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REVIEW

EAU-ESPU guidelines recommendations for daytime lower urinary tract conditions in children

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Abstract

The objective is to review the literature related to lower urinary tract (LUT) conditions in children to conceptualize general practice guidelines for the general practitioner, pediatrician, pediatric urologist, and urologist. PubMed was searched for the last 15-year literature by the committee. All articles in peer-review journal-related LUT conditions (343) have been retrieved and 76 have been reviewed extensively. Prospective trials were few and the level of evidence was low. Most of the recommendations have been done by committee consensus after extensive discussion of literature reports. History taking is an integral part of evaluation assessing day- and nighttime urine and bowel control, urgency, and frequency symptoms. Exclusion of any neurogenic and organic cause is essential. Uroflowmetry and residual urine determination are recommended in all patients to evaluate bladder emptying. Urodynamic studies are reserved for refractory or complicated cases. Urotherapy that aims to educate the child and family about bladder and bowel function and guides them to achieve normal voiding and bowel habits should initially be employed in all cases except those who have urinary tract infections (UTI) and constipation. Specific medical treatment is added in the case of refractory overactive bladder symptoms and recurrent UTIs.

Conclusion: Producing recommendations for managing LUTS in children based on high-quality studies is not possible. LUTS in children should be evaluated in a multimodal way by minimal invasive diagnostic procedures. Urotherapy is the mainstay of treatment and specific medical treatment is added in refractory cases.

What is Known:

- *Symptoms of the lower urinary tract may have significant social consequences and sometimes clinical morbidities like urinary tract infections and vesicoureteral reflux. In many children, however, there is no such obvious cause for the incontinence, and they are referred to as having functional bladder problems.*

What is New:

- *This review aims to construct a practical recommendation strategy for the general practitioner, pediatrician, pediatric urologist, and urologist for LUTS in children. Producing recommendations for managing LUTS in children based on high-quality studies is not possible. LUTS in children should be evaluated in a multimodal way by minimal invasive diagnostic procedures. Urotherapy is the mainstay of treatment and specific medical treatment is added in refractory cases.*

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Abbreviations

ESPU	European Society for Paediatric Urology
EAU	The European Association of Urology
ICCS	The International Children Continence Society
LUTS	Lower urinary tract symptoms
UTI	Urinary tract infections
OAB	Overactive bladder
UAB	Underactive bladder

Introduction

Epidemiological studies have shown that lower urinary tract (LUT) symptoms can be seen in as high as 20% of school-aged children [1]. Symptoms of LUT may have significant social consequences and sometimes clinical morbidities like urinary tract infections and vesicoureteral reflux. The most common symptom is incontinence. In the majority of children, there is no obvious cause for incontinence, and they are referred to as having functional bladder problems. Although much less frequent than the functional cases, congenital anatomical or neurologic abnormalities such as the ectopic ureter, bladder exstrophy, or myelomeningocele (MMC) may also be the cause of urinary incontinence.

The recent International Children's Continence Society (ICCS) document proposes using the term daytime lower urinary tract (LUT) conditions to group all functional bladder problems in children [1].

Following a review of the literature over the last two decades; the guideline panel assembled a document, which states the basic understanding of LUT function and dysfunction in children and clinical management suggestions based on the literature review and expert opinion.

Normal development

Normal storage and emptying of the bladder at a socially accepted place and time is mostly attained by ages 3–4. Bowel and daytime bladder control are usually attained by ages 3–4, while the attainment of nighttime bladder control is later. The children with LUT conditions would present with being still wet after the age of five, urgency, weak stream, hesitancy, frequency, and accompanied UTIs. Isolated nighttime wetting without any daytime symptoms is known as "enuresis" and considered as a distinct entity [2].

As different studies have used different definitions and criteria, it is difficult to give reliable percentages as regards to incidence of this problem. Reported prevalence ranges widely from 1 to 20% [3–11]. The prevalence seems to be increasing as awareness of this condition and access to specialized health care increases [12, 13].

