Canadian Urological Association guideline for the treatment of bladder dysfunction in children

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Introduction

Bladder and bowel dysfunction (BBD) is one of the most common reasons for referral to pediatric urology clinics, responsible for up to 40% of clinic consults.[1] BBD describes a constellation of symptoms related to voiding and defecation without a neurogenic or anatomic cause. The association of bowel and bladder symptoms is well-described.[2] The lower urinary tract symptoms (LUTS) include storage type, such as urgency, frequency, and urge incontinence, or voiding type, such as hesitancy, slow urinary flow, and intermittency. Gastrointestinal symptoms include constipation and encopresis.

The term BBD is applied to a heterogeneous group of clinical presentations. Some children present primarily with frequency, urgency with or without incontinence; others postpone their urination and do not empty their bladder. In an effort to standardize the terminology related to BBD, its subtypes and symptoms, the International Children's Continence Society (ICCS) has published a classification, which is gaining more acceptance in pediatric urology literature.[3] We have strived to align this guideline with this classification.

BBD is a known risk factor for urinary tract infection (UTI) and vesicoureteral reflux (VUR).[4] Many studies have shown the importance of BBD management in prevention of UTIs and treatment of VUR.[5] BBD is associated with reduced quality of life and significant psychosocial burden for children and families.[6] It is not uncommon for children with BBD to be stigmatized and bullied. Mood disorders and anxiety are also seen in these children.[7]

BBD is a clinical construct. Many different validated questionnaires, such as the Dysfunctional Voiding Symptom Score (DVSS) and Vancouver Symptom Score, have been designed in an attempt to standardize the diagnosis, classify the type, and evaluate the severity of this complex clinical diagnosis. These instruments have also been used to follow clinical response to treatment.[8-10]

The treatment of bowel dysfunction is an essential part of the overall management and should not be overlooked. The scope of the current guidelines is limited to the management of the lower urinary tract.

The purpose of these guidelines is to identify the best available evidence regarding the management of BBD in children, assess the level and quality of the evidence, and generate recommendations for clinicians.

Methods

A systematic approach to the literature search was used to identify the relevant studies. A comprehensive literature search strategy was written by an experienced librarian. Embase, Medline, Google Scholar, the Cochrane library, and *clinical trials.gov* were searched for randomized controlled trials (RCTs). We limited our search to randomized (or quasi-randomized) controlled trials that compared at least one active treatment modality with another, placebo, or observation. We only included studies with participants up to 18 years of age. Outcomes of interest included patient-reported outcomes, such as change in symptoms, change in scores of validated questionnaires, or uroflowmetric parameters, and the incidence of UTI. Quality of life and adverse events were also included as outcomes.

Cochrane collaborative methodology was used to assess the titles, abstracts, and articles for inclusion and exclusion, data extraction, assessment of bias, and synthesis. Each step

was independently completed by at least two investigators. Results were reviewed by the senior author, who acted as the tiebreaker in the case of disagreement. The quality of each study was evaluated based on Cochrane collaborative criteria.[11] Whenever possible, data were pooled from different studies using a random effect model metanalysis.

Finally, the recommendations were generated according to Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology, using GRADE Pro software.[12]

Results

We searched the literature up to November 4, 2019. Our literature search yielded 1069 titles, of which 179 studies were included for full review based on our a priori inclusion/exclusion criteria. We are presenting the results of our search based on the interventions.

We faced a tremendous challenge when assessing these studies. Apart from low quality of evidence in general, the literature is plagued with non-standardized use of clinical terms, incomplete reporting of results, and focus on clinically non-important outcomes. Many studies used the same nomenclature for management strategies with a vastly different protocol. This has prevented the pooling of results from many studies.

Treatments

Bladder re-training/urotherapy

We were not able to identify a study comparing urotherapy with observation only. This is understandable, given the simplicity of urotherapy and the lack of adverse events. Most studies evaluated some variations of urotherapy.

The other important note is that protocols of urotherapy varied widely in terms of method of delivery, contents, length, and frequency of treatment, as well as with inclusion of additional interventions, such as behavioral or cognitive therapy. Nevertheless, all regimens included timed voiding, fluid intake and dietary strategies, and management of constipation.

