REVIEW ARTICLE

Nocturnal enuresis

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Abstract: Nocturnal enuresis (NE) is increasingly seen as part of a heterogeneous phenomenon that at times will include daytime lower urinary tract symptoms such as urgency, frequency and wetting – with reduced bladder storage, usually due to an overactive bladder. In turn, these may be associated with constipation and/or faecal soiling. This paper discusses these considerations in the management of NE.

Key words: behavioural; enuresis; general paediatrics; nephrology/renal.

Introduction

In recent decades much has changed in our understanding of nocturnal enuresis (NE). Previous notions of voluntary control have been replaced by an appreciation of genetic and pathophysiological bases. Daytime wetting and/or urgency, with NE, once regarded as laziness, or faking ('Sham' syndrome), are now attributed mostly to an overactive bladder (OAB). NE is often part of a broader problem including daytime lower urinary tract (LUT) dysfunction (usually OAB) and constipation/faecal soiling – sometimes called 'Dysfunctional Elimination Syndrome'. An internationally recognised nomenclature for wetting disorders has facilitated scientific discourse on these issues.[1] The aim of this review is to incorporate the above changes into the contemporary understanding and management of NE for the general paediatrician.

Nomenclature

Decades of semantic confusion in describing the growing heterogeneity of NE have made communicating and interpreting scientific information most difficult. In 2006, the International Children's Continence Society (ICCS) revised their standardised terminology[1] for NE, considering pathophysiological subgroups, focusing on the role of the LUT.

ICCS definitions

Incontinence

Incontinence means continuous or intermittent, uncontrollable leakage of urine. 'Continuous' is usually a sign of ectopic ureter. 'Intermittent' can occur by day and/or night and applies to children at least 5 years old.

Enuresis

Enuresis means wetting while asleep after age 5 years. 'Nocturnal' may be added for clarity. The term 'diurnal enuresis' has been dropped. The child who wets during the day and night has daytime incontinence and enuresis (or NE).

Two subgroups of NE are included.

1 Primary/secondary NE

A child with 'Primary NE' has never been continuously dry for at least 6 months.

Secondary NE relates to relapse after at least 6 months of dryness. These children are more likely to have non-monosymptomatic nocturnal enuresis (NMNE) (see below) and respond less well to treatment.[2] Secondary NE is occasionally associated with organic or psychological causes such as urine infection, sexual abuse, diabetes mellitus/insipidus, obstructive sleep hypoventilation, neurogenic bladder or externalising disorders such as attention-deficit/hyperactivity disorder (ADHD) or conduct disorder. However, large family studies[3] have shown that secondary NE is *usually* no different aetiologically from primary, with undue emphasis on the difference being unwarranted.

2 Monosymptomatic/non-monosymptomatic NE

NE, without daytime symptoms of bladder dysfunction, is called *monosymptomatic* nocturnal enuresis (MNE). NE with *any* daytime LUT symptoms (arguably including resolved

Key Points

1. The clinical picture of non-monosymptomatic nocturnal enuresis (NMNE) is often revealed only after a careful history about daytime lower urinary tract symptoms is taken.
2. Among the identifiable causes of refractory or relapsing NE, unsuspected overactive bladder and constipation are common.
3. In NMNE, first bring the symptoms of overactive bladder under control (usually with anticholinergic medication) before dealing with nocturnal enuresis.

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symptoms) is NMNE. Daytime LUT symptoms suggesting NMNE include: wetting (not obligatory), increased voiding frequency, urgency, jiggling, squatting and holding manoeuvres. A careful history is often required to elicit these symptoms, which usually indicate an OAB – a 'filling' or storage problem. 'Emptying' problems such as straining, weak stream, intermittency, a feeling of incomplete emptying, post-micturition dribble, infrequent voiding and genital or LUT pain are specialist continence or urological issues that have been recently reviewed in this journal[4] and are outside the scope of this article.