Definition

LUT conditions in children are the result of disorders of the filling phase, the voiding phase, or a combination of both in changing severity. Mainly, the conditions are classified into either overactive bladder (OAB) or dysfunctional voiding. Overactive bladder is a term used for symptom of urinary urgency, usually accompanied by frequency and nocturia with or without urinary incontinence, in the absence of urinary tract infection. Dysfunctional voiding is a term used for increased activity of urethral sphincter or pelvic floor during voiding and presentation of a staccato pattern with or without an interrupted flow on repeat uroflow when EMG activity is concomitantly recorded in a neurologically intact child [2]. They can of course overlap and they may be contributing to each other. Dysfunctional bowel emptying is often part of the whole clinical picture and bladder bowel dysfunction (BBD) is the term used to cover associated bladder and bowel disturbances.

Pathogenesis

Incomplete or delayed maturation of the bladder sphincter complex may lead to LUT conditions. Micturition is initially a simple reflex activity of the medulla spinalis in the newborn which matures in time and is controlled by higher centers. The pons is responsible for detrusor sphincter coordination while the cortical area is responsible for inhibition of the micturition reflex and voluntary initiation of micturition. Thus, overactivity would be the result of delayed maturation of cortical control, while dysfunctional voiding would be the result of the non-maturation of the coordination. Detrusor overactivity should not be contemplated as a solitary bladder-based problem but more a symptom of a centrally located dysfunction affecting bladder, bowel, and even mood and behavior [14].

A link between lower urinary tract dysfunction and behavioral disorders such as ADHD (attention-deficit/hyperactivity disorder) has also been shown [15, 16].

Filling-phase dysfunctions

In filling-phase dysfunctions, the detrusor can be overactive, as in overactive bladder (OAB), or underactive, as in underactive bladder (UAB). Overactivity of the bladder is a common problem and mostly seen around 5–7 years of age. This may lead to disorders like urgency, frequency, and at times urgency incontinence. Some children consistently delay

micturition leading to voiding postponement. Children in this group often practice holding maneuvers such as leg crossing and squatting. Recurrent urinary tract infections are common and high pressure inside the bladder both during storage and emptying may cause vesicoureteral reflux. Constipation can be an additional etiological factor, which needs routine screening and further evaluation.

In children with an underactive detrusor, voiding occurs with reduced or minimal detrusor contractions with post-void residuals. Urinary tract infections, straining to void, constipation, and incontinence are common. Incontinence often occurs in the form of overflow incontinence when the bladder is over distended.

Voiding-phase (emptying) dysfunctions

In voiding phase (emptying), incomplete relaxation or contraction of the sphincter mechanism and pelvic floor muscles leads to staccato voiding pattern (continuous urine flow with intermittent reductions in flow rate caused by spurts of pelvic floor activity) or an interrupted voiding pattern (unsustained detrusor contractions resulting in infrequent and incomplete voiding, with fractionated micturition). This condition is defined as dysfunctional voiding and causes elevated bladder pressures during both storage and emptying and high post-void residuals. Symptoms will differ depending on the severity of incoordination between the bladder and the sphincter. Staccato voiding is in less severe forms and interrupted voiding and straining are in more severe forms. Children with dysfunctional voiding have also a high rate of constipation and recurrent UTIs [17].

Although poorly identified by parents, constipation usually accompanies other bladder symptoms in this group of children [18].

Incomplete emptying, high voiding pressures generated by bladder working against a functional obstruction caused by non-relaxing sphincter may induce not only urinary tract infections but also vesicoureteral reflux. It is been shown that LUTD is more important for the existence of UTI than VUR itself [19] Therefore, in the majority of children with dysfunctional voiding, the recurrent infections disappear following successful treatment. Spontaneous resolution of vesicoureteral reflux (VUR) is also possible after the successful treatment of dysfunctional voiding.

Diagnostic evaluation

The evaluation of LUT conditions involves medical and voiding history (bladder diaries and structured questionnaires), a physical examination, a urinalysis, and uroflowmetry with post-void residual (see the algorithm in Table 1).

The upper urinary tract also needs to be evaluated in children with recurrent infections and dysfunctional voiding. Uroflowmetry can be combined with pelvic floor electromyography to show the overactivity of the pelvic floor muscles during voiding. Urodynamic studies are not only invasive and but most often outcome will not alter treatment plan; therefore, they are not needed in the initial evaluation. Urodynamic studies are suggested for patients with therapy-resistant dysfunctional voiding and/or those not responding to treatment who are being considered for invasive treatment [19–23].

