Approach to refractory urinary incontinence in children, with special emphasis on children with intellectual and/or physical disability

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Department of Urology
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<th>Description</th>
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<tr>
<td>AAMR</td>
<td>American Association on Mental Retardation</td>
</tr>
<tr>
<td>ACh</td>
<td>Acetyl choline</td>
</tr>
<tr>
<td>ADD</td>
<td>Attention deficit disorder</td>
</tr>
<tr>
<td>ADH</td>
<td>Antidiuretic hormone</td>
</tr>
<tr>
<td>ADHD</td>
<td>Attention deficit hyperactivity disorder</td>
</tr>
<tr>
<td>ADHD-IA</td>
<td>Attention deficit hyperactivity disorder-inattentive type</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the serum concentration-time curve</td>
</tr>
<tr>
<td>AVP</td>
<td>Arginine vasopressine</td>
</tr>
<tr>
<td>BTX</td>
<td>Botulinum Toxin</td>
</tr>
<tr>
<td>BVWI</td>
<td>Bladder Volume/Bladder Wall Thickness Index</td>
</tr>
<tr>
<td>Ca</td>
<td>calcium</td>
</tr>
<tr>
<td>cAMP</td>
<td>cyclic Adenosine monophosphate</td>
</tr>
<tr>
<td>CGRP</td>
<td>Calcitonin-generelated peptide</td>
</tr>
<tr>
<td>CIC</td>
<td>Clean intermittent catheterisation</td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>dDAVP</td>
<td>Desmopressin</td>
</tr>
<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual</td>
</tr>
<tr>
<td>EBC</td>
<td>Expected bladder capacity</td>
</tr>
<tr>
<td>EEG</td>
<td>Electro-encephalography</td>
</tr>
<tr>
<td>EMG</td>
<td>Electro-myography</td>
</tr>
<tr>
<td>ER</td>
<td>Extended release</td>
</tr>
<tr>
<td>EUS</td>
<td>External urethral sphincter</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and drugs administration</td>
</tr>
<tr>
<td>ICCS</td>
<td>International children continence society</td>
</tr>
<tr>
<td>ICS</td>
<td>International continence society</td>
</tr>
<tr>
<td>IDO</td>
<td>Ideopathic detrusor overactivity</td>
</tr>
<tr>
<td>IE</td>
<td>Internationale eenheden</td>
</tr>
<tr>
<td>IM</td>
<td>Intra muscular</td>
</tr>
<tr>
<td>IP</td>
<td>Inositol 1.4.5- triphosphate</td>
</tr>
<tr>
<td>IQ</td>
<td>Intelligence Quotient</td>
</tr>
<tr>
<td>IR</td>
<td>Immediate release</td>
</tr>
<tr>
<td>L</td>
<td>Lumbar</td>
</tr>
<tr>
<td>LUT</td>
<td>Lower urinary tract</td>
</tr>
<tr>
<td>LUTS</td>
<td>Lower urinary tract symptoms</td>
</tr>
<tr>
<td>M</td>
<td>Muscarinic</td>
</tr>
<tr>
<td>MNE</td>
<td>Monosymptomatic nocturnal enuresis</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>mRNA</td>
<td>messenger Ribonucleic acid</td>
</tr>
<tr>
<td>N</td>
<td>Nicotine</td>
</tr>
<tr>
<td>NANC</td>
<td>Nonadrenergic noncholinergic</td>
</tr>
<tr>
<td>NE</td>
<td>Norepinephrine</td>
</tr>
<tr>
<td>NFU</td>
<td>Natural filling urodynamics</td>
</tr>
<tr>
<td>NGF</td>
<td>Nerve growth factor</td>
</tr>
<tr>
<td>NMNE</td>
<td>Non-monosymptomatic nocturnal enuresis</td>
</tr>
<tr>
<td>NO</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>OAB</td>
<td>Overactive bladder</td>
</tr>
<tr>
<td>PACAP</td>
<td>Pituitary adenylate cyclase activating polypeptide</td>
</tr>
<tr>
<td>PAG</td>
<td>Periaqueductal gray area</td>
</tr>
<tr>
<td>Pdetmax</td>
<td>maximum detrusor pressure</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PMC</td>
<td>Pontine micturation centre</td>
</tr>
<tr>
<td>PSC</td>
<td>Pontine storage centre</td>
</tr>
<tr>
<td>P2X</td>
<td>purinoreceptor</td>
</tr>
<tr>
<td>S</td>
<td>Sacral</td>
</tr>
<tr>
<td>SAP</td>
<td>Synaptosomal-associated protein</td>
</tr>
<tr>
<td>SP</td>
<td>Substance P</td>
</tr>
<tr>
<td>T</td>
<td>Thoracal</td>
</tr>
<tr>
<td>TENS</td>
<td>Transcutaneous electrical nerve stimulation</td>
</tr>
<tr>
<td>TRP</td>
<td>Transient receptor potential channels</td>
</tr>
<tr>
<td>U</td>
<td>Unit</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>UTI</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>(V)UDE</td>
<td>(Video)- Urodynamics</td>
</tr>
<tr>
<td>VUR</td>
<td>Vesicoureteral reflux</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Approach to refractory urinary incontinence in children, with special emphasis on children with intellectual and/or physical disability.
Part 1
Urinary incontinence, during day, night or both is despite its high prevalence one of the most distressing conditions in childhood. It is not only very unpractical and embarrassing, but it also causes a high psychological distress to children and parents. It is a very common problem in children. Urinary incontinence is the second most common chronic health problem in childhood in our Western world, only preceded by allergic conditions. The prevalence of daytime or combined daytime and nighttime incontinence in seven-years-old children has been reported between 2-4 percent.

Often the children are believed to wet their pants and /or their beds because they are too lazy or too occupied by their activities to go to the toilet in time, or because of stress and psychological problems. Punishment is often their part.

Urinary incontinence in children is, even by medical professionals, believed to be a benign disorder that either will resolve by puberty or is easily treatable with urotherapy and anticholinergics, leading to neglect of the problem and often to lack of treatment.

Otherwise, in mentally and/or motor disabled children, it is often believed that urinary incontinence is inevitable, and doesn’t need any treatment.

Reality is more complex. Recent literature demonstrates that urinary incontinence in children is multifactorial in origin. Incontinence is classically divided into functional abnormalities: over active bladder, dysfunctional voiding, and anatomical anomalies such as ectopic ureter and vaginal reflux. These two conditions are widely overlapping. Recent literature stresses the importance of behavioural factors such as voiding postponement and co morbid factors such as constipation, ADD, ADHD, autism and motor and mental disabilities which are all identified to play a role in the pathophysiology of urinary incontinence. With a multifactorial origin there is no standard treatment for urinary incontinence in childhood. Treatment should be tailored to each child individually.

Modern treatment consists of urotherapy, pharmacotherapy, neuromodulation and sometimes surgery. The exact role of each therapeutic modality has not been described until today. Many times combined therapies are needed to achieve the ultimate goal of treatment: dryness.

Knowledge of healthcare workers and compliance of patients and parents are essential to obtain this goal.
Incontinence in children is challenging, and especially those children who do not respond to standard treatment. With years of experience we have identified a large group of children with refractory, often therapy resistant overactive bladder, and we have been building our experience in the treatment of children who are developmentally challenged.

We consider children to suffer refractory urinary incontinence when toilet training is complicated because of developmental disabilities or when children with urinary incontinence do show therapy resistance. The latter is the case when adequate standard therapy for at least 18 months fails to be successful.

In this thesis we want to report our experience with these specific groups of children and more specifically we want to answer the following questions:

1. What is the role of new pharmacological agents, Tolterodine, Solifenacin and botulinum-A toxin in the treatment of overactive detrusor in children suffering urinary incontinence?
2. What is the role of the daytime alarm in the treatment of children with persistent urinary daytime incontinence?
3. What is the prevalence of urinary incontinence in developmentally challenged children, and what are possible pathophysiological mechanisms to explain this?
4. From the new knowledge of pathophysiology of incontinence in developmentally challenged children what is the role of adequate fluid intake in the treatment of these children?

The bladder is a very unique organ of the human with a dual function of both storage and emptying of urine. In order to accomplish this dual function a complex innervation of voluntary and involuntary control of function is needed.

In the bladder two regions are distinguished based on their innervation and response to pharmacological agents: the "body", which lies cranial to the level of the ureteric orifices and the "base", which is caudal to this level.