Epidemiology

The prevalence of NE is between 6% and 10% at age 7, decreasing to 2% at 15 years and 0.5–2% in adults. Boys are more affected than girls (3:2). Spontaneous annual resolution is about 15% after age 6, decreasing dramatically in adolescence.[5] Nightly wetting (as opposed to sporadic) and NMNE have a poorer outlook.[5] The community incidence of NMNE is not known, with estimates ranging widely from 20% to 80% of NE.

Inheritance

NE has a complex and multifactorial pathophysiology with genetic underpinning.[3,6] Forty three per cent of children with one and 77% with two former NE parents will have NE after age 5. Monozygotic twins have higher concordance rates than dizygotic twins.[7,8] Linkage of NE to markers on chromosomes 13,[2] 4, 8, 12 and 22 has been reported, with autosomal dominant inheritance and high penetrance suggested[9] but no major gene as yet identified. Family and twin studies suggest locus heterogeneity and poor phenotype–genotype correlation.

Pathophysiology

The phenomenon of NE rests on three pathophysiological determinants:

1 nocturnal polyuria;
2 decreased nocturnal bladder storage ability; and
3 poor arousal to the stimulus of a full bladder.

Items 1 and/or 2 might fill the bladder, hopefully waking the child to go to the toilet (nocturia). However, for NE to occur, the child must remain asleep despite the stimulus of a full bladder (Fig. 1).

Nocturnal polyuria

Normal nocturnal urine production is much less than by day, with increased urine osmolality, partly due to the nocturnal circadian peak of antidiuretic hormone (ADH) release.[10] In the1980s, a group of Danish children with NE were shown to have nocturnal polyuria and relative nocturnal ADH deficiency,[11,12] thereby defining the management of NE in Europe for 25 years. It has been shown since that not all children with NE have nocturnal polyuria, and in those who do, nocturnal ADH may be normal.[13] Nocturnal polyuria and vasopressin responsiveness are highly complex phenomena that may be influenced by:
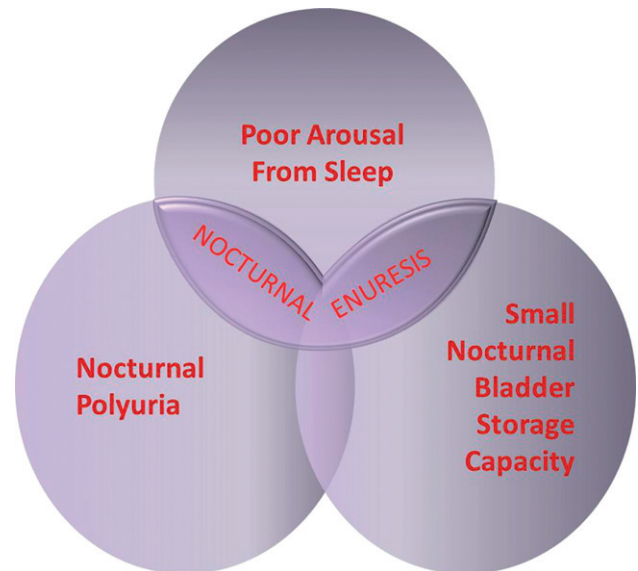

Fig. 1 The pathophysiological determinants of nocturnal enuresis.

- increased evening dietary solute load with high nocturnal urine osmolarity;[14]
- abnormal renal sodium handling (related to release of angiotensin II, aldosterone and natriuretic peptide);
- nocturnal hypercalcuria;
- abnormal circadian rhythm of prostaglandin E2;
- abnormal circadian rhythm of glomerular filtration rate;[15]
- autonomic renal changes related to supine position or brainstem autonomic control;
- innate suboptimal renal concentrating capacity; and
- obstructive sleep hypoventilation.[16]