Table 1 Management algorithm

Child with LUTS over 5 years of age
DIAGNOSTIC WORK-UP
Voiding diary 2-3 full days minimum
Bristol stool scale; Rome III criteria
Questionnaires (optional)
To evaluate voiding and bowel habits, wetting severity/frequency, fluid intake, quality of life
Physical exam
To exclude neurogenic pathology or anatomic problem (meatal stenosis, labial fusion, epispadias, skin manifestations of occult spinal dysraphism, ectopic ureter)
Urinalysis
To exclude presence of UTI or any other pathology (DM, DI)
Uroflowmetry and PVR determination (USG or bladder scan)
To evaluate urine flow and emptying efficacy
USG (optional). To determine upper tract changes, bladder wall thickness, signs of constipation and should include bladder and kidneys
Urodynamic studies (Not required unless refractory to management)
VCUG (to detect reflux, bladder neck or outlet obstruction and only required if recurrent febrile UTI is present)*
MANAGEMENT
• If UTI is present treat UTI first.
• If constipated treat bowel first with dietary changes and laxatives.
• Urotherapy is initial therapy in all cases to maintain controlled fluid intake, regular and efficient bladder emptying (see table 1).
• Medical treatment (anticholinergics); if OAB symptoms dominate and persist despite urotherapy.
• Antibiotic prophylaxis; in case of recurrent UTI
Biofeedback is optional as first line therapy as part of urotherapy program; otherwise it recommended use if refractory to urotherapy.
Neural stimulation or Botulinum toxin A injection to detrusor is suggested if refractory to urotherapy and medical treatment but still experimental.

* Any form of VCUG (radionucleotide cystogram, contrast enhanced voiding cystogram etc)

A comprehensive medical history questioning presence of any systemic diseases (like diabetes mellitus, insipidus) or psychologic, behavioral disorders, handedness, penmanship, and school performance which may be related to voiding habits should be taken initially [24]. A detailed voiding diary is an important part of the evaluation and provides a recording of voiding and defecation habits, frequency of micturition, voided volumes, number and timing of incontinence episodes, and fluid intake. Voiding diary should at least be done for at least 2 days—better 3 days—although longer observation periods are preferred [25]. A voiding diary provides information about storage function and incontinence frequency, while a pad test can help to quantify the urine loss. In the pediatric age group, where the history is taken from both the parents and child together, a structured approach is recommended using a questionnaire. Many signs and symptoms related to voiding and wetting will be unknown to the parents and should be specifically requested, using the questionnaire as a checklist. Symptom scorings have been developed and validated [26–28]. Dysfunctional voiding and incontinence scoring system are asking questions mainly in yes/no format and children and parents expected to respond this together [27]. The dysfunctional voiding scoring system is a more quantitative scoring and is an adaptation of International Prostate Symptom Scoring (IPSS) which is being used for adults [28]. It is recommended that since both are validated and commonly used; it should be the practitioner's decision to choose the one which best suits their practice and patient population. Although the reliability of questionnaires is limited, they are practical in a clinical setting to check the presence of the symptoms and also shown to be a reliable tool to monitor the response to treatment.

History taking should also include assessment of bowel function. For the evaluation of bowel function in children, the Bristol Stool Scale is an easy-to-use tool [29]. According to the Rome III pediatric criteria, functional constipation is diagnosed if at least more than 2 of the following conditions are present in a child with a developmental age of more than 4 years. (1) ≤ 2 defecations per week, (2) ≥ 1 episode of fecal incontinence per week, (3) history of retentive posturing or excessive volitional stool retention, (4) history of painful or hard bowel movements, (5) presence of a large fecal mass in the rectum, and (6) history of large diameter stools that obstruct the toilet. The updated version of the Rome III criteria is the Rome IV criteria which consider the time period of how long complaints should be present, 1 month instead of 2 months.

A non-invasive way to determine fecal retention is the estimation of rectal diameter on ultrasound. Although there is no official consensus, a distended rectum in ultrasound of 30 mm or more may be one of the signs indicative of constipation [30].

