incontinence, just as constipation treatments are. Therefore, studies evaluating standard laxative treatments for children with enuresis are important as well. The results (Study II), show that fecal disimpaction in constipated children with enuresis did not reduce wet nights on its own. Additionally, when interviewing children (Study III) and their parents about BBA and constipation treatment, they reported that the procedures were problematic. These results emphasize the importance of evidence-based treatments, as managing this condition at home is not trivial. When investigating the effect of BBA on enuresis, it should be emphasized that in other contexts of bladder disorders, BBA is demonstrably effective. When treatments are necessary, the interview study can provide strategies for handling the situations based on the experiences of children and their parents. Little is also known about the difference in prevalence of constipation in children with enuresis compared to children without bladder issues. Our results (Study IV) contribute to the understanding that children with enuresis are not more constipated than others and just because a child is constipated does not automatically mean that the bladder reacts with leakage. Constipation does not influence enuresis as much as believed. Thus, if constipation does not give bothersome symptoms for the child, it may not need to be actively looked for or treated. Additionally, the inclusion of healthy controls did contribute to the findings of their higher bladder capacity, a finding that strengthens the role of the overactive bladder in children with enuresis.

When the doctoral studies began in 2018 BBA was recommended as a first-line therapy of enuresis, i.e. before other therapies were considered, no matter the subtype (66). Ever since BBA was first advocated as an antienuretic therapy several decades ago, no one before our team had performed prospective, randomized evaluations. As time passed, and partly thanks to our RCT (Study I), treatment recommendations have been revised (2) because of the insufficient evidence for recommending BBA to children with enuresis. The international impact even made it difficult to submit Paper III, as the reviewers questioned why the interviewed children with enuresis were treated with BBA therapy, since it was stated to be ineffective.

Our results thus do not support BBA as a part of first-line antienuretic therapy. While results of BBA did not differ from those in the group receiving no treatment, the effect of alarm treatment was significantly superior to both, at least partially successful in 11 out of 22 children, which is in line with what is previously known about the alarm treatment (73). Since enuresis is a common and somatically benign condition, evaluation needs to be limited and labor-intensive therapies reserved for therapy-resistant cases (21). Nevertheless, BBA is well-established as the first-line treatment of daytime incontinence (95, 96) a condition that is overrepresented in children with enuresis (97) and it is thus not far-fetched to assume that it may be effective at least in a subgroup of children with enuresis, for instance those with underlying DO. Given the epidemiologic overlap between the two conditions and the fact that they share a common pathogenetic mechanism, i.e. DO, the assumption that BBA should help in enuresis as well is clearly plausible. A Danish group, when evaluating the effect of timer-assisted urotherapy in children with daytime incontinence with or without concomitant enuresis, found that the therapy helped against only the former condition (98). Perhaps some cases of NMNE have a behavioral component and thus might benefit from a behavior-oriented intervention such as BBA? Still, we found no effect of BBA in our study even though signs of overactive bladder were found.

Finally, it is not unreasonable that parts of BBA could have other beneficial effects, such as boosting the morale of the child with enuresis and increasing their motivation. The therapeutic liaison between the caregiver and the child is not only about making the child dry at night. On the other hand, spending months following instructions could be demoralizing for the child and family if it does not lead to success.

Providing age-appropriate information enables children to participate in decisions about their care. In the international guidelines for the treatment of enuresis [BBA (68), alarm (2) and constipation (71)] demystification and explanation of the child's condition are included in them all, reflecting a child-

oriented approach where children are taken seriously. The Convention on the Rights of the Child, ratified as law in Sweden (7), states that children have the right to the best possible healthcare and adequate medical care and the right to freely express their views on all matters affecting them. For the first time, children's and parents' experiences of management and treatment of enuresis (with or without concomitant constipation) was described. Hopefully it will provide more empowerment to the families and a new understanding when treating enuresis and/or constipation.

In the interviews a few parents expressed that improvement in the healthcare system was needed. When the child's constipation was discovered during the visit for enuresis treatment, it delayed the entire process because the child was not properly prepared. Children with BBA who participated in our interviews were not helped by the recommendations, but their statements shed light on the complicated situation that all patients with lifestyle changes face. It is important to note that the results of our qualitative study illuminate challenges that extend beyond enuresis. The management of children diagnosed with DO and daytime incontinence can for example benefit from knowledge in how hard it is for children to comply with BBA in school when forgetting instructions and lacking adult assistance. Parents have also confirmed that establishing novel routines within the home environment can be challenging. This underscores the importance of caregivers supporting families with strategies to facilitate this process since encouragement and support from healthcare professionals increases adherence (76).

