Journal of Pediatric Urology (xxxx) xxx xxx

Review Article

The efficacy of standard urotherapy in the treatment of nocturnal enuresis in children: A systematic review

Cecilie Siggaard Jørgensen [a,c,*], Konstantinos Kamperis [a,c], Johan Vande Walle [b], Søren Rittig [a,c], Ann Raes [b], Lien Dossche [b]

[a]Department of Pediatrics and Adolescent Medicine, Aarhus University Hospital, Aarhus, Denmark Palle Juul-Jensens Boulevard 99, Aarhus N DK-8200, Denmark

[b]Department of Pediatric Nephrology, Ghent University Hospital, Ghent, Belgium C. Heymanslaan 10, Ghent BE-9000, Belgium

[c]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

* Correspondence to: Dr. Cecilie Siggaard Jørgensen Department of Paediatrics and Adolescent Medicine, Aarhus University Hospital Palle Juul-Jensens Boulevard 99, DK-8200 Aarhus N, Denmark Tel.: +0045 61161606
cecisi@rm.dk (C.S. Jørgensen)
konskamp@rm.dk (K. Kamperis)
johan.vandewalle@uzgent.be (J.V. Walle)
soren.rittig@skejby.rm.dk (S. Rittig)
ann.raes@uzgent.be (A. Raes)
lien.dossche@uzgent.be (L. Dossche)

Keywords
Nocturnal enuresis; Standard urotherapy; Efficacy; Children

Received 28 May 2022
Revised 8 December 2022
Accepted 20 December 2022
Available online xxx

Summary

Introduction
Standard urotherapy in children with nocturnal enuresis (NE) is first-line treatment according to the current International Children's Continence Society (ICCS) guidelines. ICCS defines standard urotherapy as information and demystification, instruction in how to resolve lower urinary tract dysfunction, lifestyle advice, registration of symptoms and voiding habits, and support and encouragement. These interventions often are time consuming and some aspects of urotherapy, such as fluid restrictions, can be a frustrating process for a child, which emphasizes the importance of clarifying their relevance. The purpose of this review is to perform a systematic search in literature to evaluate the use of standard urotherapy in the treatment of children with primary NE (PNE).

Study design
A systematic literature search was conducted in MEDLINE, Embase, and CENTRAL based on the key concepts of standard urotherapy and NE. We identified 2,476 studies. After a systematic selection process using the Covidence tool, 39 studies were included. The quality of the studies was assessed by the QualSyst Checklist. Our protocol adheres to the PRISMA statement and was registered in PROSPERO database (CRD42020185611).

Results
Most of the 39 included studies scored low in quality. All studies combined several urotherapy interventions and studied different study populations. Twenty-two randomized controlled trials (RCTs) were included, which reported 0—92% of children being dry after urotherapy treatment. Three RCTs, all individualizing and optimizing drinking and voiding during the day and practicing optimal toilet posture, scored higher in quality based on the QualSyst score, and reported few children experiencing complete resolution of NE (5—33%). Eight studies compared the efficacy of urotherapy to a control group, however, conflicting results were found.

Discussion
This systematic review presents available literature in the field of standard urotherapy in the treatment of children with PNE. One possible explanation for low efficacy rates of urotherapy in NE is the large heterogeneity of the study populations and interventions. Additionally, the intervention period and the intensity of intervention can have an impact on the outcome.

Conclusion
The number of clinical studies on standard urotherapy in children with NE is limited and many of them are of poor quality. High quality research in a well-defined NE population is needed to establish the role of standard urotherapy in first-line treatment of children with NE or as an add-on to other first line treatments. We conclude that at present there is insufficient evidence for recommending standard urotherapy to children with PNE as a first line treatment modality.

https://doi.org/10.1016/j.jpurol.2022.12.011

Please cite this article as: Jørgensen CS et al., The efficacy of standard urotherapy in the treatment of nocturnal enuresis in children: A systematic review, Journal of Pediatric Urology, https://doi.org/10.1016/j.jpurol.2022.12.011

Introduction

Nocturnal enuresis (NE) is defined as intermittent incontinence during sleep after the age of five years [1], and is a very common childhood condition seen in 10–16% of seven-year-old children [2,3]. NE can negatively impact the child's social and psychological well-being [4]. During the previous years, a variety of different interventions have been suggested as first line treatment for NE. In 1974, Azrin et al. introduced the term "Dry-bed Training" (DBT) [5]. Originally, the DBT included inhibiting urination, positive reinforcement, training in rapid awakening, increased fluid intake, increased social motivation, self-correction of accidents and practice in toileting, combined with the use of a bedwetting-alarm device. However, over the years, many variants of the concept with or without an alarm have been described with different terminology such as "behavior modification", "behavior therapy", "bladder training", "basic bladder advice", and more. In 2014, the International Children's Continence Society (ICCS) [6] defined the concept of "urotherapy" in their guidelines as the conservative-based approach to lower urinary tract symptoms (LUTS). The treatment approach is divided into "standard therapy" and "specific interventions" (such as pelvic floor muscle retraining, neuromodulation, or intermittent catheterization). According to the ICCS [7], standard urotherapy includes 1) information and demystification, 2) instruction in how to resolve LUT dysfunction, 3) lifestyle advice, 4) registration of symptoms and voiding habits, and 5) support and encouragement. Even though LUTS are not always present in children with NE, aspects of urotherapy are widely used before starting treatment with an enuresis alarm or desmopressin (DDAVP) [1]. Since initiation of standard urotherapy may lead to significant postponement of other more efficient therapies while awaiting improvement, and

Table 1 Quality assessment of all included studies using the QualSyst checklist (QualSyst Tool) [9] Y = yes, N = no, P = partial, N/A = not applicable. The total score ranges from 0 to 1.