Urinalysis and urinary culture are essential to evaluate for urinary tract infection (UTI). On urinalysis, the specific gravity of the urine and any other evidence of underlying voiding problems based on the presence of hematuria, proteinuria, or glucosuria are noted. Since transient voiding symptoms are common in the presence of UTI, exclusion of UTI is essential before further management of symptoms.

During clinical examination, genital inspection to see any pathologies like meatal stenosis or congenital abnormalities of the urethra and observation of the lumbosacral spine and the lower extremities are necessary to exclude obvious uropathy and neuropathy.

Uroflowmetry with post-void residual evaluates the emptying ability, while an upper urinary tract US screens for secondary anatomical changes. A flow rate which reaches its maximum quickly and levels off ("tower shape") may be indicative of overactive bladder, a staccato voiding patterns may be seen in dysfunctional voiding and interrupted voiding with long intervals with straining episodes may be indicative of an underactive bladder. Plateau uroflowmetry patterns are usually seen in anatomic obstruction of flow. A single uroflowmetry test may not be descriptive of the clinical situation and more uroflowmetry tests, which are all giving comparable results, are more reliable. Uroflowmetry examination should be done when there is a desire to empty the bladder and the voided volume should at least be 50% of the age expected capacity ([age in years) + 1] × 30 mL) for the children.

Ultrasonography of the urinary tract is a very valuable tool to assess the possible abnormalities in the kidneys, ureters, and bladder. Post-voiding residual urine measurement in association with uroflowmetry is a valuable tool to assess the prognosis of the condition [29]. Besides, the urinary tract ultrasonography can give clues about the status of constipation. A rectal diameter of more than 30 mm is a significant signal for constipation as suggested above [30].

While testing the child in a clinical setting, the effect of the stress and mood changes on the bladder function should also be contemplated [32, 33].

In the case of failure after initial treatment, or in the case of former failed treatment, re-evaluation is necessary and further urodynamic studies (preferably with video if reflux or outflow obstruction is suspected) may be considered. Sometimes, there are minor, underlying, urological, or neurological problems, which can only be assumed using urodynamic studies. In these cases, structured psychological interviews to assess social stress should also be added [34, 35].

In case febrile urinary tract infections vesicoureteral reflux needs to be excluded either by voiding cystography or video urodynamic studies. Video urodynamic studies, will help to observe reflux along with bladder dynamics.

In the case of suspected anatomical problems which may cause infravesical obstruction such as posterior urethral valves, syringocoeles, congenital obstructive posterior urethral membrane (COPUM), or Moormann's ring, it may be necessary to

do cystoscopy with treatment. MRI of the lumbosacral spine and medulla can help to exclude any neuropathic pathology like tethered cord, lipoma, or other rare conditions.

Management

The treatment of LUTD includes a multimodal approach. Urotherapy involves methods such as behavioral modification, anticholinergic medication, and physiotherapy, along with treating underlying and potentially complicating conditions such as constipation and urinary tract infections. Please see Table 2 for approaches used to employ urotherapy.

Behavioral modification, mostly mentioned as a part of urotherapy, covers all non-pharmacological and non-surgical treatment modalities. It is mainly rehabilitation of the lower urinary tract and aims to normalize micturition in order to prevent further functional disorders. It includes standard therapy of hydration, bowel management, timed voiding, and basic relaxed voiding education. The child and family are informed and educated about normal bladder function and responses to urgency. Compliance with recommendations is important. It was shown that patients with good compliance with timed voiding were significantly more likely to improve than those with poor compliance. Urotherapy may often need to be combined with medical treatment including anticholinergics and antibiotics. Voiding regimens are instituted and UTIs and any constipation are treated using antibiotics and laxatives. Bowel management is an important component of urotherapy which includes instructions for timing, positioning, and a programed training of defecation. Treatment is aimed at optimizing bladder emptying and inducing full relaxation of the urinary sphincter or pelvic floor prior to and during voiding. Despite many studies done about urotherapy, still, it is unknown which aspects of urotherapy makes it successful. Gender, age subtype of LUTS, compliance, and adherence are important factors for the behavioral change and paramount importance is the attention offered to the child by the therapist [36, 37].