To understand the child's enuresis and concomitant constipation, voiding charts and bladder/bowel diaries are considered crucial in both the real-life setting and in research (2). When analysing predictive factors (Study I) for treatment success in the alarm treatment arm (the only arm in which treatment was successful), no statistically significant predictors were found. Earlier studies have indicated frequent enuresis, female sex, and family motivation as predictors of treatment success (75, 99). The fact that we could not substantiate these findings may be due to small sample size. The study was powered to find differences in treatment effect, not baseline predictors.

Diaries and charts may also be overestimated in importance. This is important to know more about especially as children and their parents in the interviews experience them as complicated and time-consuming. Moreover, using the voiding chart as a surrogate marker for bladder function could be criticized since there are other factors than just bladder function influencing when the child goes to the toilet, such as family activities, play, mealtimes and the fact that "we wee when we want" (9). It was unexpected that children who

were interviewed found it exciting to measure urine, trying to break their personal record. This is counterproductive to the recommendations in BBA. However, the voiding charts in Study IV presented significant differences in bladder volumes between children with enuresis and healthy controls. This suggests that the registrations are important, at least for research purposes, and it is important to continue the research in how important these registrations are, in enuresis and in other conditions. If they are deemed unhelpful and excluded, it will reduce the burden on families. If not, the healthcare needs to develop alternatives.

It is noteworthy that the two children who did become dry during BBA had infrequent enuresis. Since it is known that the chance for spontaneous remission is better for children with infrequent enuresis, (13) we suspect that these children either were about to get dry spontaneously or became dry just by joining the study. It's relevant to note that there were also two children who became dry in the control group and three just by meeting the research nurse (MB), and who had to be excluded before randomization. It is previously known that the mere documentation of wet nights can reduce enuresis frequency (100). Due to these circumstances a control group should always be planned for when designing enuresis studies.

During interviews parents and some of the children did suggest a mobile phone app to facilitate registrations since the mobile phone is carried everywhere. In the app it was suggested that information, preparations, reminders and instant evaluations could improve the management of treatments given. This is not in line with studies showing that children will have a greater chance of adhering to the full treatment if they have personal contact with a nurse instead of just a mobile app (76). Perhaps the solution is neither one nor the other; a combination might be best.

The Convention on the Rights of the Child states that it is important to listen to children and ensure that their voices are heard when it comes to their healthcare and treatments (6). Two treatments must be discussed in this regard: the mini-enemas and the alarm, since they caused strong negative feelings. Children experienced the enema treatment so unpleasant that they never wanted to do it again. It was the whole procedure including the rectal administration and the emptying phase that was the source of discomfort and/or pain. Most parents said they suffered with their child, a feeling that is confirmed in another Swedish interview study with parents (101). It is satisfying that the results of these two interview studies are cited, and when establishing the Swedish national guidelines for constipation treatment in children (102) alternative treatments such as high-dose PEG are described as preferable as rectal evacuation treatment for children (103). This means that, when it comes to

treatment and medical decisions, children are included in the decision-making process. However, in some cases, evacuation with enema is needed, and children in the interview study felt that distractions, often from a mobile phone, was a useful strategy.

The labor-intensive nature of the alarm is well-known (66). Nevertheless, what the children themselves think about the alarm is less well studied. Technical issues with false alarms caused confusion and some children found the alarm signal frightening and therefore they did not dare to fall asleep. This is not the intention of the alarm treatment, and the problem needs to be addressed by healthcare professionals ensuring that the equipment used functions as expected. Moreover, no matter what treatment was given, children expressed that the items connected to the treatment could expose their condition, resulting in awkward situations with embarrassment and shame.

The argument against long-term or intensified BBA as a first-line therapy in enuresis stated previous is relevant for this therapy as well: long-term constipation management is too cumbersome to qualify as a first-line therapy in enuresis. No significant difference in constipation prevalence was found between children with and without enuresis. If the constipation were central, the other children would also have bladder issues. This study does, however, not provide enough information to say for sure whether treating constipation in children with enuresis is necessary for later antienuretic therapy to work. Maybe eradication of constipation – if present – is necessary for the alarm to make the children dry? This may certainly be the case and therefore more research is needed in the field.

## Methodological Considerations

### Strengths and limitations

#### **Quantitative studies (I, II, IV)**

The quality of the studies benefits from an unselected population, representative of the enuretic population at large. The sample size was large enough not to miss any clinically relevant antienuretic effect in studies I and II. The BBA was performed by an experienced and adequately trained therapist (MB), according to ICCS guidelines and for an adequate amount of time (eight weeks). Had BBA been effective in enuresis it is likely that an effect would have been detected. Also, this was the first study to include no treatment as a comparison. This is especially important in studies of enuresis because of the nature of the condition.