1. One RCT comparing standard urotherapy with and without timer for scheduled voiding in children with urge incontinence found a significant improvement in median number of wet days/week in favor of using timer (at 12-week followup, median number of wet days/week were two and five in timer vs. standard group). Complete response was seen in 30% of children in timer group vs. none in the standard urotherapy group[13] *(GRADE level: Moderate)*.
2. One RCT compared combination of instructional home video and behavioral therapy to standard behavioral therapy in children with dysfunctional voiding and recurrent UTIs.[14] At 12 months' followup, there was no difference between the two groups in terms of resolution of incontinence or recurrence of UTI (*GRADE level: Low)*.
3. In another RCT, 150 children with BBD diagnosed using the Vancouver symptom score, were randomized to receive standard urotherapy vs. an instructional video. This study had a non-inferiority design. The authors did not find the video inferior to the standard management in reducing the symptom score at a mean followup of three months[15] (*GRADE level: Moderate)*.
4. Group urotherapy (one-hour session) and individual urotherapy (15-minute session) are equally effective in reducing symptom score and improving disease-specific quality of life in children with BBD at a median followup of 14 weeks[16] (*GRADE level: Moderate)*.

Biofeedback

1. In a RCT of 94 children with dysfunctional voiding and high post-void residual (PVR), addition of biofeedback to standard urotherapy is not associated with improvement of uroflowmetric parameters, such as average maximum flow rate, at six months of followup[17] *(GRADE level: Moderate)*. Nevertheless, PVR decreased 20 cc in average in children who received biofeedback (*GRADE level: Low)*.
2. In 40 children with dysfunctional voiding, animated biofeedback and non-animated biofeedback are no different in reducing symptom scores or improving uroflowmetric parameters, such as maximum flow rate, PVRs, and voided volumes[18] (*GRADE level: Low)*.
3. In 50 children with underactive bladder, addition of biofeedback to standard urotherapy was associated with significant reduction of perineal electromyographic (EMG) activity during voiding at six and 12 months (odds ratio [OR] 0.25, 95% confidence interval [CI] 0.07–0.83), as well as likelihood of abnormal voiding pattern (OR 0.17, 95% CI 0.05–0.53) *(GRADE level: High)*. Biofeedback also resulted in an average of two more voids per day compared to standard treatment. There was a significant reduction in post PVR at 12 months of followup (mean difference between groups: 34.5 cc) (*GRADE level: High)*. Children in the biofeedback group were twice as likely to be dry during the day at 12 months' followup (OR 2.1, 95% CI 1.36–2.84)[19] (*GRADE level: High)*.
4. Metanalysis of three RCTs in 125 children with BBD[14,20,21] did not show any difference between biofeedback (with or without pelvic floor exercise) and standard treatment in the proportion of children with resolved daytime incontinence[22] (*GRADE level: Low)*. There was also no difference in the number of children achieving daytime continence[22] *(GRADE level: Low)*.

5. Metanalysis of four RCTs (163 patients) did not show any difference between biofeedback and standard treatment in reduction of incidence of UTI in children with BBD[22] *(GRADE level: Very low)*.

Pelvic floor physiotherapy

1. Metanalysis of two RCTs[23,24] showed that the addition of pelvic floor exercise to the standard treatment in children with dysfunctional voiding is associated with lower likelihood of daytime incontinence at 12 months (OR 0.14, 95% CI 0.05–0.38, absolute effect 295 fewer per 1000) (*GRADE level: Moderate)*.
2. There was no significant difference in the likelihood of UTI or resolution of enuresis (*GRADE level: Low and moderate, respectively)*.

Neuromodulation

Parasacral transcutaneous electrical nerve stimulation (TENS)

1. One RCT did not show any benefit in adding parasacral TENS to standard treatment in improving uroflowmetric variables or clinical outcomes, such as frequency in 62 children with overactive bladder (OAB)[25] (*GRADE level: Low)*.
2. One RCT in 43 children with urge incontinence showed that the combination of parasacral TENS and oxybutynin is associated, on average, with two more dry days per week (mean difference [MD] 2.28, 95% CI 0.5–4.06) compared to TENS and placebo *(GRADE level: Low)*. In the same study, no participants in the placebo group achieved total continence, as opposed to 36% in the oxybutynin group[26] (*GRADE level: Low)*.
3. The same study also compared adding TENS or sham TENS to oxybutynin in 45 patients. There was no difference between the active and sham groups in terms of resolution of incontinence at 10-week followup (*GRADE level: Low)*.
4. In another study of 27 children with refractory urge incontinence with only four weeks' followup, S2–3 TENS was associated with three fewer days per week of incontinence compared to sham TENS. Study groups were not similar at the baseline[27] (*GRADE level: Low)*.
5. One RCT compared the combination of parasacral TENS and placebo to oxybutynin and sham TENS. Twenty-eight children with OAB were recruited.[28] At three months, there was no significant difference in the two groups regarding mean change in voiding frequency. Change in symptom score, maximum voided volume, and mean voided volumes were similar in the two groups (*GRADE level: Low)*
6. One RCT including only 16 children with OAB compared the effect of parasacral TENS to sham TENS. All patients received urotherapy as well. There was no difference in volumetric variables at two months' followup in the TENS group. Fewer patients had urgency at two months' followup (relative risk [RR] 3.75, 95% CI 1.01–13.8) (*GRADE level: Very low)*. They also reported subjective improvement based on a visual analog scale (VAS) with no confirmed validity of the measurement, which makes its interpretation unfeasible.[29]