	Study	Question/ objective sufficiently described?	Study design evident and appropriate?	Method of subject/ comparison group selection or source of information/input variables described and appropriate?	Subject (and comparison group, if applicable) characteristics sufficiently described?	If interventional and random allocation was possible, was it described?	If interventional and blinding of investigators was possible, was it reported?
Randomized controlled studies	Bollard 1977 [13]	Y	Y	P	P	N	N/A
	Doleys 1977 [20]	Y	P	N	Y	N	N/A
	Harris 1977 [15]	Y	Y	Y	Y	P	N/A
	Azrin 1978 [23]	Y	Y	Y	P	N	N/A
	Nettelbeck 1979 [16]	Y	Y	P	P	N	N/A
	Mehrotra 1980 [24]	P	P	N	N	N	N/A
	Fava 1981 [11]	Y	Y	P	N	P	N/A
	Bollard 1982 [14]	Y	Y	Y	P	P	N/A
	Keating 1983 [17]	Y	Y	P	P	N	N/A
	Lester 1991 [25]	Y	P	P	N	P	N/A
	Ronen 1995 [18]	Y	Y	P	P	N	N/A
	Kahan 1998 [27]	Y	Y	Y	P	Y	N/A
	Kruse 1999 [22]	Y	P	P	P	N	N/A
	Hamano 2000 [28]	Y	Y	P	Y	P	N/A
	Van Hoeck 2007 [12]	Y	Y	Y	P	Y	N/A
	Van Dommelen 2009 [19]	Y	Y	Y	P	Y	N/A
	Oliveira 2012 [32]	Y	Y	Y	P	Y	N/A
	Cederblad 2015 [21]	Y	Y	Y	Y	Y	N/A
	ElBaz 2015 [29]	Y	P	P	P	P	N/A
	Kajbafzadeh 2015 [33]	Y	Y	Y	Y	Y	N/A
	Ma 2017 [30]	Y	P	P	Y	P	N/A
	Hascicek 2019 [31]	Y	Y	Y	Y	Y	N/A
Cohort studies	Dische 1971 [47]	Y	Y	Y	Y	N/A	N/A
	Azrin 1979 [48]	Y	Y	Y	P	N/A	N/A
	Devlin 1990 [49]	Y	Y	Y	Y	N/A	N/A
	Hirasing 1991 [50]	P	N	N	N	N/A	N/A
	Spehr 1991 [51]	Y	Y	P	P	N/A	N/A
	Robson 2002 [52]	Y	P	Y	Y	N/A	N/A
	Al-Harbi 2004 [53]	Y	Y	Y	Y	N/A	N/A
	Marschall-Kehrel 2004 [54]	Y	P	Y	P	N/A	N/A
	Pennesi 2004 [34]	Y	Y	P	P	N/A	N/A
	Sehgal 2007 [26]	Y	P	P	P	N/A	N/A
	Glad Mattsson 2010 [35]	Y	P	P	P	N/A	N/A
	Elsayed 2012 [43]	Y	P	P	Y	N/A	N/A
	Erol 2016 [55]	Y	Y	Y	Y	N/A	N/A
	Tkaczyk 2017 [44]	Y	P	P	P	N/A	N/A
	Im 2018 [42]	Y	P	Y	Y	N/A	N/A
	Saarikoski 2018 [36]	Y	P	P	P	N/A	N/A
	Ma 2019 [45]	Y	Y	Y	Y	N/A	N/A

Please cite this article as: Jørgensen CS et al., The efficacy of standard urotherapy in the treatment of nocturnal enuresis in children: A systematic review, Journal of Pediatric Urology, https://doi.org/10.1016/j.jpurol.2022.12.011

If interventional and blinding of subjects was possible, was it reported?	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement/ misclassification bias? Means of assessment reported?	Sample size appropriate?	Analytic methods described/justified and appropriate?	Some estimate of variance is reported for the main results?	Controlled for confounding?	Results reported in sufficient detail?	Conclusions supported by the results?	Total score
N/A	Y	P	P	N	N	Y	Y	0.58
N/A	Y	P	Y	N	N	P	P	0.50
N/A	P	P	P	N	N	P	Y	0.63
N/A	Y	Y	P	N	N	Y	Y	0.67
N	P	N	N	N	N	P	Y	0.38
N/A	P	Y	N	N	N	N	P	0.25
N/A	P	P	P	N	N	N	P	0.42
N/A	Y	P	P	N	N	Y	Y	0.67
N/A	P	N	P	N	N	P	P	0.42
N/A	N	P	N	N	N	P	P	0.33
N/A	P	P	Y	Y	P	P	Y	0.67
P	Y	Y	Y	N	N	Y	Y	0.77
N/A	Y	P	N	N	N	P	P	0.42
N/A	Y	P	Y	Y	N	Y	Y	0.79
P	Y	P	Y	Y	Y	Y	Y	0.88
N/A	Y	P	Y	N	N	P	Y	0.71
N/A	P	P	Y	Y	N	Y	Y	0.79
N/A	Y	Y	Y	Y	N	Y	Y	0.92
N/A	P	P	P	Y	P	P	Y	0.63
N/A	Y	Y	Y	Y	N	Y	Y	0.92
N/A	P	P	P	N	N	Y	P	0.54
N/A	Y	Y	Y	Y	N	Y	Y	0.92
N/A	Y	Y	N	N	N	P	Y	0.68
N/A	Y	Y	N	N	N	Y	Y	0.68
N/A	P	Y	P	N	N	P	Y	0.68
N/A	P	P	N	N	N	N	P	0.18
N/A	P	Y	N	N	N	P	Y	0.55
N/A	Y	N	Y	Y	N	Y	Y	0.77
N/A	Y	P	Y	Y	N	Y	Y	0.86
N/A	Y	Y	N	N	N	Y	Y	0.64
N/A	Y	Y	Y	N	N	P	P	0.64
N/A	P	P	P	Y	N	P	P	0.55
N/A	P	N	P	N	N	P	Y	0.45
N/A	P	P	N	Y	N	P	Y	0.59
N/A	Y	P	Y	N	N	Y	Y	0.77
N/A	Y	P	Y	N	P	Y	Y	0.68
N/A	Y	Y	Y	Y	N	Y	Y	0.86
N/A	P	P	P	N	N	P	P	0.45
N/A	Y	Y	Y	Y	P	Y	Y	0.95

interventions like fluid restrictions and retention control training can be very demanding for a child, it is imperative to evaluate whether this approach is indeed evidence based. The aim of this review was to identify and present available literature on urotherapy for NE and test the hypothesis that there is evidence to support the use of standard urotherapy in the treatment of children with primary NE (PNE).

Materials and methods

The systematic review protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist for study protocols [8], and was registered in the PROSPERO database (CRD42020185611).

Search methods for identification and selection of studies

A systematic literature search was conducted in MEDLINE (via PubMed Interface), Embase (via embase.com Interface), and CENTRAL based on the key concepts of standard urotherapy and NE (Appendix 1 presents the *search string)*. Our search strategy was a combination of subject terms (Mesh/Emtree) and free-text terms. Additionally, we identified relevant studies by using the reference lists and citations from included articles. We included both interventional (pre-post study designs, non-randomized trials, and randomized controlled trials) and observational designs (cohort, case-control, and cross-sectional designs). Both prospective and retrospective studies were included. We excluded study protocols, meta-analyses, literature reviews, conference abstracts without sufficient information, and studies with a single-case design.