Unfortunately, double blinding cannot be applied to BBA or alarm therapy. Also, it was not assessed to what extent the therapies given were adhered to; however, this reflects clinical reality. Rigorous control of the adherence to instructions would constitute an intervention in and of itself. To strengthen the adherence, the children in the BBA group were equipped with objects connected to the intervention. This might be seen as a drawback since it is not what is done in clinical reality and could have resulted in a higher response rate to the therapy. That was, however, not the case. It could be argued that we should have made BBA more intense or of longer duration in our present study, and that it may then have been effective. However, that is irrelevant because such a therapy would be too labor-intensive and costly to justify as a primary treatment for enuresis, a common and benign disorder.

The conclusion that constipation treatment did not have an antienuretic effect in the constipated children can have explanations. One explanation could simply be that constipation is not part of the cause behind the enuresis and treatment is thus irrelevant to the enuresis. Or the treatment may have been too short or too inefficient and the children were in fact still constipated after the treatment. Constipation can be persistent and in some cases treatment for several months or years is needed. One problem with the study was that we did not control the children's bowel habits and rectal diameter again after we treated their constipation. This was a bargain we had to strike between the time and resources available for the researcher and the commitment of the families. The reality in first-line care is, when constipation is treated on indication of enuresis, treatment success cannot be expected to be verified before proceeding to the next step in treating the enuresis: this simply takes too much time. And evaluation of therapy adherence would likely result in more children dropping out of the study. Moreover, children in the study were from the whole county meaning that some had to travel for hours for an appointment. Also, we wanted the study to reflect clinical reality and not subject the children and families to more interventions than they were likely to be able to comply with. Again, first-line therapies of very common disorders should not be very labor-intensive.

Children with neurodevelopmental disorders are overrepresented among those with enuresis (44). At baseline, parents were asked about the presence of such a diagnosis. However, only a few children had a proper diagnosis, even though some others had suspected problems reported by parents, schools, or the investigator (MB). No validated questionnaire was used, and the children were young, mainly 6-7 years and it could be that they had problems but not yet a diagnosis. Therefore, it was chosen not to include the neurodevelopmental disorders in the analyses when looking for predictors of treatment response.

Finally, it was difficult to recruit healthy controls, also confirmed by others (104), as the participants did not gain anything except movie tickets. The children and parents who did participate said that they wanted to help the children with enuresis. In future studies, alternative recruitment strategies than advertisement and word-of-mouth referrals may be tried.

### **Qualitative study (III)**

Interviewing children is challenging but important because there is a lack of research focusing on their experience. Although it could be argued that a parent accompanying the child to the interview was unnecessary, it was important to make the child feel comfortable and confident. The children's age (mainly 6 to 7 years old) was another challenge. Only 6% of children participating in published articles are between the ages of 6 and 8 (105). Therefore, including children representing the age group in which enuresis is most common is a strength and so is revising the interview method by including objects (props). This experience underscores the importance of considering alternative methods when interviewing children.

Due to Covid restrictions, it was difficult to find alternatives to meet in a hospital setting, which was not ideal. Moreover, children and parents may have under- or over-reported their experiences, and the interviewer being their healthcare provider might be a drawback. However, since children (and parents) already had a professional relationship with the interviewer, they may have felt more comfortable sharing their experiences. The interviewer's approach was empathic and non-judgmental, and the study results present the children's honest expression of how much they disliked constipation and alarm treatment. Furthermore, children are more likely to tell the truth if questioned by someone familiar with their situation (106). The total number of included children in the present study (n=14), together with one parent, might be seen as limited but analysis of data showed redundancy and thus the sample size was large enough (92). A qualitative exploratory study design was used to find different perspectives and try to understand the informants' views instead of explaining results being generalizable to a wider population. Carefully collected, analysed and described, the findings can be transferred to similar persons or contexts. In this context, a more complete understanding is achieved by combining quantitative results with the shared experiences of children and their parents.

## Recommendations for further research

More research is needed to understand nocturnal enuresis and the differences between the subtypes. Treatments given must be grounded in science, not just experiences and assumptions, and methods need to be well-defined for the patients, otherwise they do not adhere to treatments given. This will help create a more effective healthcare system. More qualitative research is needed and including children in future research is crucial to determining their needs and how to support them. This means not only interviewing them but also including them in the process of designing the research projects. This makes sure that their needs and preferences are considered, which not only supports their rights but can also lead to better healthcare results.