The detrusor consists of a meshwork of smooth muscle fibres arranged into a single functioning unit with an ability to elicit nearly maximal active tension over a wide range of length. This allows the bladder to fill with urine at low pressure (compliance). The ability of the bladder to store urine is determined by the concomitant activity of the detrusor muscle and the bladder outlet, consisting of the bladder neck, proximal urethra and striated muscle of the pelvic floor.[1]

The bladder sphincter (external and internal) plays a major role in urinary continence by closure of the bladder neck and proximal urethra. The anatomy of the external urinary sphincter consists of a cylindrical structure, which is accentuated anteriorly and thinned out or actually absent posteriorly. It has an inner layer of smooth muscle and an outer layer of striated muscle, extending from the apex of the prostate to invest the length of the membranous urethra in males. In the females this is less well developed and extends from the bladder neck to the mid urethra. The internal sphincter has not been well delineated anatomically. It has generally been accepted that it consists of smooth muscle fibres continuing from the bladder base and trigone which traverse inferiorly through the bladder neck to extend toward the proximal urethra. Its existence has been better delineated on radiologic and urethral pressure measurement studies. During micturition, the bladder base, bladder neck and proximal urethra can be shown to contract simultaneously as a unit, producing a funnelling effect that opens up the bladder outlet with initiation of voiding.
Little is known about the natural course of development of maturation of the structure as well as function of the sphincter mechanism. Literature suggests that immature detrusor-sphincter coordination, manifested as detrusor hyper contractility and interrupted voiding, commonly occurs in the first 1 to 2 years of life causing some degree of functional bladder outflow obstruction.\[2, 3\]

The bladder and urethra function reciprocally. During bladder filling, “the urine storage phase”, the detrusor remains quiescent, with little change in intravesical pressure. During this phase, neural pathways that stimulate the bladder for micturical pressure are quiescent, and inhibitory pathways are active. The urethral outlet remains closed, with increasing external urethral sphincter contractions. This progressive increase in external urethral sphincter activity in response to increasing bladder volume is known as the “guarding reflex”. When the bladder volume reaches a critical threshold, the external sphincter relaxes, the detrusor contracts, the bladder neck opens, and elimination occurs.\[4\]
Activation, coordination and integration of various parts of the bladder-sphincter complex involves both the central somatic and autonomic nervous systems through three sets of peripheral nerves: sacral parasympathetic (pelvic nerve), thoracolumbar sympathetic (hypogastric nerves and sympathetic chain) and sacral somatic nerves (primarily the pudendal nerve) [1].

The efferent parasympathetic pathway provides the major excitatory innervation of the detrusor. [4]

Parasympathetic nerve fibres run in the pelvic nerve (S2-S4) to supply the pelvic and vesical plexuses before entering the bladder. Parasympathetic ganglia are found within these plexuses and in the bladder wall. Sympathetic nerves arise from segments T12 to L2 of the spinal cord and go to the inferior mesenteric ganglion through the sympathetic trunk. From the inferior mesenteric ganglion the nerve fibres pass to the pelvic plexus and bladder through the hypogastric nerves. There is also a sympathetic innervation originating from T10 to L2 supplying the detrusor and urethral sphincter. The somatic nerve system (pudendal nerve) supplies the periurethral pelvic floor musculature. The sensory and motor nerves carried by all three nerves innervate both the bladder and urethral sphincter. They originate from parasympathetic ganglia located in the second, third and fourth segments of the sacral spinal cord. Within the spinal cord, information from bladder afferents is integrated with that from other viscera and somatic sources and projected to the brain stem centres that coordinate the micturation cycle.

Bladder function in children is very different from adults. During the first 2 to 3 years of life there is progressive development from an initially indiscriminate infantile voiding pattern to a more socially conscious and voluntary or adult type of micturation. This is achieved through an active learning process in which the child acquires the ability to voluntary inhibit or initiate voiding at socially convenient times. This natural evolution of bladder control entails an intact nervous system and depends on at least three main events occurring in parallel: a progressive increase in bladder functional storage capacity, maturation of voluntary control over the urethral striated muscle sphincter and pelvic floor and development of direct volitional control over the bladder-sphincter unit by which the child can voluntary initiate or inhibit the micturation reflex. This process can also be influenced by an awareness of the accepted social norms in families during toilet training. [5]

All nerves connected to the bladder are able to transport information from the organ to the central nervous system (afferent impulses), which is mainly a sensory function, and to transport information from the central nervous system to the organ (efferent impulses), which is mainly a motor function.

Autonomic efferent fibres from the anterior portion of the pelvic plexus (the vesical plexus) pass along the lateral and posterior ligaments to innervate the bladder. The bladder wall is richly supplied with parasympathetic cholinergic nerve endings.
and has abundant postganglionic cell bodies. Sparse sympathetic innervation of the bladder has been proposed to mediate detrusor relaxation but probably lacks functional significance. A separate nonadrenergic noncholinergic (NANC) component of the autonomic nervous system participates in activating the detrusor, although the neurotransmitter has not been identified.\textsuperscript{[6]}

The male bladder neck receives abundant sympathetic innervation and expresses α1-adrenergic receptors. The female bladder neck has little adrenergic innervation. Nitric oxide synthase containing neurons have been identified in the detrusor, particularly at the bladder neck, where they may facilitate relaxation during micturition. The trigonal muscle is innervated by adrenergic and nitric oxide synthase-containing neurons. Like the bladder neck, it relaxes during micturition.

The peripheral nervous system

The lower urinary tract is innervated by three sets of peripheral nerves involving the parasympathetic, sympathetic and somatic nervous systems. Pelvic parasympathetic nerves arise at the sacral level of the spinal cord, excite the bladder, and relax the urethra. Lumbar sympathetic nerves inhibit the bladder body and excite the bladder base and urethra. Pudendal nerves excite the external urethral sphincter. These nerves contain afferent (sensory) as well as efferent axons.

Efferent nervous system

Parasympathetic pathways

Parasympathetic preganglionic neurons innervating the lower urinary tract are located in the lateral part of the sacral intermediate gray matter in a region termed the sacral parasympathetic nucleus. Parasympathetic preganglionic neurons send axons through the ventral roots to peripheral ganglia, where they release the excitatory transmitter acetylcholine.

Acetylcholine excitation of postsynaptic neurons is mediated by nicotinic receptors. Postganglionic axons continue for a short distance in the pelvic nerve and terminate in the detrusor layer, where they transmit ACh to the smooth muscle fibres, with consequent contractions of the bladder.\textsuperscript{[8]}

Radioligand studies have proven that the bladder body and base contain muscarinic receptors.\textsuperscript{[7]}

The major portion of neurohumoral stimulus for physiologic bladder contraction is acetylcholine-induced stimulation of postganglionic parasympathetic muscarinic cholinergic receptor sites in the bladder. In the bladder, mRNAs for all five of the pharmacologically defined receptors, M1 to M5 have been demonstrated.\textsuperscript{[8]} There is a predominance of M2 and M3 receptors. M2 and M3 receptors can be found not only on
detrusor muscle cells, where M2 receptors predominate at least 3:1 over M3 receptors, but also on other bladder structures, which may be of importance for detrusor activation. Muscarinic receptors can be found on urothelial cells, on suburothelial nerves, and on other suburothelial structures, such as interstitial cells.[9]

M3 receptors are believed to be the most important for contraction. M2 receptors have been suggested to directly contribute to contraction of the bladder in certain disease states, e.g. denervation, outlet obstruction.[10]

Muscarinic receptors are stimulated by acetylcholine. In the bladder this stimulation provokes a bladder contraction by calcium entry through nifedipine-sensitive L-type Ca²⁺ channels in addition to increased polyphosphoinositide hydrolysis resulting in inositol 1,4,5-triphosphate (IP₃) production and release of intracellular calcium stores, and a rise in intravesical pressure. [11]

Acetylcholine is the principal excitatory transmitter at the parasympathetic-detrusor cell synapse, but it is certainly not the only one. The purine, adenosine triphosphate (ATP), is considered to be a parasympathetic cotransmitter responsible for atropine resistant detrusor activation. The ATP effect appears to be mediated by stimulation of one or more members of the P2X family of purinoceptors.

In addition to the parasympathetic stimulation of bladder smooth muscle, some postsynaptic parasympathetic neurons exert a relaxation effect on urethral smooth muscle, most likely via transmission of nitric oxide (NO), causing a relaxation of the internal urethral sphincter during the elimination phase. [4]

**Sympathetic pathways**

Sympathetic outflow from the rostral lumbar spinal cord provides a noradrenergic excitatory and inhibitory input to the bladder and the urethra. Activation of sympathetic nerves induces relaxation of the bladder body and contraction of the bladder outlet and urethra, which contribute to urine storage in the bladder. The peripheral sympathetic pathways follow a complex route that passes through the sympathetic chain ganglia to the inferior mesenteric ganglia and then through the hypogastric nerves to the pelvic ganglia.

The preganglionic neurotransmitter is ACh, which acts via nicotinic receptors in the postganglionic neurons. The postganglionic axons transmit norepinephrine (NE) at their terminals. [4]

Alpha and beta adrenergic binding sites are found in human bladder and urethral tissues. Beta receptors are predominantly found at the bladder dome, alpha receptors at the base and outlet. It is believed that the adrenergic pathways facilitate bladder storage by relaxing the detrusor and contracting the outlet. [12]
Alpha-adrenergic stimulation is not prominent in the normal bladder. Alpha-adrenergic mechanisms are more important in urethral function. Substantial pharmacologic and physiologic evidence indicates that urethral tone and intraurethral pressure are influenced by α-adrenergic receptors.

Stimulation of β2- and β3-adrenergic receptors that exist in the human detrusor results in the direct relaxation of the detrusor smooth muscle. In addition, β-adrenergic-stimulated relaxation is mediated through the stimulation of adenylate cyclase and the accumulation of cyclic AMP (cAMP). The relaxation induced by adrenergic stimulation of the human detrusor is mediated mainly through β3 adrenoreceptor activation.

**Somatic pathways**

The external urethral sphincter motor neurons are located along the lateral border of the ventral horn in sacral spinal cord segments S2-S4, commonly referred to as Onuf’s nucleus. The pudendal nerve also supplies the pelvic floor muscles.[13]

The motor neuron axons release ACh which acts on nicotinic receptors in the striated muscle, inducing muscle contraction to maintain closure of the external urethral sphincter.[4]

---

**Figure 2. Innervation of the lower urinary tract**

- **Pelvic nerve (parasympathetic)**: ACh → +M3 -β3
- **Hypogastric nerve (sympathetic)**: NE → +a1
- **Pudendal nerve (somatic)**: ACh → +N
Approach to refractory urinary incontinence in children, with special emphasis on children with intellectual and/or physical disability.