The Covidence tool (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org) was used for screening and data extraction. Two reviewers (CSJ and LD) independently screened all titles and abstracts of all identified studies. On a second step, the same two

authors screened full-text articles of potentially relevant studies, or studies for which the abstracts did not provide sufficient information. Any discrepancy was discussed with a third party (KK). For the initial search, there were no language restrictions. However, for the study selection, only articles in English, German, Danish, French and Dutch, were considered.

Selection criteria of studies and outcome measures

The study population was defined as children (age 5–18 years) suffering from PNE, who were neurologically normal and otherwise healthy. To be included, the studies had to evaluate the efficacy of standard urotherapy as defined by the ICCS [6], 1) standard urotherapy vs. no active treatment, 2) one type of standard urotherapy vs. another type of standard urotherapy, 3) standard urotherapy vs. alarm treatment and/or other specific interventions, and 4) standard urotherapy vs. drug treatment (including placebo).

As primary outcomes, we evaluated the reduction in mean number of wet nights per week as well as the number of children who achieved complete dryness (complete responders). As secondary outcomes, we evaluated relapse rate, reduction in LUTS, adverse events, and adherence regarding treatment.

Data extraction, risk bias and quality assessment, and data synthesis

The reviewers independently performed structured data extraction from the original reports. Information was extracted on study design, method of recruitment, inclusion and exclusion criteria, the number and characteristics of participants, the intervention(s) and follow-up, outcomes, and power calculations.

To assess the quality of the studies, the QualSyst Checklist was used (Table 1) [9]. The QualSyst tool is developed by the Effective Public Health Practice Project (EPHPP, Canada) for Public Health purposes and can be used to assess studies with varying study designs. It is a 14 items scale, and the final score is defined by the sum of the scores obtained across rated items ("yes" = 2, "partial" = 1, "no" = 0) divided by the total possible score (i.e. excluding "n/a" questions) resulting in a range 0–1. Different cut-off points have been suggested to decide whether to include a paper or not. Since the number of publications was limited, we have chosen not to exclude manuscripts based on score but display for each article our quality assessment (Table 1). To summarize the studies, we performed a descriptive narrative synthesis, since it provides an overview of relevant information through a textual approach, which is appropriate when studies are too heterogeneous to allow for a quantitative summary [10].

Results

Included studies and study population

The PRISMA flowchart (Fig. 1) illustrates the flow of the literature search. The first systematic search identified 2,476 studies, which were all screened based on title and abstract. Of these, 102 studies were assessed for eligibility, and based on full text screening 39 studies were included in the review. Of these 39 studies, 36 studies were in English, two in German, and one in Dutch. In total, 22 randomized controlled (RCT) and 17 cohort trials were included (Table 2). Assessed by the QualSyst Checklist [9], the quality varied a lot between the different studies (Table 1). Most of the studies scored low in quality due to inappropriate study design, small sample sizes, and lack of sufficient reporting. The number of participants in the included studies varied from 18 to 666 children aged between 3 and 15 years. All studies included both genders.

Interventions

Most studies combined two or more urotherapy elements in a single trial, or in a single arm in a multi-intervention trial. The duration of intervention varied from 1 week to 1 year or until "dry". The follow-up period varied from 0 to 79 months. The different interventions are described in Table 2. No adverse events because of urotherapy intervention were reported in any study. Adherence was evaluated in 15 studies which reported a significant decrease over time.

Active comparison interventions were: unstructured play therapy (one study) [11]; placebo (one study) [12]; controls (seven studies) [13–19]; DBT with an alarm (four studies) [13,14,16,20]; alarm alone (five studies) [12,18,21–23]; amitryptiline (one study) [24]; imipramine (two studies) [25,26]; DDAVP (six studies) [22,27–31]; oxybutynin (two studies) [12,26]; flavoxate (one study) [26]; suoquan (a herbal remedy) (one study) [30]; parasacral transcutaneous electrical neural stimulation (one study) [32]; and interferential electrical stimulation (one study) [33].

Outcome

The heterogeneity of the studies regarding study design, patient population, interventions, duration of intervention(s), outcome variables, power, and choice of statistical methods makes a meta-analysis and comparisons of the included studies difficult. The number of children with a complete response (became dry) varied from 0 to 100% in the different studies. The number of children with relapse depended on follow-up time and was reported to be between 0 and 100%. Three studies [34–36] reported reduction in LUTS after urotherapy and reported that daytime symptoms improved or disappeared together with NE.

Urotherapy evaluated in RCTs

In this review, 22 RCT studies were included (Table 2). Many of these studies were of poor quality assessed by the QualSyst Checklist (Table 1). The reported number of complete responders at the end of treatment varied from 0 to 92%, and the reduction in number of wet nights varied from 12 to 98%. We want to highlight three RCT studies of higher quality based on the QualSyst score (Table 1) – Cederblad et al., 2015 [21]; Kajbafzadeh et al., 2015 [33]; and Hascicek et al., 2019 [31]. They all included an optimization of drinking and voiding during the day together with practicing relaxation and optimal posture, combined with other interventions such as positive reinforcement,

Please cite this article as: Jørgensen CS et al., The efficacy of standard urotherapy in the treatment of nocturnal enuresis in children: A systematic review, Journal of Pediatric Urology, https://doi.org/10.1016/j.jpurol.2022.12.011