Reduced bladder storage and OAB

Bladder storage can demonstrate day/night and intra/interperson variability. With OAB, the detrusor muscle (bladder wall) contracts frequently, often when the bladder is relatively empty – that is, decreased functional (not anatomical) capacity, or aborted bladder filling, with decreased storage of urine. MNE children often have normal nocturnal bladder storage but some may have nocturnal OAB.[17]

NMNE is usually associated with nocturnal and daytime OAB, the hallmark of which is urgency[1] and frequency of micturition, and sometimes small patches of wetting (i.e. urge incontinence). Children with OAB (a clinical diagnosis) usually have detrusor overactivity (a cystometric diagnosis) causing sudden rises in intravesical pressure and the above symptoms, even though the bladder is relatively empty.

The child threatened with sudden, urgent wetting may adopt a raft of defensive stratagems including jiggling, squatting on one heel (Vincent's curtsy), grabbing one's genitalia and posturing (collectively called '*hockering*' in our clinic – Fig. 2), probably aimed at tightening pelvic floor muscles to support the bladder sphincter and prevent or minimise wetting. Running to the toilet may paradoxically increase the risk of wetting, because

Fig. 2 Defensive manoeuvres against an overactive bladder.

running militates against tightening of the pelvic floor muscles. The child may therefore prefer to '*hocker*' rather than run the gauntlet to the toilet. Unable to explain themselves, they might dissemble by claiming that they do not need the toilet anyway. Frustrated parents could understandably misinterpret this as 'stubbornly waiting until the last moment' or laziness, unless the pathophysiology is properly explained to them.

The underlying cause of OAB is unknown. It may be a central imbalance of the autonomic nervous system, with parasympathetic dominance (causing bladder contraction), or perhaps inflammation of the bladder urothelium. Refractory NE is usually associated with NMNE.[5,18]

Longstanding OAB can cause and be caused by contraction of pelvic floor muscles during voiding (dysfunctional voiding (DV)), leading to incomplete bladder emptying, refractory NMNE, vesticoureteric (VU) reflux and UTI.[19]

Poor arousal from sleep

Children with NE seem to be heavy sleepers.[20] Often the bed-wetting child sleeps through the adjacent alarm while household members are woken. Evidence suggests that the arousal threshold is elevated in all sleep stages in children with NE compared with controls,[21] implying that afferent signals from the bladder find the brain unresponsive. Attention has been focused on locus coeruleus and the pontine micturition centre, although broader brainstem dysfunction may be involved.

A study of therapy-resistant NE children in Hong Kong[22] showed that while appearing to be heavy sleepers, they had in fact more overall light sleep (Stage I/II non-REM) with sleep fragmentation, rather than deep sleep (Stage III/IV non-REM). All subjects had severe OAB during sleep. The cerebral cortex was 'bombarded' by afferent input of sleep OAB with frequent cortical arousals that failed to wake the children – a presumed paradoxical elevation of conscious awakening threshold. OAB associated cortical arousals may cause a shift from deep to light sleep but not to complete awakening, perhaps because of over-stimulation of the sleep arousal centre by the OAB.[22]

Comorbidities of NE

Constipation/faecal soiling

Constipation/faecal soiling is seen especially with NMNE. The combination of NE with OAB and constipation/faecal soiling (sometimes known as dysfunctional elimination syndrome) is a risk factor for relapsing or refractory NE[23] as well as UTI.

UTI

OAB and DV both involve the bladder emptying against tightened pelvic floor muscles, which may lead to incomplete voiding or VU reflux, and hence UTI. Tightening of pelvic floor