Figure 3. Efferent pathways from the spinal cord to the bladder.

Figure 4. Efferent pathways from the spinal cord to the lower urinary tract.
Afferent pathways

Afferent axons in the pelvic, hypogastric and pudendal nerves transmit information from the lower urinary tract to the lumbosacral spinal cord. The primary afferent neurons of the pelvic and pudendal nerves are contained in sacral dorsal root ganglia S2-S4, while afferent innervation in the hypogastric nerves arises in the rostral thoracolumbar dorsal root ganglia T10-L2. The central axons of the dorsal root ganglia neurons carry the sensory information from the lower urinary tract to second-order neurons in the spinal cord. Visceral afferent fibres of the pelvic and pudendal nerves enter the cord and travel rostrocaudally within Lissauer's tract.[4]

Afferent axons, identified primarily by neuropeptide immunoreactivity for calcitonin-gene-related peptide (CGRP), pituitary adenylate cyclase activating polypeptide (PACAP), or substance P (SP), are distributed throughout the bladder wall.[14]

Pelvic nerve afferents, which monitor the volume of the bladder and the amplitude of the bladder contraction, consist of myelinated (Aδ) and unmyelinated (C) axons. The Aδ fibres are located at the smooth muscles and do sense bladder fullness. The C fibres located at the mucosa are responsible for an adequate response to stretch (bladder volume sensors) and nociception to overdistention and chemical irritants.

Glutamate is a neurotransmitter present in both the Aδ and C fibres. Substance P and calcitonin gene-related peptide are additional neurotransmitters in the C fibres.[4]

---

**Figure 5.** Afferent fibres transmitting sensory information from the lower urinary tract to the spinal cord.
Sensing bladder volume is of particular relevance during urine storage.

<table>
<thead>
<tr>
<th>Fibre type</th>
<th>Location</th>
<th>Normal function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aδ</td>
<td>Smooth muscle</td>
<td>Sense bladder fullness (wall tension)</td>
</tr>
<tr>
<td>C fibres</td>
<td>Mucosa</td>
<td>Respond to stretch (bladder volume sensors)</td>
</tr>
<tr>
<td>C fibres</td>
<td>Mucosa</td>
<td>Nociception to overdistension and chemicals</td>
</tr>
<tr>
<td></td>
<td>Muscle</td>
<td>Silent afferent (mechanoinsensitive)</td>
</tr>
</tbody>
</table>

On the other hand, afferent discharges that occur during a bladder contraction have an important reflex function and appear to reinforce the central drive that maintains the detrusor contraction.

The different kind of receptors (pressure, pain, temperature, tension) are able to intercept signals from the bladder and carry them to the central nervous system where they can be perceived at the spinal cord level and generate reflexes, or be transported to the central nervous system where they can become conscious stimuli, which can be modified by behaviour.

The pathways responsible for the different sensations from the lower urinary tract are reproduced in the next table

<table>
<thead>
<tr>
<th>Sensation</th>
<th>Pelvic afferent pathway</th>
<th>Lumbar afferent pathway</th>
<th>Pudendal afferent pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensation of filling</td>
<td>yes</td>
<td>probably</td>
<td>no</td>
</tr>
<tr>
<td>Desire to void</td>
<td>yes</td>
<td>probably</td>
<td>no</td>
</tr>
<tr>
<td>Strong desire to void</td>
<td>possibly</td>
<td>possibly not</td>
<td>yes</td>
</tr>
<tr>
<td>Pain (bladder)</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Pain (urethral)</td>
<td>probably</td>
<td>probably not</td>
<td>yes</td>
</tr>
</tbody>
</table>

Multiple reflex pathways organized in the brain and spinal cord mediate coordination between the urinary bladder and the urethra. The central pathways controlling lower urinary tract function are organized as simple on-off switching circuits that maintain a reciprocal relationship between the urinary bladder and the urethral outlet. Some reflexes promote urine storage, whereas others facilitate voiding. It is also possible that individual reflexes might be linked together in a serial manner to create complex feedback mechanisms.
Historically the urothelium has been viewed as primarily a barrier. Currently it is becoming clear that the urothelium is a responsive structure capable of detecting physiological and chemical stimuli, and releasing a number of signalling molecules. As such it displays a number of properties similar to those of nociceptive and mechanosensitive sensory neurons and can use diverse signal-transduction mechanisms to detect physiological stimuli. The urothelium expresses “sensor molecules” (receptors/ion channels) that have been identified in afferent neurons, including receptors for bradykinin, neurotrophins, purine (P2X and P2Y), norepinephrine (α and β), protease-activated receptors, acetylcholine (nicotinic and muscarinic), amiloride/mechanosensitive Na+ channels and a number of transient receptor potential channels (TRPV1, TRPV2, TRPV4, TRPM8). In addition, urothelial cells can release neurotransmitters and signalling molecules such as ATP, prostaglandins, nitric oxide, acetylcholine, NGF and SP, that influence the excitability of afferent nerves.

Chemicals released from the urothelial cells may act directly on the afferent nerves or indirectly via an action on suburothelial myofibroblast, also called interstitial cells or Cajal like cells that lie in close proximity to afferent cells. Interstitial cells are extensively linked by gap junctions and can release chemicals that in turn act on afferent nerves.\textsuperscript{[14]} Andersson et al. mentioned interstitial cells to have a pacemaking role in spontaneous activity of the bladder.\textsuperscript{[11]}

It is believed that urothelial cells and myofibroblasts can participate in sensory mechanisms in the urinary tract by chemical coupling to the adjacent sensory nerves.\textsuperscript{[14]}

**The central nervous system**

Neural control over the lower urinary tract occurs at different levels of the central nervous system. Central nervous system control over lower urinary tract function is very complex.

The main influences are inhibition of the micturition reflex, inhibition of spontaneous detrusor reflex contractions, coordination of detrusor contraction and sphincter relaxation. Understanding of the relationship between cerebral function and urologic function has increased as a result of the insights gained from functional brain imaging.

Various studies indicate that the micturition reflex is normally mediated by a spinobulbospinal reflex pathway passing through relay centres in the brain. The dorsal pontine tegumentum has been firmly established as an essential control centre for micturition in normal subjects, and has been described as the pontine micturition centre.\textsuperscript{[15]}

Brain imaging studies have implicated both the frontal cortex and the anterior cingulated gyrus in control of micturition and have indicated that micturition is controlled predominantly by the right side of the brain.\textsuperscript{[15]}
Positron emission tomography (PET) has shown increased activity in the periaqueductal gray area (PAG), the hypothalamus, and the right pontine micturition centre during micturition. Brain activity in other cortical areas and the cerebellar vermis also has been noted to occur during micturition. Bladder storage activity is mediated by a sacral-thoracolumbar reflex associated with a descending cortical control to allow one to postpone bladder emptying. In PET scanning, increased bladder volumes correlate with activity in the PAG, midline pons, mid cingulated cortex, and bilateral frontal cortex. An increase in the desire to void was associated with a decrease in brain activity, possibly because of cerebral attempts at suppressing the desire to void. Activity in the anterior cingulated and insula areas also has been noted. In functional MRI studies, activity in the parietal cortex, cerebellum, putamen, and supplementary motor area has been associated with inhibition of micturition.

The areas of the brain that control voiding include parts of the midbrain, the PAG, the cingulated cortex with connections to the insula, the hypothalamus, and the prefrontal cortex. The frontal cortex may provide inhibition, and the cerebellum is active during the storage phase and micturition. These findings can be interpreted as representing a matrix of brain areas that control various aspects of urine storage and micturation, including perceptions of fullness and desire to void that is influenced by environmental cues.

Functional MRI (fMRI) studies illustrated that the supplementary motor area, midcingulate cortex, insula, frontal operculum, and right prefrontal cortex were consistently more active when the desire to void was enhanced without allowing urine to pass (“attempted micturation”) than during a baseline task when bladder sensation was suppressed. The right anterior insula and midbrain periaqueductal gray (PAG) were more active at higher than at lower bladder volumes. Responses of the right thalamus and several other right hemispherical regions were stronger in women than in men. Using the psychophysiological interaction method illustrated that the midcingulate cortex had stronger connectivity with the PAG and medial motor areas during “attempted micturition” than during the baseline task, possibly reflecting monitoring of urethral sphincter contractions. Conversely, the left and right insula showed decreased connectivity with many other brain regions during “attempted micturition”, possibly due to predominant processing of bladder-afferent input. Functional MRI study of brain activity showed that intentional modulations of the desire to void change effective connectivity of supraspinal regions involved in bladder control.\[16\]

The pontine micturition centre (PMC) and the pontine storage centre (PSC) which is localised ventrolateral of the PMC, are the integrative centres, receiving and integrating input from afferent spinal cord nerves and more rostral brain regions and controlling an on/off switch for the lower urinary tract.

Neurons in the PSC project directly to the motoneurons in Onuf’s nucleus. Stimulation of PSC neurons causes EUS contractions.
Neurons in the PMC project to the sacral parasympathetic nucleus. Stimulation of PMC neurons results in bladder contraction and relaxation of the internal and external urethral sphincter.