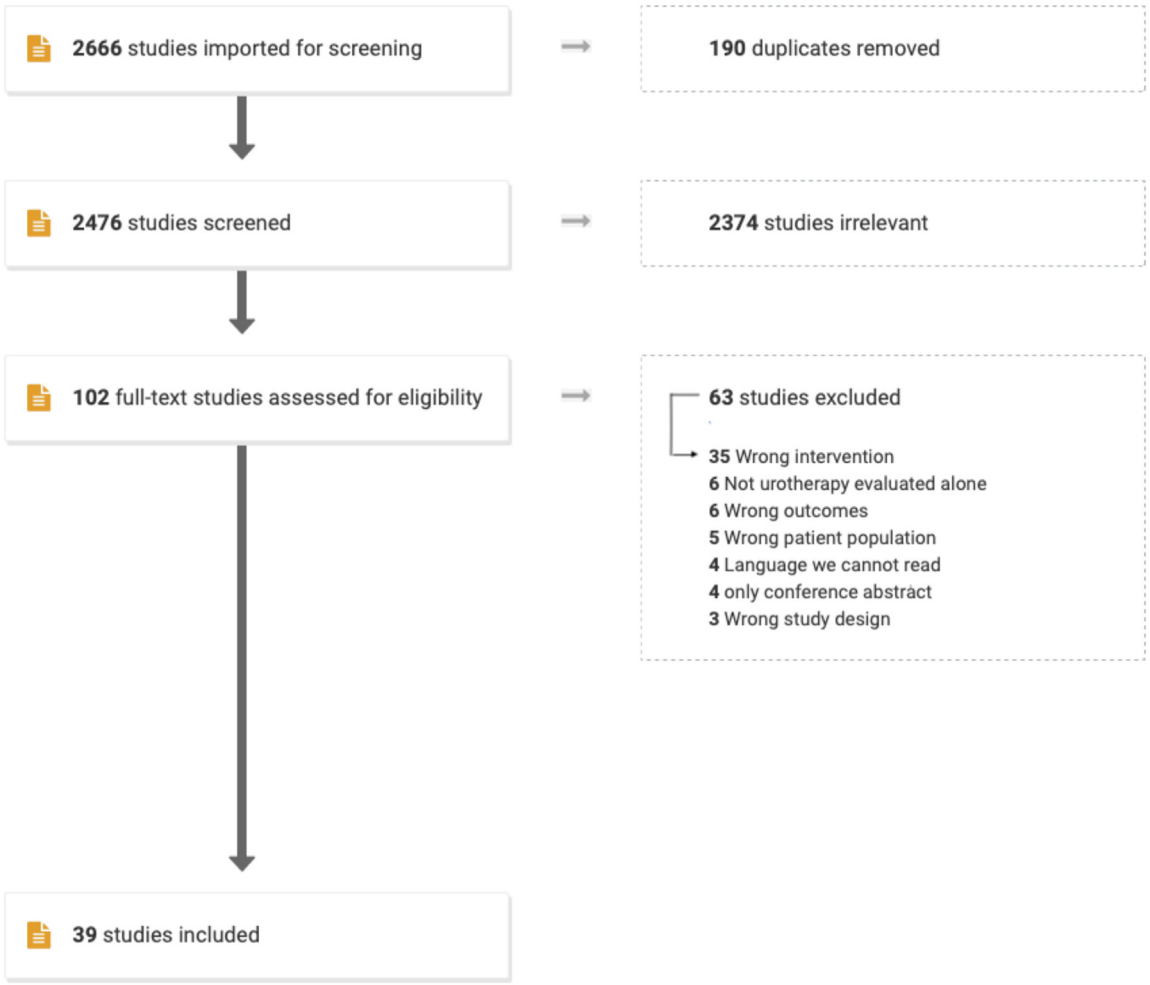

Fig. 1 PRISMA flowchart.

education, lifting the child during the night, physical activity, and diet recommendations. Despite different study populations, all three studies reported few children achieving complete response (5%, 25%, and 33%, respectively).

Kahan et al. found no additional efficacy of positive reinforcement, education, fluid restriction, and retention control to DDAVP treatment in 221 children with monosymptomatic nocturnal enuresis (MNE) when evaluating reduction in number of wet nights [27]. In contrast, ElBaz et al. found the combination of six behavioral modifications to be as good as DDAVP treatment in reducing the number of wet nights in 40 children with PNE without daytime incontinence (DI) [29].

Urotherapy vs no treatment (control-group)

Eight studies compared the efficacy of urotherapy to a control group or to placebo (Table 2). Four of these studies [13,14,16,17] evaluated the DBT [5]. They reported different results with number of complete responders from 0 to 78%. Harris et al. [15] evaluated the efficacy of rewards systems, retention control training, physical activity, and required drinking during the day in 18 children with PNE without DI and reported no significant efficacy in reduction of number of wet nights compared to a control group. Ronen et al. [18] combined cognitive treatment to increase self-control of the child and retention control training. It was compared to positive reinforcement in 77 children with PNE and they reported a reduction in number of wet nights of respective 89% (cognitive treatment and retention control training) and 82% (positive reinforcement). Both results were significantly different from a control group. Van Dommelen et al. [19] randomized 570 children with MNE into four groups with different interventions which were lifting the child during the nights with and without a password (the child needed to say a password to ensure the child was awake), using a reward system, and a control group. They reported that lifting without a password was the only intervention leading to significant improvement compared to the control group (37% vs. 21% with complete response). Van Hoeck et al. found holding exercises to significantly increase bladder capacity in children with MNE, however, only 3% became dry [12].

Discussion

This systematic review presents available literature regarding the use of standard urotherapy in the treatment of children with PNE. Even though many international

Please cite this article as: Jørgensen CS et al., The efficacy of standard urotherapy in the treatment of nocturnal enuresis in children: A systematic review, Journal of Pediatric Urology, https://doi.org/10.1016/j.jpurol.2022.12.011

Table 2 Description of all 39 included studies and main effect parameters.