Table 2 Methods to achieve the goals of urotherapy

- Information and education, which involves information about normal LUT function: normal bladder capacity/voided volume, frequency of voiding, and how a child deviates from normal function.
- Instructions about how to change behavior to manage the problem like regular voiding habits, sound voiding and defecation posture on a sitting position with support under feet, pelvic floor awareness and training to relax the pelvic floor, and avoiding holding maneuvers.
- General advice about fluid intake, dietary exclusion of caffeine and soda; prevention of constipation by dietary modifications.
- Record-keeping of symptoms and voiding habits using bladder diaries or frequency volume charts.
- Support and encouragement via regular follow-up by the caregiver.

Recurrent urinary infections and constipation should also be treated and prevented during the treatment period. In the case of combined bladder and bowel dysfunction, it is advised to treat bowel dysfunction first [12]. As bowel dysfunction is more socially isolating than urinary incontinence, and in the light of evidence that amelioration of underlying constipation can relieve bladder symptoms, most clinicians begin with a treatment of the bowel. Strategies include disimpaction (if needed), prevention of stool re-accumulation, and post-prandial efforts to empty the bowel while maintaining optimal defecation dynamics. Once stools are being passed regularly, treatment focuses on teaching awareness of age-appropriate fullness in the bladder, and training unopposed emptying (without straining or pelvic floor muscle recruitment), at pre-scheduled times. LUTS may disappear after the successful management of bowel dysfunction.

The addition of other approaches as below may be needed for cases who do not show satisfactory response to urotherapy and who have some conditions which may need specific treatment.

- Physiotherapy includes pelvic floor muscle awareness practices with repeated sessions of biofeedback visualization of uroflow curves and/or pelvic floor activity and relaxation.
- Clean intermittent self-catheterization for high volumes of post-void residual urine despite urotherapy and biofeedback.
- Antimuscarinic drug therapy, if detrusor overactivity is present.
- If the bladder neck is associated with increased resistance to voiding, alpha-blocker drugs may be introduced.

Most often, these patients would need urodynamic studies to delineate the underlying problem that may need specific treatment.

Treatment efficacy can be assessed by improvement in bladder emptying and resolution of associated symptoms. Controlled studies of the various interventions are needed. As with detrusor overactivity, the natural history of untreated dysfunctional voiding is not well delineated and optimum duration of therapy is poorly described. A high success rate has been described for urotherapy programs, independent of the components of the program [38, 39]. However, the evidence level is low as most studies of urotherapy programs are retrospective and non-controlled. Some recent controlled studies show the efficiency of urotherapy over pharmacologic treatment and suggest its use as the initial treatment [40].

Specific interventions

As well as urotherapy, there are specific interventions, including physiotherapy (e.g., pelvic floor exercises), biofeedback, alarm

Table 3 Antimuscarinic agents available for the treatment of overactive bladder

	Dosage		FDA or EMA approval
Oxybutynin	0.1–0.3 mg/kg	Most commonly used Several studies yet level of evidence is low High rate of withdrawal due to adverse effects	Yes
Propiverine	5–15 mg BID	Single randomized controlled study [46]	Yes
Tolterodine	No suspension forms 0.5–2 mg BID*	Several studies high placebo effect but less side effects [45]	Off label
Solifenacine	No suspension forms 2.5–10 mg/day*	Favorable results with less side effects [47]	Pending
Trospium chloride	No suspension forms 10–20 mg BID*	Small series	Off label
Fesoterodine	No suspension forms 4–8 mg/day*	Only one small trial Similar tolerability and effects	Off label

*Trial doses; otherwise, pediatric dosing is currently unavailable or not applicable for these drugs

therapy, and neurostimulation. Although good results with these treatment modalities have been reported, the level of evidence remains low since only a few RCTs were published [41–44].

A systematic review reports that biofeedback is an effective, non-invasive method of treating dysfunctional voiding, and approximately 80% of children benefited from this treatment. However, most reports were of the low level of evidence and studies of more solid design such as RCT is needed [48].

A multi-center controlled trial of cognitive treatment, placebo, oxybutynin, bladder, and pelvic floor training did not report better results with oxybutynin and pelvic floor training compared with standard therapy [31].