Glutamic acid, the major excitatory neurotransmitter, appears to function as the on switch for the EUS. Suppression of glutamatergic transmission serves as the final signal for EUS relaxation and bladder elimination. Several other supraspinal neurotransmitters have mandatory roles in lower urinary tract function. Norepinephrine and serotonin appear to have a positive neuromodulatory effect on EUS contraction. Dopamine and γ-aminobutyric acid, a principal inhibitory neurotransmitter in the brain, contribute to coordination of lower urinary tract function.[4]

*Figure 6. Major reflex pathways*

- Major reflex pathways from the pontine micturation centre to the lower tract stimulating initiation and completion of micturation
- Major reflex pathways to the lower urinary tract initiating and maintaining urine storage
- Major reflex pathways from the pontine micturation centre in the brainstem to the lower urinary tract via the spinal cord regulating both micturation and urine storage
**Storage reflexes:** Until the volume of urine in the bladder reaches a critical threshold for voiding, the detrusor is quiet. During filling the bladder has a low and relatively constant level of internal pressure. This is, to some extent, achieved passively because of 1) the viscoelasticity of detrusor muscles and 2) the stimulatory parasympathetic pathway that is quiescent. During the storage of urine, distension of the bladder produces low-level bladder afferent firing. Afferent firing in turn stimulates the sympathetic outflow to the bladder outlet (base and urethra) and pudendal outflow to the external urethral sphincter. The responses occur by spinal reflex pathways and represent “guarding reflexes”, which promote continence. Sympathetic firing also inhibits detrusor muscle and transmission in bladder ganglia.

**Voiding reflexes:** at the initiation of micturation, intense vesical afferent activity activates the brainstem micturation centre, which inhibits the spinal guarding reflexes (sympathetic and pudendal outflow to the urethra). The pontine micturation centre also stimulates the parasympathetic outflow to the bladder and internal sphincter smooth muscle. Maintenance of the voiding reflex is through ascending afferent input from the spinal cord, which may pass through the periaqueductal gray matter before reaching the pontine micturation centre.

*Figure 7. The mechanism of storage and voiding reflexes*
Chapter 2  Urinary incontinence in children

2.1. Terms and Definitions

Until recently many definitions have been used to define urinary incontinence. This inconsistent terminology is not only confusing but it also complicates interpretation and comparison of scientific data.

Therefore we use the new Standardized ICCS Terminology in this thesis.[17]

According to the new ICCS terminology document urinary incontinence means uncontrollable leakage of urine which can be continuous or intermittent.

Continuous incontinence is a phenomenon that is almost exclusively associated with congenital malformations, i.e. ectopic ureter, or iatrogenic damage to the external urethral sphincter. This term is applicable to children of all age since even infants have a filling and emptying cycle of their bladder and are dry between voiding.

Intermittent incontinence is urine leakage in discrete amounts. It can occur during the day and/or the night, and is applicable to children who are at least 5 years old.

Enuresis means intermittent incontinence while sleeping.

Enuresis can be subdivided into:
1. monosymptomatic enuresis: enuresis in a child without any other Lower Urinary Tract (LUT) symptoms
2. nonmonosymptomatic enuresis: enuresis in a child with other LUT symptoms, such as day-time incontinence, urgency, holding manoeuvres, etc.

According to the onset of enuresis it can be subdivided into:
1. primary enuresis: enuresis in a child who has previously been dry for less than 6 months
2. secondary enuresis: enuresis in a child who has previously been dry for at least 6 months

Urinary incontinence may be due to disturbances of the filling phase, the voiding phase or a combination of both. In the new ICCS terminology these conditions are termed LUT conditions or functional bladder disorders.

The classification of daytime LUT conditions is not that straightforward. There's a considerable overlap between conditions, borderline cases are common and the pathogenetic rationale for the grouping of various symptom complexes into specific conditions is often not fully evidence based. Furthermore, there is often an evolution in time.
Therefore ICCS advises to assess and document 4 parameters in these patients:
1. **incontinence**
2. **voiding frequency**
3. **voided volume**
4. **fluid intake**

These conditions are applicable from the age at which bladder control is attained or 5 years. In order to achieve greater pathogenic and clinical relevance this is often more important than to subgroup children into the various recognized syndromes listed below.

The daytime LUT conditions:
1. **Overactive Bladder**: the condition afflicting patients experiencing urgency symptoms and **Urge incontinence**: incontinence in patients experiencing urgency. The term “overactive bladder” replaces the former “bladder instability”.
2. **Voiding postponement**: incontinence in the presence of habitual holding manoeuvres
3. **Underactive bladder**: term reserved for children with low voiding frequency and a need to increase intra-abdominal pressure to initiate, maintain or complete voiding, i.e. straining. Replaces the term “lazy bladder”.
4. **Dysfunctional voiding**: the urethral sphincter is contracted during voiding. The term cannot be applied unless repeat uroflow measurements show curves with a staccato pattern or unless verified by urodynamic investigation.
5. **Obstruction**: due to a mechanical or functional, static or phasic impediment to urine outflow during voiding. It is characterized by increased detrusor pressure and a decreased urine flow rate.
6. **Stress incontinence**: leakage of small amounts of urine at exertion or at increased intra-abdominal pressure for various reasons. It is rare in neurologically normal children.
7. **Vaginal reflux**: toilet trained prepubertal girls who experience incontinence in moderate amounts, consistently occurring within 10 minutes after normal voiding, experience vaginal reflux if no underlying mechanism other than vaginal entrapment of urine is obvious.
8. **Giggle incontinence**: is a rare syndrome in which apparently complete voiding occurs specifically during or immediately after laughing. Bladder function is normal when the child is not laughing.
9. **Extraordinary daytime urinary frequency**: this term applies to children who void often and with small volumes during the daytime only. Daytime voiding frequency is at least once hourly and average voided volumes are less than 50% of EBC, usually much smaller. Incontinence is not a usual or necessary ingredient in the condition and nocturnal bladder behaviour is normal for the age of the child. The term is applicable from the age of daytime bladder control or 3 years.
Decreased daytime voiding frequency: three or less voidings per day
Increased daytime voiding frequency: eight or more voidings per day

Expected bladder capacity for age (EBC): age related expected maximum voided volume, calculated via the formula \((30 + (\text{age in years} \times 30))\) ml, and used as a standard for comparisons. This formula is useful up to age 12 years, after which age expected bladder capacity has to be around 300 ml.

Voided volume: voided volume at micturition, as documented in a bladder diary. Replaces the term “bladder capacity”

Maximum voided volume: the largest voided volume, as documented in a bladder diary. Replaces the term “functional bladder capacity”. Maximum voided volume is considered small if found to be less than 65% of EBC and large if greater than 150% of EBC.

Residual urine is the amount of urine left in the bladder immediately after voiding. Normal residual volume is 0 ml, while 20 ml or more on repeat measurements is pathological.

Polyuria is defined as a 24-hour output of more than 2 l/m² body surface area. This is applicable in children of all ages.

Nocturnal polyuria is defined as nocturnal urine output exceeding 130% of EBC for age.

In children with enuresis nocturnal urine output can be determined by measuring the netto weight of the diaper increased with the volume of the first morning void.

Also for video-urodynamic findings terminology has changed. Instead of “detrusor instability” the term “detrusor overactivity” is now recommended to describe the cystometric observation of involuntary detrusor contractions during the filling phase. Detrusor-sphincter dyssynergia defines the cystometric observation of a detrusor voiding contraction concurrent with an involuntary contraction of the urethra. Detrusor underactivity is the cystometric observation of detrusor contractions of reduced strength and/or duration

2.2. Prevalence

It is very difficult to determine the exact prevalence of urinary incontinence in children, based on literature, due to the fact that different studies have used different definitions and criteria.
As most studies do not look for the type of daytime incontinence, i.e. filling or emptying problems, only a general prevalence concerning daytime incontinence can be estimated without going into pathophysiological details.

In normal, non-developmentally challenged children, daytime or combined daytime and night-time incontinence, at least once a week, occurs in about 2-4 percent of 7-year old children and is more common in girls than in boys. [18, 19]

Overall prevalence varies from 1 to 20 percent. In general for 6-7 year old children it is between 2 and 4 percent, and rapidly decreases during the following years.[19-29]

The prevalence of enuresis in 7-year old children varies between 5 and 10 percent. [28, 30-36]

This decreases to between 1.2 and 4.7 percent at the age of 11 to 12 years. [28, 31, 33, 34, 36-40]

At the age of 16 to 17 years a further decrease is seen to 0.5 -1.1%. [28, 41, 42] Children with the severest form of bedwetting are likely to persist with the problem and to have the more complex form (non-monosymptomatic). [43]

Daytime incontinence is more frequent in girls (female: male ratio 1.6), enuresis is more frequent in boys (male: female ratio 1.6) [19, 30, 44]

Although spontaneous resolution of enuresis and urinary incontinence during daytime has been documented in the previous studies, these problems may persist in some cases.

Enuresis is found in 0.5% of the adults. [45] This means that 5% of the children suffering enuresis are at risk for life-long problems if not treated adequately during childhood. The spontaneous cure rate is estimated to be 14% annually between 5 and 9 years age and 16% between 10 and 19 years.[46]

Swithinbank et al. found a prevalence of daywetting in 12.5% of the children at the age of 10-11 years which decreased to 3% at the age of 15-16 years. [42] This means that the prevalence of daytime incontinence diminishes by 1-2% per year.

In developmentally challenged children, i.e. mentally and/or motor disabled patients, the incidence of urinary incontinence is higher than in the normal population.