	Patients characteristics									
Study	Country	Study design[a]	Number of participants (male)	Age (range (mean2 ± SD))	NE-type[b]	Positive reinforcement/ reward systems/ avoidance of punishment	Education	Fluid restriction in the evening	Required drinking	Individual drinking and voiding regime
Bollard 1977 [13]	AU	RCT	34 (19)	4-13 (8)	NE without DI					
Doleys 1977 [20]	USA	RCT	19 (13)	Group 1: 6.6 Group 2: 7.8	PNE	X	X		X	
Harris 1977 [15]	CA	RCT	18 (12)	5–13	NE	X			X	
Azrin 1978 [23]	USA	RCT	55 (41)	3-14 (7.1)	PNE without DI					
Nettelbeck 1979 [16]	AU	RCT	24 (14)	4-14 (8.3)	PNE without DI					
Mehrotra 1980 [24]	IN	RCT	60		PNE without DI	X		X		
Fava 1981 [11]	IT	RCT	20	Group 1: 8.0 ± 1.7	NE without DI	X				
Bollard 1982 [14]	AU	RCT	30 (18)	7-13 (8.9)	NE					
Keating 1983 [17]	USA	RCT	30 (18)	4-14 (8.1)	PNE					
Lester 1991 [25]	IT	RCT	132	6–11	PNE	X				
Ronen 1995 [18]	IL	RCT	77 (37)	7–14	NE without DI	X				
Kahan 1998 [27]	IL	RCT	221		NE	X	X	X		
Kruse 1999 [22]	SE	RCT	22 (14)	10-16 (12.4)	NE		X	X		X
Hamano 2000 [28]	JP	RCT	114 (88)	Group 1: 9.2 ±-2.2 Group 2: 9.4 ± 2.3	NE	X		X		
Van Hoeck 2007 [12]	BE	RCT	149 (108)	5-12 (7.5)	NE					X
Van Dommelen 2009 [19]	NL	RCT	570	4–5	PNE	X				
Oliveira 2012 [32]	BR	RCT	45 (16)	6–16	MNE	X		X		X
Cederblad 2015 [21]	SE	RCT	40 (29)	6–8	PNE		X			X
ElBaz 2015 [29]	EG	RCT	40	6-15, 9.5 ± 2.9	PMNE			X		X
Kajbafzadeh 2015 [33]	IR	RCT	54 (31)	6–14	NE	X	X	X		X
Ma 2017 [30]	CN	RCT	369 (216)	5-15, (8 ± 2.8)	PNE					X
Hascicek 2019 [31]	TR	RCT	63 (40)	6-12 (8.3 ± 1.4)	PNE	X		X		X
Dische 1971 [47]	UK	CS	144 (93)	4–15	PNE	X				
Azrin 1979 [48]	USA	CS	44 (29)	3-15 (6.8)	PNE					
Devlin 1990 [49]	IE/UK	CS	127 (84)	6-17 (8.8)	MNE	X	X			
Hirasing 1991 [50]	NL	CS	36 (23)	6–14	MNE					
Spehr 1991 [51]	DE	CS	122 (37)	4–13	MNE og NMNE					X
Robson 2002 [52]	CA	CS	23 (14)	4-14 (8.7)	MNE			X		X
Al-Harbi 2004 [53]	SA	CS	26 (17)	6-14, 9.6 ± 2.6	PMNE	X	X	X		
Marschall-Kehrel 2004 [54]	DE	CS	259 (167)	5-18 (8.1)	NE without DI					X
Pennesi 2004 [34]	IT	CS	250 (159)	5-17 (8.1)	PNE without DI	X	X			X
Sehgal 2007 [26]	IN	CS	116 (64)	5–14	PNE	X		X		
Glad Mattsson 2010 [35]	SE	CS	200 (84)	3-14 (7.2)	MNE		X			X
Elsayed 2012 [43]	EG	CS	122 (68)	5-9 (6.8)	PNE	X				
Erol 2016 [55]	TR	CS	50 (21)	5-15, (9.11 ± 2.4)	PMNE	X		X		
Tkaczyk 2017 [44]	TR	CS	49 (36)	5-16 (7.2)	PNMNE		X	X		X
Im 2018 [42]	KP	CS	111 (76)	5-13, (6.8 ± 1.8)	NE		X			X
Saarikoski 2018 [36]	FI	CS	58 (24)	6-12 (8)	MNE		X	X		X
Ma 2019 [45]	CN	CS	666 (349)	5-14 (6.5)	PNE	X	X	X		X

[a] RCT = randomized controlled trial, CS = cohort study.

[b] DI = daytime incontinence, PNE = primary nocturnal enuresis, SNE = secondary nocturnal enuresis (the child has been dry for more than 6 months [1]), MNE = monosymptomatic nocturnal enuresis (NE without any other LUTS [39]), NMNE = non-monosymptomatic nocturnal enuresis.

[c] Robson 2002 (caffein); Elsayed 2012 (calcium and sodium); Oliveira 2012 (caffein); Elbaz 2015 (eat food that soften stool); Kafbafzadeh 2015 (caffein, citric fruits, soft drinks, chocolate, irritating foods, increase fiber diet); Erol 2016 (caffein, coke, carbonated beverages and salty food), Ma 2017 (healthy life style); Tkaczyk 2017 (milk products); Im 2018 (lifestyle modifications); Saarikoski 2018 (juice, fruit, soft drinks, increase wholesome food); Hascicek 2019 (fast-food, healthy diet).

[d] Based on Azrin et al., 1974 [5] including inhibiting urination, positive reinforcement, training in rapid awakening, increased fluid intake, increased social motivation, self-correction of accidents and practice in toileting, however, with different training protocols, different training settings, and different trainers.

Please cite this article as: Jørgensen CS et al., The efficacy of standard urotherapy in the treatment of nocturnal enuresis in children: A systematic review, Journal of Pediatric Urology, https://doi.org/10.1016/j.jpurol.2022.12.011

Intervention									Duration		Outcome		
Waking or lifting (+/-a password)	Retention control training	Cleanliness training	Relaxation and optimal posture	Physical activity	Avoid specific diet[c]	Easy access to toilets	Stop use of diapers	Dry-bed training[d] without an alarm	Duration of interventions (months)	Follow-up (months)	Number of children undergoing urotherapy with complete response at the end of treatment (%)	Reduction in number of wet nights/week at end of treatment (%) for children undergoing urotherapy	Number of children with relapse (%) after urotherapy treatment
								X	13 weeks or dry	6	0 (0)	4 (57)	
	X						X		5-12 or dry	6–11	0 (0)	8%	
	X			X					35 days	9 weeks		0.6	
								X	12 or dry	Up to 12	51 (92)	98%	20%
								X	2	2		2.8 (48)	
X									5 weeks	4–5	3 (15)		
X									3	1 year	8 (80)		0 (0)
								X	2 or dry	2	2 (20)	2 (40)	2 (100)
								X	Untill dry	8	18 (78)		6 (33)
X	X								6	12	105 (80)		
	X								3	6		82%, 95% (two groups)	
	X								2	2	12 (16)	2.5 (45)	6 (50)
									12		5 (38)	85%	
	X								3	3	14 (23)	35 (58), more than 50% reduction	5 (36))
	X								3	End of treatment	1 (3)		
X									6 or dry	3 years	32% for all interventions		
					X				6	6	6% (more than 90%)	28%	
			X	X					1	End of treatment	1 (5)	12%	
			X	X	X	X			2	2	35%	65%	39%
			X		X				2	1 year	7 (25)	2.1 (39)	1 (14)
X	X		X		X				2	3	5 (6)		1 (20)
X			X		X				2	2	33%		
							X		6 or dry	Up to 4.5 y	47 (37)		1 (2)
								X	12	12	44 (100)	96%	3 (7)
	X	X	X						2	12	22 (17)		1 (5)
								X	Untill dry	6	31 (86)		23 (75)
									1–12 weeks	1–1.5 year	119 (98)		6 (5)
X			X		X				0.5–3	0.5–3	5 (22)	2 (34)	
	X								1-8 visits	3–12	12 (46)	67%	
									2 weeks	3–79	42 (16)	1 (2)	
			X						4	2–18	111 (60) (>90% dry nights)		9 (8)
X	X								4	End of treatment	51%		0 (0)
			X						2 half-day sessions	12	64 (35)		
	X				X				4	4	16 (22)		
X		X			X	X	X		12	18	27 (54)		4%
			X		X				3	3	9 (18)	34%	
					X				1	12	0 (0)		
			X		X				2–3	3–6	50% more than 50% reduction	38%	
X	X	X							3	End of treatment	Normal weight: 27%		