Normal

Overactive Bladder

Dysfunctional Voiding

Outflow Obstruction

Underactive Detrusor
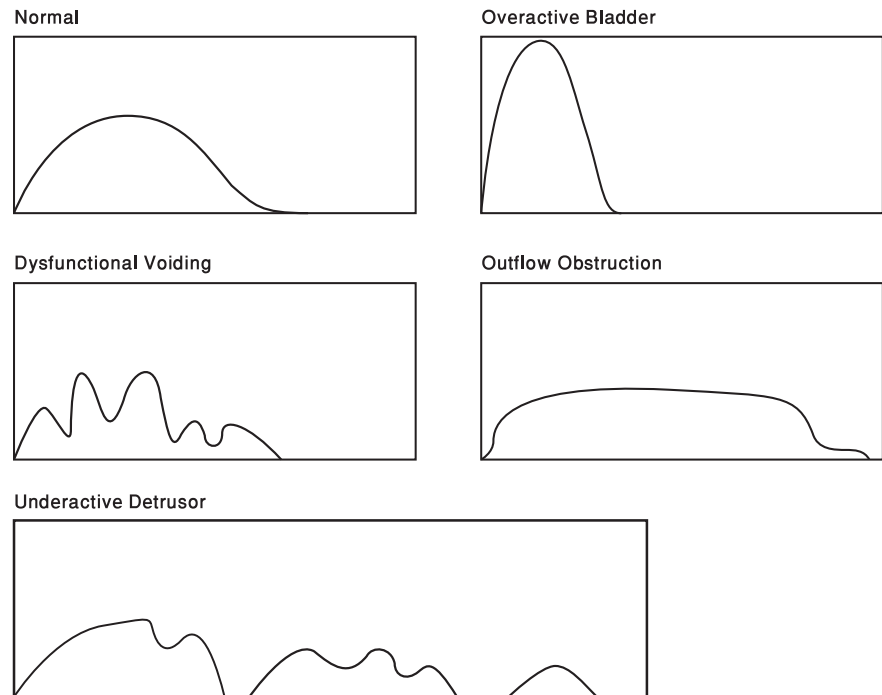
Fig. 3 Diagramatic uroflow curves (mls/min vs. time) and their possible significance. Modified from von Gontard A, Neveus T. *The Management of Disorders of Bladder and Bowel Control in Childhood*. Cambridge University Press, 2006.

muscles might also cause the 'milk back' of non-sterile urine from the perineum to the bladder.[24]

Psychological and behavioural problems

Psychological factors are no longer considered to be a primary cause of NE. Children with NE have poor self-esteem, anxiety, feel stigmatised and blamed as they get older, and expend much effort in concealing their problem.[25] However, in MNE, these tend to resolve once they attain continence, with no long-term psychological comorbidities. NMNE and secondary NE are more likely to be associated with neurobehavioural externalising conditions such as ADHD[26–29] leading to speculation concerning a common neurobiology.[30]

Management of NE (Fig. 4)

The age for commencing treatment should be decided on an individual basis. Children older than about 10 years should probably be seen urgently because of poor quality of life[31] and ongoing anxiety. Children under 6 years seldom require treatment.[32]

Initial interview

1 Reassure the child that it is not their fault.
2 Explain the inherited nature and prevalence of the problem.
3 Take a careful history for NMNE and unsuspected constipation/faecal soiling.
4 Voiding and fluid intake diary for 24–48 h helps support a history of OAB and will detect other problems such as poor intake or polydypsia. Expected bladder capacity (EBC) = (age

in year + 1) × 30 mls (up to age 12 years).[1] Voiding frequent small volumes, often well below the EBC, suggests OAB.
5 Urine – culture, glucose.
6 For NMNE, especially if refractory to treatment, consider:
   • renal and bladder ultrasound (US) (bladder wall thickening suggests chronic OAB or DV[33]);
   • immediate post-voiding bladder US for residual volume (normally <5 mL; 5–20 mL should be repeated; >20 mL repeatedly suggests DV or other LUT pathology)
   • Uroflow – usually in specialist centres. Uroflow measures voiding flow against time. The normal curve is smooth and bell shaped, whereas OAB may give a sharp upstroke and downstroke. Figure 3 shows diagrammatical representation of some typical curves and their significance. In clinical practice they are not always pathognomonic, usually requiring repetition and reproducibility before interpretation.