## Conclusion

Basic bladder advice lacks therapeutic effect in nocturnal enuresis and treatment of constipation is also, by itself, ineffective to get children dry at night. Overall, we found no support for a major link between constipation and enuresis. And since laxative therapy, basic bladder advice and the enuresis alarm were all found to be cumbersome by the children and their families we recommend that only the evidence-based procedure – i.e. the enuresis alarm – be used as a standard management of nocturnal enuresis. Furthermore, to adhere to treatment children with nocturnal enuresis express that they need more support from their parents. The healthcare provider, in collaboration with the parents, needs to find options to suit the individual child.

## Clinical implications

As previously stated, the case for BBA's role in enuresis treatment rests partly on its limited side effects. But seen from a wider perspective the therapy may not be as harmless as assumed. Putting aside the considerable cost of employing skilled nurses for repeated sessions with the family and the fact that BBA delays access to effective treatment, possible negative effects of BBA are yet to be studied. The child and family may experience frustration and, in the worst case, lose confidence in the healthcare provider. First-line treatments of relatively benign conditions such as enuresis should be easy to administer and adhere to, at least if the effectiveness of the treatment is questionable.

Furthermore, urotherapists represent a scarce resource, not readily available outside tertiary care. If these personnel could be unburdened by such a labor-intensive assignment as BBA on children with enuresis, this would give them more time to help other patients, such as those with daytime incontinence, in an evidence-based way. The same arguments can, although with perhaps less force, be applied to constipation treatment. This therapy is in some instances regarded as cumbersome and/or an intrusion in the child's private sphere. We should strive to treat children, not diagnoses or ultrasonographical findings. Fecal impaction *per se* should perhaps not be treated if it is asymptomatic.

It should be noted that BBA is so much more than voiding schedules and instructions about toilet posture. The therapist educates the child about bladder function and their condition, boosts morale and creates an alliance with the family. But encouragement is an important part of *all* relationships between patient and caregiver; this is indeed part of good doctoring and good nursing in general.

# Populärvetenskaplig sammanfattning

Vart tionde barn lider av sängvätning (även kallat nattväta). Att kissa i sängen kan sänka barnets självförtroende och förmågan att ta sig an livets möjligheter. Övernattning hos kompisar eller fotbollscuper på helger är för de flesta barn något att se fram emot, medan det för barn med nattväta kan innebära ångest inför en hotande pinsam katastrof. Vi vet att barns utveckling är mycket känslig; att slippa dålig självkänsla är därför viktigt och barnen bör få bästa möjliga chans att bli fria från sin nattväta.

Att kissa i sängen och att kissa på sig på dagen är sannolikt vanligare om man dessutom är förstoppad. Denna koppling beror åtminstone delvis på att den fyllda ändtarmen hos förstoppade barn trycker på urinblåsan bakifrån och gör att den lättare drar ihop sig och tömmer sig utan förvarning. Rekommendationen har hittills varit att barn med samtidig nattväta och förstoppning bör behandlas med tarmreglerande läkemedel oavsett om de egentligen har besvär från tarmen, i förhoppningen att detta skall göra barnen torrare. Den vetenskapliga grunden för detta var dock dåligt undersökt innan vår forskargrupp började granska metoden.

Två vetenskapligt utvärderade förstahandsbehandlingar finns mot sängvätning: larmbehandling, då en detektor i underkläderna eller under lakanen utlöser ett högljutt larm när den blir våt, samt ett läkemedel som minskar urinproduktionen under natten. Utöver larmbehandling och läkemedel erbjuds i regel blåsträning som syftar till att hjälpa barnet att ta kontroll över urinblåsan genom beteendeförändringar. Under träningen får barnet bland annat instruktioner om att sprida drickandet jämnt fördelat över dagen, kissa regelbundet efter ett schema och sitta på rätt sätt vid toalettbesöken. Rekommendationen har länge varit att erbjuda sådan träning innan behandling med larm eller medicin påbörjas, men det har inte testats tillräckligt på vetenskapligt vis om det fungerar. Med det här forskningsprojektet ville vi utreda både tarmbehandlingens och blåsträningens eventuella nytta hos barn som lider av nattväta.