Please cite this article as: Jørgensen CS et al., The efficacy of standard urotherapy in the treatment of nocturnal enuresis in children: A systematic review, Journal of Pediatric Urology, https://doi.org/10.1016/j.jpurol.2022.12.011

guidelines consider urotherapy as first line treatment of NE and urotherapy is widely used, most high-quality studies reported low efficacy rates when evaluating complete response and reduction in number of wet nights. Our findings are in line with the 2013 Cochrane review by Cadwell et al. [37,38]. The Cadwell review was performed before the new ICCS standardization [6] thereby using the term "behavioral interventions" and only RCTs were included. The added value of this systematic review is the inclusion of articles published after 2013 (including high quality studies) together with inclusion of both interventional and observational designs. This can be important in a research area where only few high-quality studies are available.

One possible explanation behind the main finding of low efficacy rates of urotherapy in NE is the large heterogeneity of the study populations. Many of the included studies were published before the ICCS introduced the subdivision of NE into MNE and non-MNE (NMNE) [39], and before the general acceptance of targeting therapy towards the underlying pathophysiology, e.g. nocturnal polyuria and reduced functional bladder capacity. Standard urotherapy as defined by the ICCS [7] includes many different elements. Most of the included studies in this review combined two or more urotherapy modalities, which makes it difficult to ascertain the value of specific elements and which underlying pathophysiologic mechanisms are targeted. Urotherapy has proven efficacy in the treatment of DI and urgency [40], and therefore it is hypothesized that urotherapy is more effective in children with NMNE, where bladder dysfunction is part of the pathophysiology. However, other elements of urotherapy such as fluid restriction during the evening could be more effective in the subpopulation of children with underlying nocturnal polyuria [41]. If we look into studies including children with LUTS, Im et al. [42] treated 111 children with overactive bladder and NE with standard urotherapy according to the ICCS guidelines for one month combined with treatment of constipation. Although none of these children experienced complete response at the end of treatment, urgency improved more quickly than NE. Hamano et al. found daytime functional bladder capacity to be a valuable negative predictor of response to DDAVP, but not of response to urotherapy when combining positive reinforcement, fluid restriction, and retention control training [28]. If we then look into studies evaluating urotherapy in the treatment of children without LUTS (MNE according to the ICCS criteria), eight of nine studies reported that less than one third of the children achieved complete response [12,19,27,28,31,32,43,44]. When evaluating predictive factors for response to urotherapy, studies report gender (males), maternal education level, NE frequency [30], and absence of overweight and obesity [45] to influence response. Lester et al. found the efficacy of urotherapy to be age dependent, and report a higher compliance and a higher response rate in older children [25].

One can argue that the intervention period can have an impact on the outcome. When evaluating the three highlighted RCT studies, the duration of intervention in the study by Cederblad et al. [21] was 1 month and the study reported 5% of children achieving complete response, compared to 2 months of intervention in the study by Kajbafzadeh et al. [33] and Hascicek et al. [31], who reported 25% and 30% of children obtaining complete response. Also, the intensity of the interventions might affect the response. Hascicek et al. found that complete response to urotherapy was improved significantly to a level comparable with DDAVP treatment if a written checklist of behavioral instructions was offered to the parents of children with PMNE [31], which should intensify the urotherapy treatment. Mattsson et al. invited 200 children with bladder dysfunction and incontinence to participate in voiding schools in small groups, which is a multidisciplinary combined in- and outpatient bladder rehabilitation program for children with urinary incontinence. They reported significant improvement in both DI and NE [35]. This might indicate that an intense regimen is needed to experience improvements in symptoms, which could also be the case with DBT where some studies report good results.

Most of the included studies evaluate urotherapy as an independent treatment. A recently performed RCT including 60 treatment-naïve children with PNE and without DI compared 1) a strict drinking and voiding regimen and optimal toilet posture, 2) an alarm, and 3) a control group. They concluded that standard urotherapy was ineffective as first-line treatment [46]. Currently, ICCS recommends characterization of the individual child before start of treatment of NE often including diaries of drinking and voiding habits [39]. If these diaries show abnormal patterns, one can expect that advice is given together with start of alarm or DDVAP, because of safety regarding DDAVP and with the aim of increasing the efficacy of treatment. Urotherapy as positive reinforcement and education could also be important for the child's experience of treatment and factors such as self-esteem and adherence to treatment. Urotherapy might be more efficient as an add-on to other first line treatments instead of an independent intervention. Furthermore, registration of symptoms can be important for evaluation of response to other treatments. Low cost and no risk for the child are benefits for choosing urotherapy as first treatment.

Some important limitations of this study are as mentioned the large heterogeneity of included study populations partly due to different terminologies, as well as a variability in combinations of interventions, which makes a comparison of the studies difficult. Furthermore, reporting bias of response is a limitation. According to the QualSyst Checklist (Table 1), many studies are of poor scientific quality. Only studies in English, German, and Dutch were included, which could possibly lead to a certain amount of bias.

Conclusions

This systematic review presents available literature in the area and is the first evaluation of evidence since the current ICCS terminology was introduced. Many studies are of poor scientific quality, and the large heterogeneity of included studies made comparisons and conclusions difficult. High quality studies present limited efficacy of urotherapy in the treatment of NE. However, interventions like education, registration of symptoms, and support and encouragement might be important for the efficacy of other treatments.

We conclude that at present there is insufficient evidence for offering standard urotherapy to children with NE

Please cite this article as: Jørgensen CS et al., The efficacy of standard urotherapy in the treatment of nocturnal enuresis in children: A systematic review, Journal of Pediatric Urology, https://doi.org/10.1016/j.jpurol.2022.12.011

as first line treatment modality. This review highlights the need for high quality RCTs in well-characterized patient populations to clarify whether specific elements of urotherapy are effective in subgroups of children with NE or could play a role as add-on therapy to existing evidence-based treatment options.

Source of funding

No grants or financial support has been received.

Each author listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript.

Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

[1] Nevéus T, Fonseca E, Franco I, Kawauchi A, Kovacevic L, Nieuwhof-Leppink A, et al. Management and treatment of nocturnal enuresis-an updated standardization document from the International Children's Continence Society. J Pediatr Urol 2020;16:10—9. https://doi.org/10.1016/j.jpurol.2019.12.020.