MNE[34]

Alarms

Bedwetting alarms (pad and bell or personal/body worn alarm) for 8–12 weeks are the mainstay of therapy for MNE. Both alarm types appear equally effective.[35,36] With proper explanation and compliance, initial success for MNE is as high as 80%[36–38] with relapse rates of 4–55%,[38] although poor patient characterisation makes study interpretation difficult.[39] Waking the child to the alarm, if they do not wake spontaneously is considered important as is ongoing encouragement and motivating. Once the child has 'learned' to be dry for about 10 nights, there may be a benefit in 'overlearning' by drinking a

glass of water before bed[37] to further challenge the nocturnal bladder.

Despite over 75 years of experience of alarm use, the mode of action is unclear. They appear to increase nocturnal bladder storage.[40,41] The term 'conditioning alarm' implies that the alarm creates a conditioned response (i.e. waking) to the stimulus of a full bladder. If this were so, then children should become dry by waking at night to urinate, whereas most children who become dry sleep through the night.

Desmopressin

Desmopressin (1-deamino-8-D-arginine vasopressin (DDAVP)) is a synthetic analogue of ADH. About 60% of children respond, but the relapse rate is much higher than the alarm.[42] Hence, it is mostly used as a stopgap (sleepovers and school camps) rather than cure. In Australia, it is available on Authority when alarms have failed. It is occasionally used as medium-term therapy in adolescents with repeated alarm failure or who find alarms intrusive. Desmopressin is usually given within an hour of bedtime. Drinking is not allowed until they have passed urine the next morning.

After isolated reports of water intoxication/hyponatraemia with the nasal spray (10 mcg/actuation), which unpredictably, occasionally has a long half-life, the trend is towards using desmopressin tablets (200 mcg, 1–2 before bed)[43] or sublingual melts (120 mcg, 1–2 before bed)[44] with safer pharmacokinetics.

Other treatments

Tricyclics (imipramine in particular) are no more successful than desmopressin, have a much higher relapse rate,[45] and in accidental overdose (usually in the younger siblings) cause life-threatening cardiotoxicity. Therefore, they are eschewed for MNE, although in specialised clinics, they still have a minor role. The mode of action may be any or a combination of: anticholinergic bladder relaxation, increased bladder sphincter tone, bladder urothelium anaesthetic or change in sleep architecture.[46]

Simple treatments such as fluid restriction before bed, waking ('lifting') the child to the toilet, have usually been tried prior to seeking help. These steps are harmless and probably reduce washloads/week, but their contribution to long-term success is questionable.[32,47] Reward charts have shown some success but imply that NE is within the child's voluntary control. Bladder training involving 'holding on' or 'stretching the bladder' does not work.[48,49] There is no good evidence supporting complementary medicine[50] with the possible exception of acupuncture.[34]

NMNE (Fig. 4)

One must first control daytime symptoms of OAB and bowel problems before treating NE, then manage as per MNE.

Anticholinergics – for OAB

Oxybutynin is an anticholinergic with strong anti-spasmodic properties. Anti-muscarinic side effects include dry mouth (with

theoretical risk of tooth decay), flushed appearance, mood and personality changes, constipation, headaches, epistaxis and blurred vision.[51] There are no clear dose recommendations. Initial low dose, with upward titration, hopefully permits benefit before side effects appear (which disappear rapidly upon ceasing the medication). Usual starting dose is 2.5 mg bd increasing over 3 weeks to 5 mg bd, for a period of 6 months – years.

Alternatives include oxybutynin slow-release (adults 5–30 mg/d), oxybutynin patch 3.9 mg (worn for 3–4 days) or tolterodine, a newer anticholinergic that is more bladder specific (1–2 mg bd).