In literature a wide variation of prevalence has been described, varying between 23% and 86%. [18, 47-58] This is due to the fact that a lot of these studies were performed on a small population and because the included patients were inadequately categorized without taking into account the pathophysiology, age, mental and motor development and type of incontinence. We described in our studies that between 39.6% and 47.4% of the developmentally challenged children have achieved continence spontaneously. [59] No significant differences in continence pattern was found between those who were mentally, motor and mentally and motor disabled.
Based on the publication of von Wendt L. et al. 7-year old children with mild mental retardation differ relatively little from healthy children with respect to enuresis, i.e. 11.1% versus 9.8%. On the other hand the prevalence of daytime incontinence (16.7%) is significantly higher in those children suffering mild mental retardation than in the normal population (3.4%).[48]

The prevalence of urinary incontinence is directly related to the degree of mental development. The more severe the mental retardation the higher the prevalence of urinary incontinence. [48, 55, 60]

Not only intellectual capacity, but also the motor capacity is correlated with the development of continence. The more immobile the higher the prevalence of urinary incontinence. [49, 53]

Also in developmentally challenged children spontaneous cure of enuresis and daytime urinary incontinence has been described, though less frequent than in the normal population. The study of von Wendt et al. illustrates that only in the mild mental retarded children an equal cure pattern for enuresis is found as in normal children. The prevalence of daytime incontinence remains even in the mild mental retarded children higher than in the normal population. The more severe the retardation the higher the risk of persisting enuresis and urinary incontinence during the day. [48]

2.3. **Pathogenesis**

2.3.1. **Pathogenesis of urinary incontinence**
Urinary incontinence in children may be caused by a congenital anatomical anomaly such as exstrophy vesicae, epispadias or ectopic ureter, iatrogenic such as a trauma to the sphincter or neurological such as myelomeningocele. These causes are not discussed in this thesis.

In the majority of incontinent children no obvious reason for this incontinence can be given and they suffer so called "idiopathic" or "functional" incontinence. This functional urinary incontinence may be caused by disturbances of the filling phase, the voiding phase or a combination of both. [61]

2.3.1.1 **Over active bladder**
Detrusor overactivity is the most common cause of LUTS in children. In the study of Ruarte et al. up to 57.4% of the incontinent children suffered overactive bladder. [62] It appears to have a peak incidence between ages 5 to 7 years. [63]

Overactive bladder is not completely understood and it is thought to be a multifactorial problem.
The higher cortical centres in the brain, pons, spinal cord, the peripheral autonomic somatic and sensory afferent receptors in the lower urinary tract as well as anatomical components of the lower urinary tract are involved in micturation. Overactivity of the bladder can be caused by disturbance of one or more of these elements.

For many years it was thought that myogenic abnormalities were the primary cause of overactive bladder. Nowadays new insights rather see this myogenic problems as a consequence of a neurological or a anatomical obstructive pathology.\[64\]

Bladder control is believed to be under influence of the central nervous system. The pontine region is considered to be responsible for detrusor sphincter coordination and the cortical area is responsible for detrusor overactivity control.\[65\]

The prevailing theory is that overactive bladder is due to a delay in the acquisition of cortical inhibition over uninhibited detrusor contractions in the course of achieving the mature voiding pattern of adulthood. The site of maturational delay is thought to lie in reticulospinal pathways of the spinal cord or it could be in the inhibitory centre in the cerebral cortex.

Thus bladder maturation follows maturation of cortical inhibition processes.

In his paper Franco I. concludes that we probably have to move away from the vesicocentric thinking towards a corticocentric mode of thinking to explain detrusor overactivity. As such detrusor overactivity may be the results of a centrally located dysfunction affecting bladder, bowel, sexual function and even mood and behaviour.\[64, 66\] Functional MRI future studies will probably illuminate this enigma.\[67\]

The concept of delay of maturation of cortical control in ideopathic detrusor overactivity (IDO) in children seems to be incorrect but more complex central nervous system mechanisms could be at the base of this problem. Concepts of feed forward loops from the generation of a high pressure system during voiding or filling are more frequently described in animal experiments. Both the interplay of neural drive with motor control and the dynamic nature of the growing bladder could be causative. This in contrast to the adult population where detrusor overactivity is considered a chronic condition whose origin is unrelated to functional use. There is no long-term data to determine if childhood detrusor overactivity predicts detrusor overactivity during adulthood.\[65\]

Some rare longitudinal studies show a link between paediatric LUTS and adult LUTS, where adults with a history of paediatric LUTS have a higher risk to develop LUTS in adulthood.\[68\] Others have shown that adults with LUTS and a history of childhood LUTS often have more severe symptoms.\[69\]

The term detrusor overactivity is used to describe the symptom complex of urgency, with or without urge incontinence. This urge syndrome is characterized clinically by frequent episodes of an urgent need to void, countered by contraction of the pelvic
floor muscles and holding manoeuvres, such as squatting and the "Vincent curtsey sign". The symptoms arise from detrusor overactivity during the filling phase. These involuntary detrusor contractions are countered by voluntary contraction of the pelvic floor muscles to postpone voiding and minimize wetting.

It is thought that active external sphincter contraction may cause a temporary reflex relaxation in the detrusor, therefore, affording momentary relief from the effects of uninhibited bladder contractions. Persistent isometric contractions of the detrusor against the tightened sphincter or incomplete sphincter relaxation lead to detrusor hypertrophy. This hypertrophy leads to a gradual decrease in maximum voided volume and increased detrusor overactivity, creating a vicious cycle. [64]

Both the detrusor contraction and the increased activity of the pelvic floor muscles can be registered urodynamically.

It has been postulated that such a strong bladder and pelvic floor muscles contractions can damage the bladder mucosa. Some of these children may note suprapubic or perineal pain. Hoebeke et al. described a cohort of patients suffering nighttime pain syndromes based on pelvic floor spasms. Pelvic floor relaxation feedback was successfully used in these patients. [70]

Mucosal damage due to decreased blood flow and relative hypoxia during the periods of increased detrusor pressure during the involuntary overactive detrusor contractions may lead to UTI’s. Up to 60% of the children with UTI’s suffer detrusor overactivity. [71]

During the contraction of the overactive detrusor the bladder neck is opened and urine flows into the proximal urethra. Due to the “milk-back phenomenon” contaminated urine flows back into the bladder during the contraction of the pelvic floor muscles. This may cause UTI’s. [72-74]

Even in continent children with recurrent UTI’s and vesicoureteral reflux, over active bladder should be considered. The factor incontinence is often masked by the inadequate fluid intake in these patients.

Several authors have confirmed the relationship between detrusor overactivity and vesicoureteral reflux. [2,75,76] Koff demonstrated that the treatment of detrusor overactivity reduced the incidence of infection and increased the rate of reflux resolution. [77]

Constipation and faecal incontinence are often diagnosed in children with over active bladder. [77,78] Koff et al. demonstrated that constipation and bowel distension may lead to deformation of the bladder, which in turn may lead to detrusor overactivity and thus to urinary incontinence. [77] Söderstrom et al. in a cohort study of all schoolchildren in the first and fourth grade, including 2222 students, demonstrated that children with daytime incontinence often have faecal soiling and vice versa, whereas bedwetting
and faecal incontinence have little or no association.\textsuperscript{[29]} The study from Mc Grath et al. showed that, also in enuretic children, up to 36.1\% were identified as constipated by the clinician-based scoring method.\textsuperscript{[79]} They should be classified as non monosymptomatic nocturnal enuresis.

2.3.1.2 \textit{Dysfunctional voiding}

Dysfunctional voiding refers to the inability of the urinary sphincter or pelvic floor muscles to relax completely during voiding. There are no clear data on the possible causes of dysfunctional voiding. There is no identified underlying neurologic abnormality. In neurological conditions this same inability of the sphincter to relax during voiding is well known and described as detrusor sphincter dyssynergia.

Without overt neuropathy, overtraining of the pelvic floor muscles may be at the origin of dysfunctional voiding.\textsuperscript{[80]} This overactivity of the pelvic floor muscles, with a subsequent insufficient relaxation during voiding, may be caused by detrusor overactivity.\textsuperscript{[81]}

Insufficient relaxation of the pelvic floor muscles may also be a learned condition. Too strict toilet training programs, constipation, episodes of dysuria and sexual abuse have been described as possible aetiology.

Poor toilet conditions and privacy issues have also been identified as possible causes.\textsuperscript{[82]}

In some girls an anatomical anomaly of the external meatus may be the reason of dysfunctional voiding. Anterior deflection of the urine stream causes a stimulation of the clitoris with subsequent reflex activity of the bulbocavernosus muscle causing intermittent voiding.\textsuperscript{[83]}

Children suffering dysfunctional voiding usually present with urinary incontinence, urinary tract infections and constipation.

During repeated uroflowmetries they demonstrate fluctuating or intermittent uroflow patterns.

Bladder volume is usually larger than age-expected capacity. Residual urine is often present. Detrusor overactivity may be seen but may also be absent.

Initially children with dysfunctional voiding often show signs of the “compensatory” overactivity of the bladder along with poor emptying ability, such as: small bladder capacity, increased detrusor thickness, decreased detrusor contractility, impaired relaxation of the external urinary sphincter and pelvic floor muscles during voiding, weak or interrupted urinary stream and large post-void residual urine. Secondary vesicoureteral reflux, faecal incontinence or constipation may also occur.\textsuperscript{[84, 85]}
On the long term, routine incomplete emptying of the bladder can progress to detrusor over-distension associated with chronic urinary retention, the so called detrusor underactivity.