Projektet har inneburit att en stor grupp med barn som kissade i sängen undersöktes för att se om de också var förstoppade. Om de var det så fick de förstoppningsbehandling i ett par veckor. Antalet ”våta nätter” under 2 veckor uppskattades före och efter behandlingen. Dessutom jämfördes de förstoppade

barnen med de som inte var förstoppade avseende blås- och njurfunktion. Utöver barnen med nattväta så undersökte vi barn som inte hade några som helst besvär med sin kissblåsa. Vi ville veta hur många av dem som var förstoppade eftersom vi trodde att barn med nattväta oftare drabbades av förstoppning än andra. I det avseendet visade det sig att vi hade fel. Barnen med nattväta var inte mer förstoppade, men de hade en mindre kissblåsa. Det fyndet ger oss en lite tydligare bild om att nattväta delvis kan bero på att barnens kissblåsa är bråkigare än andras, dvs lättare drar ihop sig under sömn.

Därefter ville vi utreda blåsträngens effekt på nattvätan. Vi delade därför slumpvis in barnen i tre grupper; en som fick blåsträng i 8 veckor, en som gavs larmbehandling i 8 veckor och en som inte fick någon behandling alls under lika lång tid. Antalet våta nätter dokumenterades under två veckor före och i slutet av behandlingarna. Valet av larm och blåsträng motiverades av att de båda innebar rätt så mycket arbete för familjen och därför tyckte vi att det blev en rättvis jämförelse. Läkemedelsbehandlingen var inte aktuell eftersom det enbart består i att ta en tablett. De barn som inte fick någon behandling alls var viktiga att jämföra de andra två grupperna med eftersom nattväta växer bort. Ingen vet när det sker men sannolikt kunde en eller flera barn bli torra under studiens gång bara av sig själva och därför behövs jämförelsegruppen utan behandling.

Våra resultat var entydiga. Tyvärr gjorde förstoppningsbehandlingen inte barnen torrare på natten, och så var bara larmbehandlingen effektiv. Blåsträngingen gjorde inte barnen torrare på natten än gruppen som inte fick någon behandling alls. När vi intervjuade barnen om hur de hade upplevt behandlingarna de fått var de tydliga med att vissa behandlingar var jobbiga att genomföra och de önskade att det skulle finnas andra sätt att genomföra behandlingarna på. Barnen kunde också se att det fanns sådant som var spännande och roligt med behandlingarna och de skaffade sig strategier för att klara av dem. Detta är viktig kunskap för oss i vården när vi ska hjälpa barn som kissar i sängen framöver.

Med hjälp av resultaten av dessa studier kan vi ge bättre rekommendationer om hur nattvätande barn skall behandlas: framför allt kan vi föreslå att man inte slösar tid med blåsträng dagtid utan direkt sätter i gång behandling med larmet eller läkemedel så fort barnet blivit stort nog att besväras av sin sängvätning. De barn som är förstoppade ska inte vilseledas av att de blir torra bara av att behandla förstoppningen. I stället kan aktiv behandling av nattvätan sättas in samtidigt som förstoppningen behandlas och på så vis får barnen bättre vård och sjukvårdens resurser används mer effektivt.

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# Appendix I Checklista

## BASLINJEDATA, CHECKLISTA PATIENTER

Pat nr: ..... Längd: ..... Vikt: ..... Ålder: ..... o flicka o pojke

**MOTTAGNINGSBESÖK**, datum: .....

### ANAMNES

- Ingen eller marginell daginkontinens
- Ingen neurologisk sjukdom, allv urologisk missbildning eller njursjukdom
- Ingen tidigare enuresbehandling
- Tidigare Minirinbehandling
  - Minirin fungerade  bra  inte alls
  - Primär enures  ja  nej
- Brukar barnet ofta kissa i sängen
- flera gånger samma natt?  ja  nej  vet ej
- Behöver dricka på natten?  ja\*  nej
- Urinvägsinfektioner  $\geq 2$  års ålder  flera\*  en  nej
- Hereditet? (förälder, syskon)  ja  nej  vet ej
- Svår att väcka?  mycket  ganska  nej
- Neuropsykiatriska problem?  ja  nej  kanske
- Urgency?  ofta  ibland  nej
- Tidigare daginkontinens? (>4 års ålder)  ja  nej

### Senaste 4 veckorna

- Bajsar < 3 ggr/vecka?  ja  nej
- Avföringsinkontinens  $\geq 1$  ggr/v?  ja  nej
- Smärtsam/hård avföring?  ja  nej
- Tydligt att barnet går och håller sig?  ja  nej
- Stor avföring som är svår att spola ner?  ja  nej
- Upplever föräldrarna barnet som förstoppat  ja  nej

### FLUOMETRI, RESIDUALURIN (bifoga kurva!)

ua (klock- eller tornformad kurva, resurin max 20 mL)  patologisk: .....