Posterior tibial transcutaneous electrical stimulation (PTTENS)

1. A small RCT compared PTTENS with sham treatment in 20 patients with refractory OAB. The study showed increase in mean voided volumes (MD change 84.2 cc) but no change in bladder capacity, PVR, and clinical variables, as measured by a non-validated symptom score[30] (*Grade level: Low)*.
2. In one study of 37 children with refractory OAB, PTTENS was compared to sham TENS. The authors reported subjective improvement with no quantifiable measures.[31] It showed a favorable response towards TENS at three months, as 14/21 had full response, as opposed to 0/16 in the control group (*GRADE level: Very low)*.

Inferential pelvic transcutaneous electrical nerve stimulation

1. One study compared inferential pelvic transcutaneous electrical nerve stimulation to standard urotherapy in 36 children with underactive bladder.[32] At 12-month followup, the results were favoring TENS: number of voids per day were, on average, 1.6 times higher *(GRADE level: Very low)*; bladder capacity was lower by 117 mL (95% CI 46–188) *(GRADE level: Low)*; voiding time was 18 second shorter (95% CI 8–27) *(GRADE level: Low)*; and PVR was smaller by approximately 10% of bladder capacity *(GRADE level: High)*. Urinary flow rate was similar in the two groups *(GRADE level: High)*. Number of voids per day did not change significantly at 12 months *(GRADE level: High)*.

Pharmacotherapy

1. Solifenacin: A randomized placebo-controlled trial comparing solifenacin and placebo in 189 children and adolescents showed that mean voided volume per micturition was 12.1 mL higher (95% CI 0.2–24) in 148 children (5–12 years old) who received solifenacin[33] *(GRADE level: Low)*. The magnitude of change was not clinically significant. The maximum voided volume per micturition was higher by an average of 31.9 mL (95% CI 4.3–59.5) (*GRADE level: Low)*. The study did not show any other significant effect on more clinically important outcomes, such as number of voids or wet days. Due to low number of adoles-

cents (41), the study did not reach any conclusion in this group.

2. Propiverine: One RCT[34] compared propiverine to placebo in 164 children 5–17 year of age with OAB. Endpoints were assessed at eight weeks. Efficacy was compared in the two groups. Mean voided volume was higher by an average of 26.3 ml. in the treatment group (95% CI 18.0–34.6) (*GRADE level: Moderate*). Treatment was associated with a modest reduction in daily voiding frequency (0.8 fewer voids per day, 95% CI 0.11–1.5) over placebo (*GRADE level: Moderate)*.
3. Two randomized placebo-controlled studies were reported in a single publication comparing extended-release tolterodine with placebo in children with urge incontinence.[35] The baseline characteristics of participants were slightly different. Outcomes were evaluated at 12 weeks. The effect of drug was more obvious in patients with more than six voids per day. Pooling the results of the two studies showed a modest 1.4 fewer (95% CI 0.13–2.71) urge incontinence episodes per week (*GRADE level: Moderate)*.
4. A randomized placebo-controlled study in 42 children presenting with daytime incontinence showed that terodiline is associated with a modest effect of one fewer (95% CI 0.17–1.83) wet episode per day (*GRADE level: Low)*. There was no effect on nighttime enuresis. Inclusion criteria were broad and vague, preventing pooling data with other studies.[36]
5. In a subgroup of a complex RCT[37] including 63 children with OAB divided into two groups, adding oxybutynin or placebo to cognitive therapy was not associated with a different cure rate at 12 months' followup (43% vs. 33%, OR 1.18, 95% CI 0.43–3.21) (*GRADE level: Low)*.

Adverse events

Nijman et al did not show any difference in adverse events, such as headache, gastrointestinal issues (diarrhea/nausea/vomiting), or UTI in children receiving tolterodine vs. placebo *(GRADE level: Moderate)*. The study did not report the incidence of constipation. One percent of patients had serious adverse events, but none of them have been attributed to the treatment.[35] A study by Marschall-Kehrel did not show an increase in adverse events in children treated with propiverine *(GRADE level: Moderate)*. They reported a 2% incidence of constipation in the treatment group.[34]

Discussion

The primary objective of this guideline is to provide recommendations for urological management of children with BBD based on best-available evidence. The guideline does not include the primary treatment of gastrointestinal symptoms, such as constipation, although we recognize this is an important part of the comprehensive management. The guideline is based on the findings of RCTs. To maintain the highest quality of recommendations, we excluded observational studies.