Non-pharmacological interventions[4,52]

1 Fluids – Children with NMNE typically drink less than their peers, presumably in an unconscious attempt to minimise wetting.[53] Normalising fluid intake in healthy children is physiological, widely recommended, but lacks solid evidence to support it. Increasing fluids beyond normal intake may aggravate symptoms.[53]
2 Regular/timed toileting × 5–8/day.
3 Treat constipation.
4 For DV, specialised physiotherapists (urotherapists) or continence clinics can assist in pelvic floor relaxation techniques while voiding.[4,54]

Refractory NE

1 Reconsider possible constipation.
2 Refractory MNE often requires reclassification as NMNE and treatment with anticholinergics.[55] Even true MNE may warrant a trial of anticholinergics for unsuspected nocturnal OAB[18,56] (Fig. 4).
3 Some children go to bed with maximally concentrated urine (high dietary solute/protein load after school) hence neither endogenous nor exogenous ADH can further concentrate it. Avoid protein and salt rich foods after school and increase low solute drinks in the morning.[14]
4 Desmopressin may be tried 1–2 h before bed because of occasional slow onset of action.[57]
5 Combinations of desmopressin, anticholinergics and/or imipramine may be effective especially in NMNE.[56,58] There is conflicting evidence about the use of demopressin together with alarm.[59,60]
6 Retry alarm after about 6 months.
7 Refer to a continence clinic or urotherapist.[61]

Motor and Intellectual Disability

NE in physically and/or intellectually disabled children is common,[62] often compounded by a tendency to constipation, poor fluid intake,[63] OAB, DV and poor mobility. Long-term incontinence is more commonly associated with higher degrees of motor rather than intellectual disability. Correcting the above factors and treating NE by conventional methods is often successful. Otherwise, refer to a specialist service. Fatalism and pessimism about long-term continence acquisition are usually unwarranted.
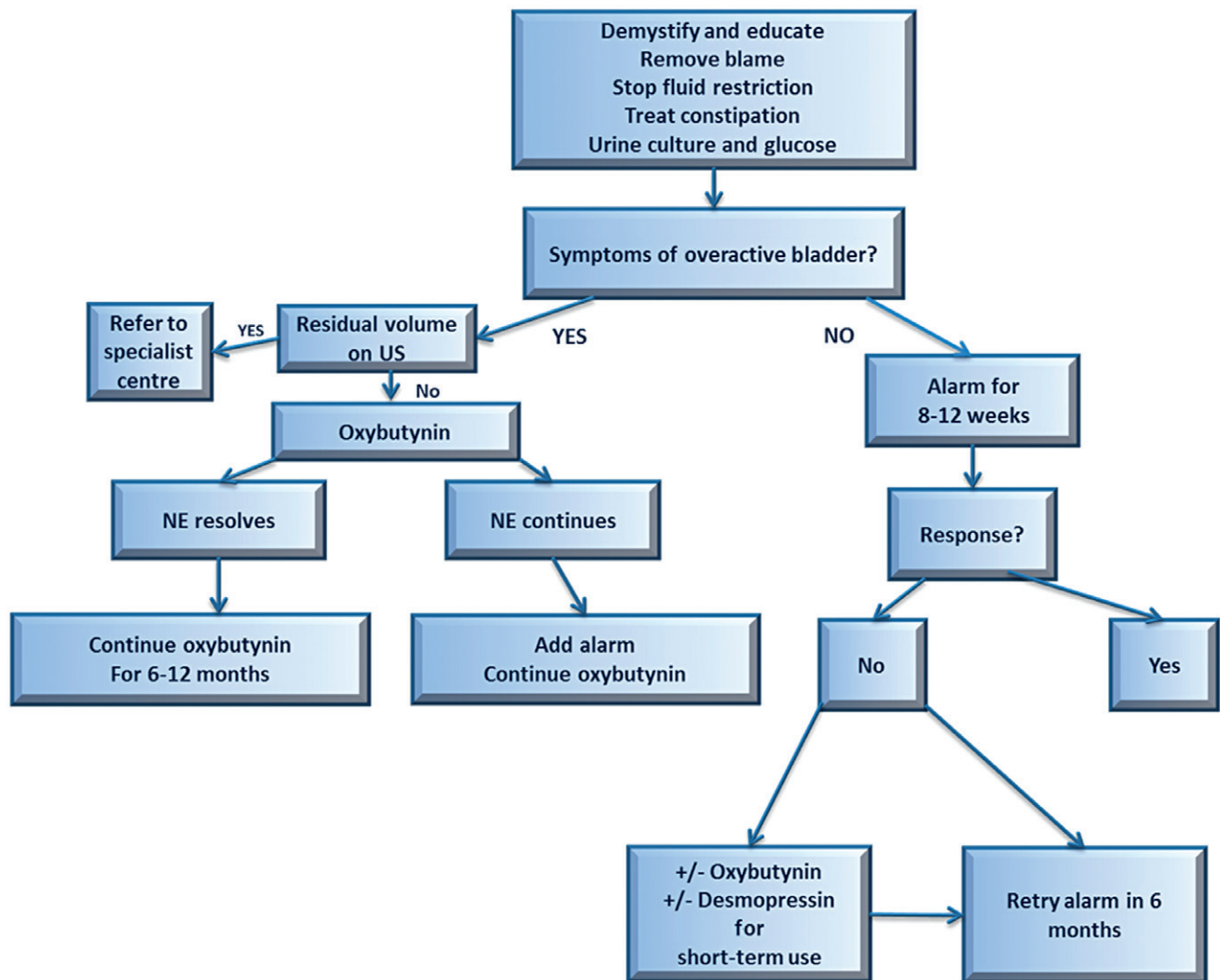
Fig. 4 Management algorithm for nocturnal enuresis (NE).