[2] von Gontard A, Heron J, Joinson C. Family history of nocturnal enuresis and urinary incontinence: results from a large epidemiological study. J Urol 2011;185:2303—6. https://doi.org/10.1016/j.juro.2011.02.040.

[3] Yeung CK, Sreedhar B, Sihoe JD, Sit FK, Lau J. Differences in characteristics of nocturnal enuresis between children and adolescents: a critical appraisal from a large epidemiological study. BJU Int 2006;97:1069—73. https://doi.org/10.1111/j.1464-410X.2006.06074.x.

[4] Redsell SA, Collier J. Bedwetting, behaviour and self-esteem: a review of the literature. Child Care Health Dev 2001;27:149—62.

[5] Azrin NH, Sneed TJ, Foxx RM. Dry-bed training: rapid elimination of childhood enuresis. Behav Res Ther 1974;12:147—56.

[6] Austin PF, Bauer SB, Bower W, Chase J, Franco I, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: update report from the Standardization Committee of the International Children's Continence Society. J Urol 2014;191:1863—1865.e13. https://doi.org/10.1016/j.juro.2014.01.110.

[7] Austin PF, Bauer SB, Bower W, Chase J, Franco I, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: update report from the standardization committee of the International Children's Continence Society. Neurourol Urodyn 2016;35:471—81. https://doi.org/10.1002/nau.22751.

[8] Research SMC. Methods used in developing and applying quality indicators in primary care. Qual Saf Health Care 2002;11:358—64.

[9] Kmet LMLRC, Cook LS. Standard quality assessment criteria for evaluating primary research papers from a variety of fields. Edmonton: Alberta Heritage Foundation for Medical Research (AHFMR) AHFMR - HTA Initiative; 2004. #13.

[10] Ioannidis JP, Patsopoulos NA, Rothstein HR. Reasons or excuses for avoiding meta-analysis in forest plots. BMJ 2008;336:1413—5. https://doi.org/10.1136/bmj.a117.

[11] Fava GA, Cracco L, Facco L. Positive reinforcement and enuresis. Ital J Psychol 1981;8(2):149—52.

[12] Van Hoeck KJ, Bael A, Van Dessel E, Van Renthergem D, Bernaerts K, Vandermaelen V, et al. Do holding exercises or antimuscarinics increase maximum voided volume in monosymptomatic nocturnal enuresis? A randomized controlled trial in children. J Urol 2007;178:2132—6. https://doi.org/10.1016/j.juro.2007.07.051.

[13] Bollard RJ, Woodroffe P. The effect of parent-administered Dry-Bed training on nocturnal enuresis in children. Behav Res Ther 1977;15:159—65.

[14] Bollard J, Nettelbeck T, Roxbee L. Dry-bed training for childhood bedwetting: a comparison of group with individually administered parent instruction. Behav Res Ther 1982;20:209—17.

[15] Harris LS, Purohit AP. Bladder training and enuresis: a controlled trial. Behav Res Ther 1977;15:485—90. https://doi.org/10.1016/0005-7967(77)90004-3.

[16] Nettelbeck T, Langeluddecke P. Dry-bed training without an enuresis machine. Behav Res Ther 1979;17:403—4.

[17] Keating JC, Butz RA, Burke E, Heimberg RG. Dry bed training without a urine alarm: lack of effect of setting and therapist contact with child. J Behav Ther Exp Psychiatr 1983;14:109—15.

[18] Ronen T, Rahav G, Wozner Y. Self-control and enuresis. J Cognit Psychother: Int Q 1995;9:249—58. https://doi.org/10.1891/0889-8391.9.4.249.

[19] van Dommelen P, Kamphuis M, van Leerdam FJ, de Wilde JA, Rijpstra A, Campagne AE, et al. The short- and long-term effects of simple behavioral interventions for nocturnal enuresis in young children: a randomized controlled trial. J Pediatr 2009;154:662—6. https://doi.org/10.1016/j.jpeds.2008.12.001.

[20] Doleys DM, Ciminero AR, Tollison JW. Dry-bed training and retention control training: a comparison. Behav Ther 1977;8:541—8.

[21] Cederblad M, Sarkadi A, Engvall G, Nevéus T. No effect of basic bladder advice in enuresis: a randomized controlled trial. J Pediatr Urol 2015;11:153.e1—5. https://doi.org/10.1016/j.jpurol.2015.03.004.

[22] Kruse S, Hellström AL, Hjälmås K. Daytime bladder dysfunction in therapy-resistant nocturnal enuresis. A pilot study in urotherapy. Scand J Urol Nephrol 1999;33:49—52.

[23] Azrin NH, Thienes PM. Rapid elimination of enuresis by intensive learning without a conditioning apparatus. Behav Ther 1978;9:342—54.

[24] Mehrotra SN, Liu L, Srivastava JR, Singh SB. Evaluation of various methods in treatment of enuresis. Indian Pediatr 1980;17:519—22.

[25] Iester A, Marchesi A, Cohen A, Iester M, Bagnasco F, Bonelli R. Functional enuresis: pharmacological versus behavioral treatment. Child's Nerv Syst : ChNS : Official J Int Soc Pediatr Neurosurg 1991;7:106—8. https://doi.org/10.1007/bf00247867.

[26] Sehgal R, Paul P, Mohanty NK. Urodynamic evaluation in primary enuresis: an investigative and treatment outcome correlation. J Trop Pediatr 2007;53:259—63. https://doi.org/10.1093/tropej/fmm019.

[27] Kahan E, Morel D, Amir J, Zelcer C. A controlled trial of desmopressin and behavioral therapy for nocturnal enuresis. Medicine 1998;77:384—8.

[28] Hamano S, Yamanishi T, Igarashi T, Ito H, Murakami S. Functional bladder capacity as predictor of response to desmopressin and retention control training in monosymptomatic nocturnal enuresis. Eur Urol 2000;37:718—22. https://doi.org/10.1159/000020224.

[29] ElBaz F, Zahra S, Khairy M. Assessment of the efficacy of desmopressin in treatment of primary monosymptomatic nocturnal enuresis in Egyptian children. Egypt J Med Hum Genet 2015;16:257—62. https://doi.org/10.1016/j.ejmhg.2015.02.006.