This so called dysfunctional voiding cycle in which children evolve from overactive bladder along dysfunctional voiding to underactive bladder has been documented but is not applicable to all children with these problems. In a large study of our group on urodynamics in children with functional voiding disorders we found that children with dysfunctional voiding are younger than those with OAB, which is an argument against this dysfunctional voiding cycle.[84]

As mentioned by Chiozza et al. urinary symptoms associated with dysfunctional voiding range from urgency to complex incontinence patterns during day and night.[86]

Symptoms of dysfunctional voiding are significantly more common in children suffering Attention Deficit Hyperactivity Disorder.[87, 88]

The incidence of vesicoureteral reflux is higher in children with dysfunctional voiding than in children with normal voiding. Moreover it concerns more frequently high degree vesicoureteral reflux.[84, 89]

Urinary tract infections and kidney damage are common sequels of dysfunctional voiding.[90]

2.3.1.3 Underactive detrusor
Children with an underactive detrusor usually present with urinary incontinence and urinary tract infections. They typically demonstrate low voiding frequency and an inability to empty their bladder using the detrusor contraction alone. They often have to use abdominal straining to empty their bladder. Voiding time is prolonged, with low pressure and intermittent.

Urodynamic evaluation is the only way to diagnose this condition. On urodynamics the bladder has a larger than normal capacity, a normal compliance and a reduced or absent detrusor contraction during voiding. Abdominal straining is often necessary to void.

2.3.1.4 Voiding postponement
Children postpone imminent micturation until overwhelmed by urgency, resulting in urge incontinence.

Voiding postponement is characterized by the clinical symptom of wetting associated with repetitive delay of micturation and low voiding frequency, which can be readily diagnosed by history and flow charts.[91]
Uroflowmetry is usually normal in voiding postponement. Lettgen found only 20% of the patients with voiding postponement had a fluctuating voiding pattern. A higher incidence of clinically relevant behavioural symptoms, especially attention and delinquent problems, was found in the voiding postponers compared to patients suffering OAB.[91]

### 2.3.1.5 Giggle incontinence

Giggle incontinence is characterised by a partial to complete bladder emptying provoked by laughing. This may continue into the children’s teenage years, and intermittently into adulthood. It occurs in girls and occasionally in boys and is generally self-limiting.

The aetiology of giggle incontinence is not defined.

Urodynamic studies do not show any abnormalities, there is no anatomic dysfunction, there are no neurologic anomalies, the upper tracts appear normal on ultrasound and urinalysis is normal.[92, 93]

It is postulated that the giggle incontinence can be due to the fact that laughter induces a generalized hypotonic state with urethral relaxation. However this effect has not been demonstrated on either smooth or skeletal muscle.

Others have suggested that giggle incontinence is due to laughter triggering the micturation reflex and overriding inhibitory mechanisms. One small study hinted at an association with cataplexy.[94] The latter probably explains why methylphenidate was found to be a viable treatment option for giggle incontinence.[94, 95]

### 2.3.1.6 Vesicovaginal reflux

Vesicovaginal reflux may be the cause of urinary leakage that occurs in girls a short time after voiding to completion. In most cases the leakage is only a few millilitres. It is a common cause of urinary leakage in schoolgirls. In their study performed on a group of 169 girls referred to a specialist clinic because of daytime incontinence, Mattsson et al. found that in more than 10% of these girls, vesicovaginal reflux was the causal problem.[96]

Urine may become entrapped in the vagina due to labial adhesions, a funnel shaped hymen, or an inappropriate position on the toilet.

Hoebeke et al. demonstrated that meatal anomalies may cause vaginal voiding but the issue is still controversial.[83]

Obesity may be an associated risk factor.[65]
2.3.1.7 **Dysfunctional elimination syndrome**

The term dysfunctional elimination syndrome is used to describe dysfunctional emptying of bowel and/or bladder with symptoms of detrusor overactivity, constipation and infrequent voiding.

Children with a dysfunctional elimination syndrome commonly complain of urinary incontinence, non-monosymptomatic enuresis, recurrent urinary tract infections, imperative urgency to void and exceptional urinary frequency. [97] Even idiopathic urethritis in childhood has been related to dysfunctional elimination syndrome. [98]

On investigation they often have poor voiding efficiency, vesicoureteral reflux, constipation, faecal incontinence, no regular bowel routine and infrequent toileting.

It is seen more frequently in girls. The incidence is unknown. [99]

The dysfunctional elimination syndrome is significantly associated with the presence of vesicoureteral reflux and urinary tract infections. It has been reported that VUR is slower to resolve and breakthrough UTI are significantly more common in children suffering the dysfunctional elimination syndrome. [77, 100-104]

A study by Bower W.F. et al showed that childhood lower urinary tract dysfunction may have a negative impact on bladder and bowel function in later life. [97]

The genitourinary tract and the gastrointestinal system are independent, sharing the same embryologic origin, pelvic region and sacral innervation. Until recent the co-existence of voiding disturbances and bowel dysfunction was considered coincidental. Now it is accepted that, in the absence of anatomical abnormality, they are interrelated. The common neural pathways, or the mutual passage through the pelvic floor musculature, may provide a theoretical basis for this relationship, as may be the acquisition of environmental and developmental learning. The latter can be influenced by episodes of urinary tract infections, constipation, anal pain or trauma and poor toilet facilities. [78, 82, 105]

Abnormal recruitment of the external anal sphincter during defecation or at call to stool is considered causative, in that it elicits concomitant urethral sphincter and pelvic floor co-contractions. Thus in both systems a functional obstruction to emptying is generated. In the case of the urinary system, high pressure generated by the detrusor muscle to overcome decrease in urethral diameter can stimulate detrusor hypertrophy, detrusor overactivity, and lead to incompetence of vesicoureteric junctions. In the early stages of defecation disorders, bowel emptying is incomplete, infrequent and poorly executed. As the dysfunction progresses stool quality becomes abnormal, the child develops distension of the rectum and descending colon, seems to lose normal sensation and develops faecal retentive soiling. If constipation was not present as a predisposing factor, it rapidly develops. [105]
2.3.2. Pathophysiology of monosymptomatic enuresis

Three mechanisms are recognized as pathogenetic factors in enuresis:

- polyuria during sleep: due to a lack of arginine vasopressine (AVP) release or response, or relative increased solute excretion during the night \[106-108\]
- reduced bladder capacity and/or detrusor overactivity \[109\]
- disturbed arousal mechanisms: inability to wake from sleep when the bladder is full or empties too early \[110-112\]

It is the interaction of at least two of this factors that is responsible for enuresis.

2.3.2.1 Increased nocturnal urine output – nocturnal polyuria

Humans have a circadian rhythm of urine output resulting in a nocturnal reduction in diuresis to approximately 50% of daytime levels and a corresponding increase of urine osmolality during sleep.\[113-115\] Infants still have an immature circadian rhythm of several vital functions including sleep and renal function (solute and water-excretion). Vande Walle et al. illustrated that development of a proper circadian rhythm of the renal function is a maturation effect.\[116\] The decrease in nocturnal diuresis is largely attributed to nocturnal release of arginine vasopressine (AVP) that regulates free water excretion.\[117\] Several authors questioned these findings, but a recent study by Rittig et al. confirms the importance of a circadian rhythm of vasopressin.\[106\] This subtype of patients is likely to be desmopressin responders, indirectly confirming the vasopressin theory. Whether the low nocturnal vasopressin level is the primary defect or a secondary compensatory phenomenon remains unclear.

In children this hormonal release causes an increased urine concentration and reduced urine volume during sleep. This is why non-enuretic children sleep through the night without wetting their bed.

The circadian rhythms in urine output are fully developed at the age of three and remain unchanged at least until puberty.\[117\]

Two thirds of the children with mono-symptomatic enuresis have a lack of circadian rhythm of vasopressin release, resulting in a high nocturnal diureses, exceeding the bladder capacity.\[107, 118, 119\] A study by Devitt indicated that 18 percent of children have normal levels of plasma vasopressin release but remain enuretic.\[119\]

A small group of mono-symptomatic enuretic children are only partially responding to desmopressin.\[120\]

Our own findings demonstrated that, at least for the population with desmopressin resistant nocturnal polyuria, pathogenesis might be more complex. We have documented absent circadian rhythm of glomerular filtration\[121\], abnormal circadian pattern in calciuria\[122\], abnormal circadian rhythm of renal tubular sodium handling \[122\] and increased osmotic excretion overnight to be causes of nocturnal polyuria.
Nocturnal polyuria due to disturbed osmotic and sodium excretion during the day might be successfully treated with furosemide administered in the morning.[123]

Rittig et al. reported on the importance of a circadian rhythm of bloodpresssure. Several vasoactive hormones, such as angiotensine II, aldosterone and natriuretic peptides play a role in the regulation of solute excretion. All of these hormones have a circadian rhythm.[124] Their role in the pathogenesis of nocturnal polyuria, in contrast to that of prostaglandins, remains to be elucidated. The role of an abnormal circadian rhythm of prostaglandins in persistent nocturnal polyuria was documented by Kamperis et al.[117]

Overall control of these physiological circadian rhythms is achieved through an internal biological clock in the suprachiasmatic nucleus of the anterior hypothalamus.[125] In addition, the supine position, reduction in activity, and the altered hemodynamic and sympathetic system status during sleep also add to the complexity of the process.[126, 127]

Nocturnal urine output varies from night to night.[128] Long-term home recordings in enuretic children demonstrated that nocturnal polyuria is only present on wet nights, whereas the nocturnal urine production on dry nights is significantly lower or normal.[129] The nocturnal polyuria is higher in children with enuresis who respond best to desmopressin (dDAVP).