Future Direction

Greater understanding of the sleep/arousal mechanisms in NE should give clues regarding therapy-resistant enuresis as well as psychological comorbidity. Evaluating individual aspects of uro-therapy will rationalise treatment. Research is needed on the role and pharmacokinetics of anticholinergics, especially combined with alarm, desmopressin and tricyclics.

Multiple Choice Questions

1. The inheritance of nocturnal enuresis is mostly:
   A: Autosomal dominant with poor penetrance
   B: Autosomal dominant with high penetrance
   C: X linked recessive
   D: X linked dominant
   E: Autosomal recessive
ANSWER B: See paragraph in manuscript headed 'Inheritance'

2. Monosymptomatic Nocturnal Enuresis
   A: Is associated with externalizing disorders such as ADHD
   B: Responds poorly to bed wetting alarms
   C: Is best managed with reassurance after age 7 years because of a high rate of spontaneous resolution
   D: Is best managed with anticholinergics such as oxybutynin as a first line intervention.
   E: Usually has no long-term psychological implications
ANSWER E:
   MNE responds well to alarms. It is NMNE, not MNE, that is associated with externalizing disorders such as ADHD, responds poorly to alarms, and often needs anticholinergic medications. The prognosis is poor with NMNE hence one would advocate active treatment rather than reassurance and non-intervention after age 7 years.

3. Desmopressin:

   A: Has a better cure rate than the alarm

   B: Is associated with water intoxication and dilutional hyponatremia

   C: Should be used before trying the alarm

   D: Is contraindicated for use in combination with anticholinergics

   E: Administration by the intranasal route is increasingly favoured.

ANSWER B:

The only serious side effect of desmopressin is water intoxication; hence, the child should not drink until they have passed urine the next morning. The cure rate with desmopressin is poor compared with the alarm even though both have similar chance of success for initial remission. Hence, the alarm is the preferred starting option. Desmopressin is available on authority in Australia for use only after failing the alarm. It is not contraindicated for use with anticholinergics and the combination may be useful in refractory cases. The intranasal route is falling out of favour because of occasional long half-life and hence possible water intoxication. The oral route is now mandatory in many parts of Europe and the USA.

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