### URINSTICKA

ua (inga leukocyter, nitrit neg)  Avvikelse: ..... (skicka odling)

REKTALDIAMETER: ..... mm

### KISS/BAJSLISTA

Utlämnat: .....  Återlämnat: ..... Dröjsmål: ..... veckor

Antal luckor: ..... Kommentarer till listan: .....

### BEDÖMNING FÖRSTOPPNING

Inte förstoppad  Förstoppad, på grund av .....

Hur viktigt är det för dig att snart bli torr?  0  1  2  3  4  5  6  7  8  9  10

Hur viktigt är det för dig att ditt barn snart blir torr?  0  1  2  3  4  5  6  7  8  9  10

\*barnläkarundersökning krävs

## Appendix II Kiss och bajsdagbok

### **Enuresstudien – Rätt behandling till rätt barn. *Innan studiestart***

Vi veta mer om hur dina njurar, din urinblåsa och din tarm fungerar. Därför vill vi att du dels fyller i en lista över våta/torra nätter och tarmtömningar under 14 dagar, dels mäter hur mycket du kissar under ett par dygn, förslagsvis under en helg.

**Kod:** .....

### **Kiss- och bajsdagbok *utan* behandling**

Fyll i torra och våta nätter, pappa/mamma skall inte väcka dig på natten. Markera de dagar som du bajsar. Sätt kryss i rutorna!

	<b>Datum</b>	<b>Torr natt</b>	<b>Våt natt</b>	<b>Vaknade kissnödig och gick på toa- letten under natten</b>	<b>Tarm- tömning</b>
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					



## Appendix III Intervjuguide

Under studien har ni fyllt i flera dagböcker för att vi ska se hur du (barnet) kissar och bajsar. Du har också fått en behandling (för förstoppning/basala uroråd/larm)

Har lagt fram sådant som representerar de behandlingar/undersökningar som barnet har erfarenhet av. Barnet uppmanas välja det som hen vill börja prata om och berätta för intervjuaren vad det är och används för.

Kan du (barnet) berätta om hur det var att fylla i kiss och bajsdagboken?

*Har deras listor framme för att hjälpa till att minnas tillbaka.*

Hur gjorde ni hemma hos er?

Vad var lätt/ svårt?

Fanns det situationer (hemma/skolan) då det var svårt att fylla i listorna?

Vilka råd skulle du vilja ge till andra som ska fylla i dagboken?

Du (barnet) har också fått behandling för att sluta kissa i sängen, berätta hur det var!

*Har sakerna de använde för förstoppningsbehandling/basala uroråd/ larmbehandling framme för att hjälpa till att minnas tillbaka.*

Hur gjorde ni hemma hos er?

Vad var lätt/svårt?

Fanns det situationer (tex i skolan/ resa) då det var svårt?

Vilka råd skulle du vilja ge till andra som ska genomföra samma behandling som du fick?

Vill du som förälder förtydliga eller lägga till något om det vi har pratat om?

## Appendix IV Information om studien - barn

Hej!

Jag har hört att du kissar i sängen. Visste du att kanske vart tionde barn i lågstadiet har samma problem? Vi försöker ta reda på hur vi bättre ska kunna hjälpa de här barnen att bli torra. Om du vill får du vara med i vår forskning och hjälpa oss med det här. På det viset kan vi förbättra behandlingen av nattväta i Sverige och resten av världen.

När du och dina föräldrar kommit överens om att vara med i forskningen kallas ni till Barn- och ungdomsmedicinska mottagningen i Falun för att träffa mig, jag är barnsjuksköterska och specialist på urinvägarna och tarmen (kiss och bajs).

Vid första besöket görs en undersökning av din tarm med ultraljud, det är ofarligt och gör inte ont (och du behöver inte ens ta av dig underkläder). Det är bra om du inte kissat precis har innan besöket! Med ultraljudsmaskinen kan vi se om det finns för mycket bajs i tarmen som behöver komma ut. Vi vet att en del barn slutar kissa i sängen när tarmen behandlas. Du kommer också att få kissa på en specialtoalett som mäter kisstrålen, och sen tittar vi med ultraljudsapparaten om kissblåsan blivit tom. På det här viset vet vi bättre hur din kissblåsa fungerar. Du kommer dessutom tillsammans med mamma eller pappa att få svara på frågor, en del på mottagningen och en del hemma. Hemma kommer du också att under ett par dagar få fylla i listor över hur ofta du kissar och bajsar.