[30] Ma Y, Liu X, Shen Y. Effect of traditional Chinese and Western medicine on nocturnal enuresis in children and indicators of treatment success: randomized controlled trial. Pediatr Int : Official J Japan Pediatr Soc 2017;59:1183–8. https://doi.org/10.1111/ped.13417.
[31] Hascicek AM, Kilinc MF, Yildiz Y, Yuceturk CN, Doluoglu OG. A new checklist method enhances treatment compliance and response of behavioural therapy for primary monosymptomatic nocturnal enuresis: a prospective randomised controlled trial. World J Urol 2019;37:1181–7. https://doi.org/10.1007/s00345-018-2478-1.
[32] Oliveira LF, Oliveira DM, Paula LIS, Chaoubah A, Figueiredo AA, Barroso UO, et al. Para-sacral transcutaneous electrical neural stimulation (PSTENS) in children with monosymptomatic enuresis. J Urol 2012;187:e244–5. https://doi.org/10.1016/j.juro.2012.02.678.
[33] Kajbafzadeh AM, Sharifi-Rad L, Mozafarpour S, Ladi-Seyedian SS. Efficacy of transcutaneous interferential electrical stimulation in treatment of children with primary nocturnal enuresis: a randomized clinical trial. Pediatr Nephrol 2015;30:1139–45. https://doi.org/10.1007/s00467-014-3039-5.
[34] Pennesi M, Pitter M, Bordugo A, Minisini S, Peratoner L. Behavioral therapy for primary nocturnal enuresis. J Urol 2004;171:408–10. https://doi.org/10.1097/01.ju.0000097497.75022.e8.
[35] Glad Mattsson G, Brännström M, Eldh M, Mattsson S. Voiding school for children with idiopathic urinary incontinence and/or bladder dysfunction. J Pediatr Urol 2010;6:490–5. https://doi.org/10.1016/j.jpurol.2009.11.004.
[36] Saarikoski A, Koppeli R, Taskinen S, Axelin A. Voiding school as a treatment for daytime incontinence or enuresis: assessing the effectiveness of intervention by measuring changes in wetting episodes. J Pediatr Urol 2018;14:256.e1–7. https://doi.org/10.1016/j.jpurol.2017.12.015.
[37] Caldwell PH, Nankivell G, Sureshkumar P. Simple behavioural interventions for nocturnal enuresis in children. Cochrane Database Syst Rev 2013. https://doi.org/10.1002/14651858.CD003637.pub3. CD003637.
[38] Huang T, Shu X, Huang YS, Cheuk DK. Complementary and miscellaneous interventions for nocturnal enuresis in children. Cochrane Database Syst Rev 2011:CD005230. https://doi.org/10.1002/14651858.CD005230.pub2.
[39] Neveus T, Eggert P, Evans J, Macedo A, Rittig S, Tekgul S, et al. Evaluation of and treatment for monosymptomatic enuresis: a standardization document from the International Children's Continence Society. J Urol 2010;183:441–7. https://doi.org/10.1016/j.juro.2009.10.043.
[40] Schafer SK, Niemczyk J, von Gontard A, Pospeschill M, Becker N, Equit M. Standard urotherapy as first-line intervention for daytime incontinence: a meta-analysis. Eur Child Adolesc Psychiatr 2018;27:949–64. https://doi.org/10.1007/s00787-017-1051-6.
[41] Rittig S, Knudsen UB, Norgaard JP, Pedersen EB, Djurhuus JC. Abnormal diurnal rhythm of plasma vasopressin and urinary output in patients with enuresis. Am J Physiol 1989;256:F664–71.
[42] Im YJ, Lee JK, Park K. Time course of treatment for primary enuresis with overactive bladder. Int Neurourol J 2018;22:107–13. https://doi.org/10.5213/inj.1836020.010.
[43] Elsayed ER, Abdalla MM, Eladl M, Gabr A, Siam AG, Abdelrahman HM. Predictors of severity and treatment response in children with monosymptomatic nocturnal enuresis receiving behavioral therapy. J Pediatr Urol 2012;8:29–34. https://doi.org/10.1016/j.jpurol.2010.12.011.
[44] Tkaczyk M, Maternik M, Krakowska A, Wosiak A, Miklaszewska M, Zachwieja K, et al. Evaluation of the effect of 3-month bladder basic advice in children with monosymptomatic nocturnal enuresis. J Pediatr Urol 2017;13:615.e1–6. https://doi.org/10.1016/j.jpurol.2017.03.039.
[45] Ma Y, Shen Y, Liu X. Association between enuresis and obesity in children with primary monosymptomatic nocturnal enuresis. Int Braz J Urol : Official J Braz Soc Urol 2019;45:790–7. https://doi.org/10.1590/s1677-5538.Ibju.2018.0603.
[46] Borgström M, Bergsten A, Tunebjer M, Hedin Skogman B, Nevéus T. Daytime urotherapy in nocturnal enuresis: a randomised, controlled trial. Arch Dis Child 2022. https://doi.org/10.1136/archdischild-2021-323488.
[47] Dische S. Management of enuresis. Br Med J 1971;2:33–6. https://doi.org/10.1136/bmj.2.5752.33.
[48] Azrin NH, Thienes Hontos P, Besalel-Azrin V. Elimination of enuresis without a conditioning apparatus: an extension by office instruction of the child and parents. Behav Ther 1979;10:14–9.
[49] Devlin JB, O'Cathain C. Predicting treatment outcome in nocturnal enuresis. Arch Dis Child 1990;65:1158–61.
[50] Hirasing RA, Reus H. Dry bed training in nocturnal enuresis. Ned Tijdschr Geneeskd 1991;135:1750–3.
[51] Spehr C, De Geeter P. Faulty voiding and drinking habits-a contribution to the genesis of enuretic syndrome? Urol Ausg A 1991;30:231–4.
[52] Robson LM, Leung AK. Urotherapy recommendations for bedwetting. J Natl Med Assoc 2002;94:577–80.
[53] Al-Harbi SM, Needlman RD, Khan AS, Patni T. Intensive behavioral therapy for primary enuresis. Saudi Med J 2004;25:934–40.
[54] Marschall-Kehrel AD, Mürtz G, Kramer G, Jünemann KP, Madersbacher H, Hjalmas K. A suggested treatment algorithm in nocturnal enuresis with emphasis on partial responders. Urol Ausg A 2004;43:795–802. https://doi.org/10.1007/s00120-004-0587-5.
[55] Erol M, Özkuvancı Ü, Yiğit Ö, Fucucuoğlu D, Gayret Ö B, Aksu S. Motivation therapy in children with primary monosymptomatic nocturnal enuresis. Haseki Tip Bulteni 2016;54:7–12. https://doi.org/10.4274/haseki.2795.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpurol.2022.12.011.

Please cite this article as: Jørgensen CS et al., The efficacy of standard urotherapy in the treatment of nocturnal enuresis in children: A systematic review, Journal of Pediatric Urology, https://doi.org/10.1016/j.jpurol.2022.12.011