In an RCT on underactive bladder without the neuropathic disease, transcutaneous interferential electrical stimulation and animated biofeedback with pelvic floor exercise have been shown to be effective [49]. In some cases, pharmacotherapy may be added. Anticholinergics have been shown to be effective, though the level of evidence level was low. Some studies on orthosympathomimetics have been published with a low level of evidence [50, 51].

Overactive bladder (OAB) is common in the pediatric population. Although a stepwise approach starting with behavioral therapy is advised; antimuscarinic agents remain to be the mainstay of medical treatment for OAB. Oxybutynin is the most commonly used antimuscarinic in the pediatric population. The response to antimuscarinics varies and many experience serious side effects. Although there have been reports about the use of tolterodine, fesoterodine, trospium, propiverine, and solifenacin in children, to date, all except oxybutynin are off label. A few RCTs have been published, one on tolterodine showed safety but not efficacy [52], while another on propiverine showed both safety and efficacy [53]. The recent study on solifenacin showed its efficacy with side effects like constipation and electrocardiogram changes [54] (see Table 3).

The difference in results is probably due to the study design. Despite the low level of evidence for the use of anticholinergics and antimuscarinics, their use is recommended because of the large number of studies reporting a positive effect on OAB symptoms. Although α-blocking agents are used occasionally, an RCT showed no benefit [51]. Botulinum toxin injection seems promising but can only be used off label [55].

A meta-analysis reports that neurostimulation therapy may lead to better partial improvement of non-neurogenic overactive bladder; however, it may not render a definitive complete response. Office-based neurostimulation seems more efficacious than self-administered neurostimulation [56]. These

Table 4 Level of evidence for different recommendations and strength ratings for recommendation

Recommendations	LE	Strength rating
Use 2-day voiding diaries and/or structured questionnaires for objective evaluation of symptoms, voiding drinking habits, and response to treatment.	2	Strong
Use a stepwise approach, starting with the least invasive treatment in managing daytime lower urinary tract dysfunction in children.	4	Weak
Initially offer urotherapy involving bladder rehabilitation and bowel management.	2	Weak
If bladder bowel dysfunction is present, treat bowel dysfunction first, before treating the lower urinary tract condition.	2	Weak
Use pharmacotherapy (mainly antispasmodics and anticholinergics) as second-line therapy in overactive bladder.	1	Strong
Use antibiotic prophylaxis if there are recurrent infections.	2	Weak
Re-evaluate in case of treatment failure; this may consist of (video) urodynamics MRI of lumbosacral spine and other diagnostic modalities, guiding to off-label treatment which should only be offered in highly experienced centers.	3	Weak

LE, level of evidence

new treatment modalities can only be recommended for standard therapy-resistant cases.

Although there are many studies reporting different management options, as there are few randomized prospective trials, the evidence level is generally low. Table 4 shows the levels of evidence and recommendation strength for various recommendations.

Despite early successful treatment, there is evidence that there is a high recurrence rate of symptoms in the long term which necessitates long-term follow-up [29] and many patients may present themselves later in adulthood with different forms of LUTD [55].

Conclusion

LUT conditions in children may occur as high as 20% in school-aged children. History taking is an integral part of evaluation assessing day- and nighttime urine and bowel control, urgency, and frequency symptoms. Exclusion of any neurogenic and organic cause is essential. Uroflowmetry and post-void residual urine determination are recommended in all patients to evaluate the general performance of bladder emptying. Urodynamic studies are reserved for refractory or complicated cases.

Urotherapy is the mainstay of treatment and should initially be employed in all cases except those who have UTIs and constipation. The aim of urotherapy is to teach the child and family about bladder and bowel function and guides them to achieve normal voiding and bowel habits. Specific medical treatment is added in the case of refractory OAB symptoms and recurrent UTIs.

Authors' contributions Serdar TEKGUL reviewed and classified the literature since 2003, drafted the initial manuscript, reviewed, revised the manuscript, and is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Hasan Serkan Dogan, Raimund Stein, Guy Bogaert, Shabnam Undre, Rien Nijman, Christian Radmayr, Josine Quadackers, Lisette 't Hoen, Radim Kocvara, and Mesrur Selcuk Silay have revised critically the manuscript for important intellectual content before and during the guidelines committee meeting on February 9, 2019, and have approved the current version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent There was no need for informed consent.

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