Efter det kommer alla barn som vill vara med att lottas in i tre grupper och få olika slags behandlingar under 8 veckor. Grupperna är:

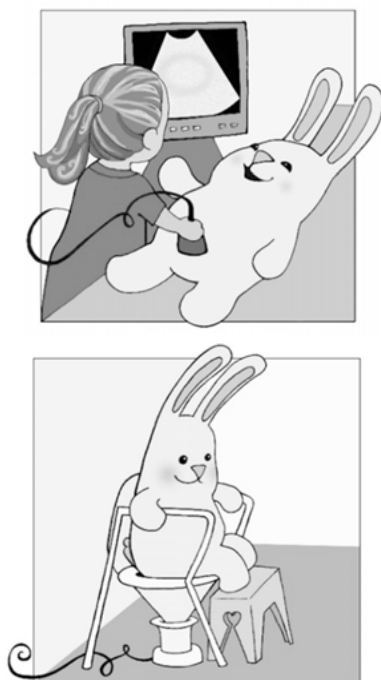
- Uroråd (kisstips dagtid)
- Alarmbehandling (klocka som larmar när det kommer kiss i sängen)
- Ingen behandling alls

Gruppen med barn som inte får någon behandling alls kallas kontrollgrupp. Det är viktigt i forskning att ha en kontrollgrupp så att man har något att jämföra med. Annars kan man inte ta reda på om behandlingarna är bra eller dåliga. Efter att forskningen är över (8 veckor) får ALLA barn som kissar i sängen behandling direkt.

Jag kommer att hålla kontakten med dina föräldrar på telefonen och vi ses när det gått 8 veckor. Du och dina föräldrar får svara på frågor och berätta hur ni tycker att det har gått. Om du fortfarande kissar i sängen hjälper jag dig tills det har gått över.

En del barn och föräldrar vill jag intervjua lite extra, vi får se om det blir ni 😊

Hoppas vi ses! *Malin Borgström*



## Appendix V Information om studien - föräldrar

### **Studieinformation**

(Förälder)

#### **Studie om behandlingsstrategier vid enures (nattväta)**

##### ***Förfrågan om deltagande***

Ditt barn har enures, som är den medicinska termen för nattväta. Denna åkomma drabbar uppemot vart tionde barn vid skolstarten. Tillståndets orsak har med njurarna, urinblåsan och sömnen att göra. Du tillfrågas härmed om du vill låta ditt barn delta i en studie för att hitta rätt behandling till rätt barn. Läs noggrant igenom denna information och tveka inte att ställa frågor om något är oklart innan du fattar ditt beslut.

##### ***Bakgrund och syfte***

Traditionellt har behandlingen av nattväta vilat på tre ben. Rekommendationen har varit att som första steg genomföra basal blåsträning (uroråd) och, om detta inte hjälper, gå vidare med läkemedlet desmopressin (för att minska urinproduktionen nattetid) eller larmbehandling (som påverkar sömnen). Trots detta är det många barn som inte blir hjälpta.

Om olika barn har olika orsak till sin nattväta så svarar de också olika bra på olika behandlingar. Vi vill undersöka om behandlingen kan individualiseras utifrån information som ges vid utredningen av barnet, så att rätt behandling kan ges från första början. Förhoppningsvis har barnet då en större chans att bli torr vid första försöket.

##### ***Hur går studien till?***

Att delta i studien innebär att ni får träffa en urotarmterapeut (sjuksköterska som är specialiserad på urinblåsa och tarm) och får svara på ett antal frågor om blås- och tarmfunktion. Barnet får sin blåsfunktion undersökt med urinflödesmätning (kissa på en specialtoalett) och ultraljudsundersökning för att

se ev kvarvarande urin i urinblåsan. Ändtarmens diameter/fyllnad uppskattas också med hjälp av ultraljud. Dessa undersökningar är fullständigt smärtfria och ofarliga, och innebär inte heller att sjuksköterskan behöver titta innanför barnets underkläder. Undersökningarna ingår dessutom redan som rutinundersökningar av barn med kissproblem. Skulle en dold förstoppning upptäckas kommer den behandlas, för att se om det räcker för att göra barnet torrt på natten.

Alla familjer kommer att få en dagbok att fylla i hemma. I denna registreras:

- Våta och torra nätter under 14 dygn
- Vakna nattkissningar under 14 dygn
- Blåstömningsvolymen vid varje kissning under 2 dygn
- Vätskeintag under 2 dygn
- Vägning av lakansskydd/blöjor under 3 nätter
- Tarmtömningar under 14 dagar

När dagboken är ifylld (och en eventuell förstoppning är behandlad) lottas alla deltagande barn in i tre lika stora grupper, som kommer att få olika behandling i åtta veckor.