The development of the guideline followed the Canadian Urological Association-recommended methods to identify, assess, and synthesize the best-available evidence. The steps in this endeavour include a systematic search of the literature using a comprehensive search strategy written by experienced medical librarian, review of the titles abstracts, data extraction, and assessment of bias from included studies by two investigators in an independent fashion. Whenever possible, the results of the studies were pooled using meta-analytic methods. We used the GRADE system to assess the evidence and develop recommendations. Although a full explanation of the GRADE methodology is outside the scope of this manuscript, a short description may be helpful.

The GRADE methodology is used to reduce the confusion arising from multiple systems for grading evidence and provide the clinicians the level of certainty for each recommendation.[12] The evidence for each study or pooled results of several studies are judged based on risk of bias, imprecision of the effect size, inconsistency, indirectness of findings in terms of sample or outcomes, and when applicable, publication bias. Once the assessment is completed a rating is applied to the recommendations (Table 1).

During this review, we encountered several prevalent challenges that made assessment of the quality, estimation of the effect size, and pooling of the data very onerous. Unclear or suboptimal randomization (selection bias), non-blinded studies (performance bias), and incomplete reporting (reporting bias) are among the most common issues affecting the quality of the evidence. The inclusion/exclusion criteria for recruiting patients are vastly different among the studies. This is magnified by the lack of a common terminology for the conditions under the rubric of BBD that has been partly remediated by the efforts of ICCS.[2] Studies used different interventions, although they may have been named similarly. For example, the words urotherapy or bladder re-training encompass a wide variety of regimens that include patient education, timed voiding, fluid management, behavioral modification techniques, and many more interventions with different timeframe and

Table 1. Definition of GRADE ratings

Rating	Definition
Very low	The true effect is probably markedly different from the estimated effect
Low	The true effect might be markedly different from the estimated effect
Moderate	The authors believe that the true effect is probably close to the estimated effect
High	The authors have a lot of confidence that the true effect is similar to the estimated effect

application methods. In addition, many studies focused on surrogate outcomes that are not clinically important, such as uroflowmetric parameters (mean voided volumes, maximum voided volumes. etc.) and either ignored more clinically relevant outcomes (incontinence, resolution of symptoms, etc.) reported by the patients or could not reach a conclusion due to small sample size. Followup lengths were also very variable.This heterogeneity in population, interventions, and outcomes prohibited us from pooling the data and performing meta-analyses in many occasions.

Summary of recommendations

1. Urotherapy/bladder re-training with timer to assist scheduled voiding is recommended over the same treatment without timer *(GRADE level: Moderate)*.
2. Face-to-face (group or individual) bladder re-training and video instructions are equally effective *(GRADE level: Low to moderate).*
3. In children with underactive bladder, addition of biofeedback to standard urotherapy is beneficial *(GRADE level: High).*
4. Biofeedback in children with other types of BBD is not associated with improved outcomes *(GRADE level: Low)*.
5. Addition of pelvic floor muscle physiotherapy to urotherapy has a beneficial effect on resolution of daytime incontinence in children with dysfunctional voiding *(GRADE level: Moderate).*
6. Parasacral transcutaneous electrical nerve stimulation (PS-TENS)
    a. No evidence to support PS-TENS as an effective adjunct to urotherapy or oxybutynin for OAB *(GRADE level: Low).*
    b. TENS may be useful in management of refractory urge incontinence in the short-term by reducing the number of wet days *(GRADE level: Low).*
7. Inferential transcutaneous electrical nerve stimulation may increase the voiding frequency and improve uroflowmetric parameters (e.g., PVR) in children with underactive bladder in the short-term. However, there is no evidence it is more effective than urotherapy in the long-term management *(GRADE level: High).*
8. Anticholinergics:
    a. Solifenacin: May increase the mean and maximum voided volumes in children with OAB, but it may not be different from placebo in improving incontinence or number of daily voids (off-label use) *(GRADE level: Low).*
    b. Propiverine: May increase mean voided volumes and modestly reduce daily frequency compared to placebo in children with OAB *(GRADE level: Moderate).*
    c. Tolterodine extended-release may result in a small decrease in urge incontinence in children with OAB (average 1.4 incontinence episodes per week) when compared to placebo (off-label use) *(GRADE level: Moderate).*
    d. We found no evidence of difference between oxybutynin and cognitive therapy in cure rate of incontinence in children with OAB *(GRADE level: Low).*

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Prior to publication, this guideline underwent review by the CUA Guidelines Committee, CUA members at large, and the CUA Executive Board.

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