By the time the child becomes adolescent, the circadian rhythm becomes less prominent. In adolescents and adults with enuresis there is no diurnal rhythm of plasma vasopressin concentration. The changes in nocturnal diureses occur from a decrease in the urinary sodium excretion that is not due to differences in concentration of AVP but due to lack of sensitivity to AVP with resultant increased urine output.[106, 130]

There may be a small sub-group of children with impaired renal sensitivity to vasopressin or desmopressin.[107, 131]

2.3.2.2 Reduced bladder capacity and/or detrusor overactivity

An overactive detrusor was believed to be characteristic for non-monosymptomatic enuresis. For a long time it was thought that bladder function was normal in monosymptomatic enuretic children. Norgaard et al. challenged this theory. They described detrusor overactivity during artificial nighttime bladder filling.[132] Watanabe et al. discovered that 32 percent of the children suffering enuresis had detrusor overactivity resulting in bedwetting on cystometry performed during sleep.

It was accepted that the bladder capacity of enuretic children was smaller than that of dry children. Logically, a reduced maximum voided volume should be an important cause of nocturnal enuresis. Review of the literature shows conflicting data. Some studies confirmed this hypothesis[109, 133], others reported no differences in bladder capacity in children with enuresis compared to age-matched dry children.[134]
Most of the studies on bladder capacity and enuresis neglected circadian changes in bladder reservoir function. Maximum voided volume varies between night and day in normal children. Nighttime maximum voided volume is 1.6-2.1 times larger than daytime maximum voided volume.\[135\]

C.K. Yeung et al. demonstrated that a reduction in nocturnal maximum bladder capacity appears to be a common factor, probably the main cause of a mismatch between nocturnal urine output and bladder storage capacity in patients with severe bedwetting refractory to treatment. This reduction in nocturnal maximum bladder capacity may occur only after sleep at night in association with the appearance of detrusor overactivity in children with normal daytime urodynamics and maximum voided volume, or may be a manifestation of occult voiding dysfunction or bladder outlet obstruction that affects the bladder reservoir function both day and night.\[136\]

Troup et al. demonstrated that this difference in maximum voided volume in enuretic children and dry children is functional and not anatomical.\[137\]

This reduced maximum voided volume, when smaller than 70% of the expected bladder capacity for age, is likely to result in poor response to the treatment with dDAVP.\[138\]

Ultrasound studies of the bladder revealed an increase in bladder wall thickness in children suffering enuresis.\[139\] According to the study of Sreedhar et al. increased bladder wall thickness and reduced maximum voided volume predicted the response to therapy in children with primary nocturnal enuresis.\[140\]

Bower et al. demonstrated that adults with refractory monosymptomatic nocturnal enuresis showed significantly higher childhood scores of urgency, frequency, urge incontinence, infrequent voiding and small voided volumes.\[69\] This suggest that in adolescents and adults the bladder component plays an important role in enuresis as these populations do not show the nocturnal polyuria problem seen more commonly in younger children.

**2.3.2.3 Sleep, arousal and CNS function**

Nocturia and enuresis are due to the fact that the bladder fills to its capacity during sleep and that there is a need to empty the filled bladder. Polyuria and/or reduction of the bladder capacity, due to detrusor overactivity, during sleep do not explain why the enuretic child doesn’t wake up from the sensation of a full or contracting bladder. So enuresis results from the child’s inability to wake up from sleep to empty the bladder in a proper way.

Enuretic children are often reported to be deep sleepers, difficult to arouse at night.\[112,141\]
Wolfish et al. found that enuretic children wet most frequently during the first two thirds of the night, and that arousal attempts were less successful in children with enuresis than in normal children.\cite{110,142}

Using EEG recordings during sleep, Watanbe et al. found that full bladder signals were insufficient to wake children with enuresis completely, leaving them in a drowsy condition while bedwetting.\cite{143}

The observation by C.K. Yeung et al. of detrusor overactivity appearing only after sleep at night in some children with normal daytime urodynamics may also be related to a deficiency of inhibitory signal processing in the brainstem that accounts for the inability to inhibit both detrusor activities and micturation during sleep.\cite{109} Theoretically neurological impairment of a tiny brain area in the vicinity of the pontine micturation centre, the posterior hypothalamus (responsible for secretion of antidiuretic hormone) or the locus coeruleus which may be the cortical arousal centre could be the anatomical location of most pathophysiological described mechanisms for nocturnal enuresis.\cite{144}

According to these findings Yeung et al. questioned the classic deep sleep theory. They found evidence of disturbed superficial sleep in children with enuresis. Children had more light sleep associated with frequent cortical arousals but were unable to awaken.

Dhondt et al. found evidence of disrupted sleep architecture in children with refractory nocturnal enuresis, with a high incidence of periodic limb movements during sleep at night and increased cortical arousability leading to awakening. These results are also in contrast with the classical accepted deep sleep theory.\cite{145}

Other investigators observed a reduced prepulse inhibition of startle in enuretic children, suggesting a dysfunction of the pedunculopontine tegmental nucleus might be a reason for nocturnal enuresis.\cite{146-148}

### 2.3.2.4 Genetic factors

Genetic studies illustrated that multiple genes may be involved in enuresis. Four gene loci, 8, 12, 13 and 22 have been identified and the existence of others is presumed.\cite{149} This illustrates the locus heterogeneity.

Most commonly, nocturnal enuresis is inherited via an autosomal dominant mode of transmission with high penetrance. No clear association between mode of inheritance and specific phenotype was found. In fact, nocturnal enuresis as well as urinary incontinence during day and night seems to have a comparable risk.\cite{149,150}

Loeys et al. confirmed a linkage of nocturnal enuresis to a region on chromosome 22q11, 13q13-14 and 12q. The results of this study support the hypothesis of genetic and phenotypic heterogeneity of nocturnal enuresis mentioned by von Gontard et al.\cite{150-152}
According to von Gontard et al., certain syndromes of daywetting follow their own genetic mechanisms. The association with the genetics of nocturnal enuresis is unknown.[149]

2.3.3. Comorbidity

2.3.3.1 Constipation and faecal incontinence

The interrelation between GU and GI systems has been described before. Constipation and faecal incontinence is common in children with urinary incontinence and enuresis.[156, 157] The reported prevalence of constipation among enuretic children ranges from 7.06% to 69.8%.[153, 154] Koff et al. demonstrated that constipation and bowel distension may lead to deformation of the bladder, which in turn may lead to detrusor overactivity and thus to urinary incontinence.[77] Söderstrom et al. demonstrated that children with daytime incontinence often have faecal soiling and vice versa.[29]

2.3.3.2 Psychological and social disturbances

According to Jainson et al., children with daytime wetting have a higher risk of parent-reported psychological problems than children who have no daytime wetting. The reported rates of attention and activity problems (24.8%), oppositional behaviour (10.9%), and conduct problems (11.8%) in daytime wetting children were around twice the rates in children without daytime wetting.[155]

In a study by von Gontard et al., 40% of the children with enuresis had clinically significant behavioural problems, according to the child behavioural checklist and psychiatric diagnosis.[156]

Children with secondary nocturnal enuresis and voiding postponement carry the highest risk for a mental disorder and those with urge incontinence and primary monosymptomatic nocturnal enuresis the lowest. Internalizing disorders (such as depressive and anxiety disorders) are less common than externalizing ones (such as ADHD). In addition, subclinical emotional and behavioural symptoms are common. These will often recede upon attaining dryness and self-esteem can increase.[157]

2.3.3.3 Attention Deficit Hyperactivity Disorder (ADHD)

There is ample evidence for a higher ADHD prevalence in children with enuresis than in a comparison group without continence problems and up to 32% of the children with ADHD show urinary problems.[87, 158-161]

Kodman-Jones et al. found an incidence of ADHD in daytime wetting children without infection of 21% which is higher than the 3 to 5% found in the general population.[162, 163]

Baeyens et al. found that the prevalence of ADHD is significantly higher, up to 40%, in children suffering nocturnal enuresis. Moreover, they found that the older the children,
the higher the prevalence of the inattentive subtype. According to organic parameters, no difference was found between the enuresis group and the children with associated diurnal symptoms, except for a slightly higher incidence of nocturnal polyuria in children with an ADHD hyperactive/impulsive subtype. The data of this study indicate that despite the high incidence of ADHD in enuretic children, ADHD is not associated with a single phenotype of enuresis.[164]

Crimmins et al. found the treatment of urinary incontinence in children with ADHD to be impaired, compared to those without ADHD. Moreover, treatment seems to be directly affected by compliance and IQ.[165]

Further studies by Baeyens et al. indicated children with ADHD to be at risk for persistent enuresis.[162, 166]

Startle eyeblink modification (SEM) research by Baeyens et al. showed a brainstem inhibition deficit in children with enuresis. This could explain why these children are unable to stay dry at night. Moreover, children with ADHD-IA fail to optimize sensory gating. In children with enuresis, this can result in an impairment of stimulus identification leading to an inadequate or absent arousal effect. This additional impairment might explain why the combination of enuresis with ADHD-IA is more prevalent in older, therapy-resistant children.[167]

### 2.3.3.4 Upper airway obstruction.

Upper airway obstruction is a common problem in healthy children. Due to glossoptosis and neuromotorical failure it is an even more common problem in disabled children suffering cerebral palsy, Down syndrome and Prader-Willi syndrome.[168, 169]

Children with upper airway obstruction do have a higher incidence, up to 42%, of nocturnal enuresis and upper airway obstruction is very common, up to 65.6%, in children suffering nocturnal enuresis. [168-170] Several explanations, such as increased bladder pressure due to increased respiratory efforts against obstructive airways, decreased levels of antidiuretic hormone and increased levels of atrial natriuretic peptide in patients with obstructive sleep apnoea have been mentioned in literature.[170]

Complete resolution of nocturnal enuresis after adenotonsillectomy was found in 33% to 63% of the patients.[170-172] Firoozi et al. even found an additional decrease in daytime urinary frequency and episodes of incontinence. The mechanism of the latter remains unclear. [170]
Chapter 3  Mental and Motor disabilities

3.1. Definitions

3.1.1. Mental retardation
Mental retardation is a state of functioning that begins in childhood and is characterized by limitations in intelligence and adaptive skills. Two definitions are commonly used. One is published by the Diagnostic and Statistical Manual (DSM) IV and the other by the American Association on Mental Retardation (AAMR).