Grupperna är:

- A) Behandling med basala uroråd
- B) Behandling med larm
- C) Ingen behandling alls

Barnen som får behandling (grupp A och B) har telefonkontakt med urotarmterapeuten redan efter två veckor. I slutet av studien görs ovanstående dagboks registreringar igen. Alla föräldrar kommer att tillfrågas om upplevelsen av behandlingen (eller den uteblivna behandlingen). De barn som fortfarande kissar i sängen efter de åtta veckorna kommer att få fortsatt hjälp av barnkliniken.

En del barn och föräldrar kommer att tillfrågas om medverkan i intervju. Intervjuerna sker med barnet och den vuxne tillsammans och den görs av urotarmterapeuten. Intervjuerna spelas in och skrivs sedan ut ordagrant. Texten hanteras på ett sätt så den inte kan kopplas till vilken person som sagt vad. Det är endast forskargruppen som har tillgång till materialet. När arbetet godkänts kommer inspelningarna raderas. Intervjuerna beräknas ta ca 30 minuter, beroende på hur mycket ni vill berätta.

### ***Vilka är riskerna?***

Att delta i studien innebär inga risker för ditt barn. Behandlingarna, som redan är vedertagna, ställer vissa krav på både barnet och föräldrarna. Oavsett vilken behandling barnet får (eller inte får) kommer de som fortfarande kissar i sängen efter studiens slutförande erbjudas tid till barnkliniken för bedömning och ställningstagande till andra behandlingsalternativ.

För barnen i grupp C fördröjs den aktiva behandlingen med åtta veckor.

### ***Finns det några fördelar?***

Genom att delta i studien får ni direkt kvalificerad hjälp, av urotarmterapeut, vilket annars bara erbjuds äldre barn med svårbehandlad nattväta. Väntetiden för att få ett larm på Barnmottagningen i Falun är normalt sett ca tre månader. Således är det en fördel att delta trots att ni kan lottas till den grupp (grupp C) som inte får någon behandling alls under 8 veckor.

### ***Hantering av data och sekretess***

Projektet kommer att samla in och registrera information om ditt barn, detta sker via samtal med dig och ditt barn samt via de listor ni fyller i. Materialet förvaras under 10 år och kommer att hållas inlåst på Barn- och ungdomskliniken så att inte obehöriga kan ta del av dem. Viss data förs in i barnets journal. Data som är av intresse för studien kodas och kommer att registreras i en elektronisk databas, kodnyckeln kommer att förvaras hos inlåst på kliniken. Studieresultatet sammanställs och kan komma att överföras till länder utanför EU. Resultaten kan i kodad form komma att presenteras på vetenskapliga

kongresser och publiceras i vetenskapliga artiklar. Ansvarig för dina personuppgifter är Landstinget Dalarna. Enligt EU:s dataskyddsförordning har du rätt att kostnadsfritt få ta del av de uppgifter om dig som hanteras i studien, och vid behov få eventuella fel rättade. Du kan också begära att uppgifter om dig raderas samt att behandlingen av dina personuppgifter begränsas. Om du vill ta del av uppgifterna ska du kontakta Malin Borgström, [malin.borgstrom@regiondalarna.se](mailto:malin.borgstrom@regiondalarna.se). Dataskyddsombud på Landstinget Dalarna är Carl Gudmundsson och han nås på [carl.gudmundsson@regiondalarna.se](mailto:carl.gudmundsson@regiondalarna.se). Om du är missnöjd med hur dina personuppgifter behandlas har du rätt att lämna in klagomål till Datainspektionen, som är tillsynsmyndighet.

### ***Försäkring***

Ditt barn är försäkrat genom Patientskadeförsäkringen.

### ***Frivillighet***

Du som förälder skriver på en separat samtyckesblankett som gäller ditt barns deltagande i studien. Deltagandet är frivilligt och ni kan när som helst välja att avbryta deltagandet. Om ni väljer att inte delta eller vill avbryta deltagandet behöver ni inte uppge varför, och det kommer inte heller att påverka ert barns framtida vård. Om du vill avbryta ditt deltagande ska du kontakta den ansvariga för studien (se nedan).

### ***Hur får jag information om studiens resultat?***

När studien är klar kommer resultaten att presenteras på en vetenskaplig kongress och genom publikation i en vetenskaplig tidskrift. Om du och ditt barn vill ta del av resultaten kan ni kontakta ansvarig läkare eller studiesköterska, som kan förmedla var ni kan hitta informationen.

### ***Ansvariga***

Om du har frågor angående något i studien så går det bra att kontakta studieansvarig sjuksköterska, Malin Borgström.

**Med vänlig hälsning,**

MALIN BORGSTRÖM, barnsjuksköterska, urotarmterapeut & doktorand.  
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