3.1.1.1 DSM definition
DSM IV defines Mental Retardation by three co-existing criteria:

- Significant sub-average intellectual functioning
- Adaptive functioning deficit or impairment
- Onset before 18 years of age

The severity of cognitive impairment is characterized by the extent of deviation of the IQ below 100, the estimated mean for the population. The lower limit of normal is considered to be two standard deviations below the mean or an IQ of 70. Gradations of severity include IQs in the following ranges:

- Mild: from between 50 and 55 to approximately 70
- Moderate: from between 35 and 40 to between 50 and 55
- Severe: from between 20 and 25 to between 35 and 40
- Profound: from < 20 to 25
- Unspecified: not testable but presumed low

Adaptive skills are skills of daily living that are needed to live, work and play in the community. They include communication, social and interpersonal skills, self-care, home living, use of community resources, self-direction, functional academic skills (reading, writing and basic mathematics), work, leisure, and health and safety. Adaptive functioning is considered to be impaired when there is a deficit in at least two of these areas compared to children of the same age and culture.

3.1.1.2 AAMR definition
The DSM IV definition has been expanded by the American Association of Mental Retardation (AAMR) to reflect the personal functioning of a child within the context of community environment, peers, and culture, and incorporates a description of supports that are needed in the context of a child-community functional fit. According to AAMR definition, “mental retardation is a disability characterized by significant limitations both in intellectual functioning and in adaptive behaviour as expressed in conceptual, social, and practical adaptive skills” with onset before 18 years of age. Limitation in intellectual
ability corresponds to an IQ less than 70 to 75. The AAMR describes the pattern and intensity of supports as intermittent, limited, extensive, or pervasive.

A number of assumptions are essential to the application of the AAMR definition:

- Limitations in function must be assessed relative to the child’s age, culture and environment
- A valid assessment considers differences in language and culture, as well as those in communication, motor, sensory, and behavioural factors
- Individuals often have strengths as well as limitations
- An important purpose of characterizing limitations is to identify supports that are needed
- Providing appropriate individualized support over a sustained period usually will improve the life functioning of a person with mental retardation.[173] Children with mild or moderate mental retardation are educable or at least trainable, whereas children suffering severe and profound mental retardation are considered to be non-trainable.[175]

Mental disorders affect approximately 30 to 70% of children with mental retardation, which is up to 5 times more than non-retarded children.[176] Commonly associated mental disorders are: autism and autistic spectrum disorder, Attention Deficit Hyperactivity Disorder (ADHD), eating disorders, depression and anxiety.[177]

3.1.2. **Motor disability**
Motor disabilities are disabilities that affect a person’s ability to learn motor tasks (moving and manipulating objects) such as walking, running, skipping, sitting, handwriting and others. To be considered a disability, the problem must cause a person to have motor coordination that is significantly below what would be expected for age, and the problem must interfere with the activities of learning and daily living.

3.2. **Incidence and aetiology of developmental disabilities**
Mental retardation is a common problem. Up to 10% of the school-aged children are learning impaired and as many as 3% of the children in the US manifest some degree of mental retardation. A study performed in Aberdeen, Scotland, showed that the prevalence of mild mental retardation is about 1/77 and of severe mental retardation is 1/300.[175] For the vast majority of individuals with mental retardation (45-63%) no aetiology is identifiable.[178] More than 800 recognized syndromes are associated with mental retardation, of which Trisomy 21 or Down Syndrome is certainly the best known. Environmental factors, such as Foetal Alcohol Syndrome and peri- and postnatal conditions, such as CMV, rubella and hypo-ischemic encephalopathy, may also be responsible for mental retardation.[175]
The second most important cause of developmental disability is cerebral palsy.

Cerebral palsy is a non-progressive injury of the brain occurring in the perinatal period that produces a neuromuscular disability or a specific symptom complex or cerebral dysfunction.

The incidence of cerebral palsy is about 1.5 per 1000 births.\(^{[179]}\)

Twenty percent of the mentally retarded individuals suffer cerebral palsy, and 50% of the cerebral palsy patients are mentally disabled.\(^{[175, 180]}\)

### 3.3. Pathophysiology of urinary incontinence in developmentally challenged children

To develop continence several conditions, such as physical maturation of the bladder and the neurological system, and a normal development of the mental and motor capacity are required.

#### 3.3.1. Dysfunction of the lower urinary tract

Several studies documented dysfunction of the lower urinary tract as an aetiologial factor of incontinence in children with a developmental disability.

Decter et al. performed an urodynamic evaluation in 57 patients suffering cerebral palsy and urinary problems. Eighty-six percent of the patients were found to have a “partial upper motor neuron lesion, 9.5% had a mixed upper and lower neuron lesion and 1.5% showed an incomplete lower motor neuron lesion. Only 3% had a normal urodynamic investigation.\(^{[54]}\)

Other studies confirmed the high incidence of overactive detrusor in incontinent developmentally disabled children.\(^{[55, 181]}\)

In neurologically normal children (3-16 years old) the incidence of overactive detrusor varies between 47% and 57%, which is significantly lower than the 74% up to 97% found in developmentally challenged children.\(^{[55, 182-184]}\)

Mayo et al. stated that in 50% of the children who suffered difficult voiding, this was due to a failure of pelvic floor relaxation rather than to dysfunctional voiding.\(^{[47]}\)

On the contrary Bross et al. showed an overactive detrusor and dysfunctional voiding in 28 of the 29 patient that underwent an urodynamic investigation. Only 1 patient had a normal urodynamic pattern.\(^{[184]}\) Interestingly these pathological urodynamic findings can be found in both symptomatic and asymptomatic patients, and as such are not representative for the severity of complaints.\(^{[185]}\)
The type of damage responsible for urinary incontinence in cerebral palsy patients seems to be localized anatomically above the brainstem for those suffering detrusor overactivity and coordinated sphincter. It was suggested that disturbed modulating effects on autonomic function due to brain lesions in children with cerebral palsy might account for overactive bladder.\cite{186} Spinal cord damage might account for those individuals with cerebral palsy suffering dysfunctional voiding. This lumbosacral cord damage is probably due to severe anoxia.\cite{54}

3.3.2. Reduced bladder capacity
Reduced bladder capacity is another major factor in the pathophysiology of urinary incontinence in physically and intellectually disabled children. Several studies illustrated that 75% up to 92% of these children have a too small bladder capacity.\cite{47, 54, 55, 60, 187}

Both neurological involvement of bladder function leading to hyperreflexia of the detrusor and low compliance, and restricted fluid intake because of swallowing problems in some and nursing habits in most of these children could be at the origin of this phenomenon.

3.3.3. Mental development
Mental development certainly plays a role in achieving continence. Children with mild mental retardation seem to differ relatively little from healthy children with respect to bowel control and nightwetting. Daywetting on the other hand is clearly more frequent among mildly retarded children.\cite{48} Only in moderately mentally retarded individuals the development of urinary and bladder control differs clearly from healthy individuals.\cite{48, 60}

Reid et al. found that intellectual delay is not a barrier to successful management except for patients with a severe degree of mental retardation.\cite{55}

Understanding of bladder sensations and acting appropriately are essential skills to obtain bladder control. In case of mental retardation this could be a problem.

3.3.4. Motor capacity
Motor capacity is another important aetiological factor. To become continent a person should be able to go to an appropriate place to void (the toilet), to undress and understand how to use the toilet facilities. This requires a degree of mobility, stability and upper arm function.

Literature illustrates that the higher the degree of mobility the higher the incidence of achieving continence.

Bross et al. concluded that urinary symptoms and pathological urodynamic findings increase along with the degree of motor function impairment.\cite{185}
According to Roijen et al. intellectual capacity and motor capacity (degree of spasticity) do influence the development of urinary continence in cerebral palsy independently. [49]

3.4. Comorbidity

3.4.1. Constipation and faecal incontinence
Constipation is an important comorbidity in the process of incontinence in developmentally challenged children. It is well known that there's a correlation between constipation and urinary incontinence, bladder overactivity, dysfunctional voiding and recurrent urinary tract infections. [26, 188]

Children suffering intellectual and physical disabilities are more prone to constipation and faecal incontinence than normal children. Böhmer et al. found an incidence of 70% for constipation in intellectually disabled children. [189] In cerebral palsy patients constipation is significantly more present. [58] Up to 90% of the cerebral palsy children are constipated and 47% suffer faecal incontinence, though most of them only to a minor degree. [190]

3.4.2. Attention Deficit Disorder (ADHD)
ADHD and autism are more frequent in mentally disabled children. [177] There is a large etiologic heterogeneity of ADHD among intellectual developmental disabilities. [191] As mentioned before there is a proven correlation between ADHD and urinary incontinence. [87, 155, 157, 163]

3.4.3. Sleep disorders
Sleep is a complex neurological function. In children with brain damage, the autonomic nervous system, which is involved in pineal melatonin secretion and sleep regulation, might be affected. [192]

Sleep is also vulnerable to several other factors common in cerebral palsy. Muscle spasms, decreased ability to change body position during sleep, epilepsy which is known to disturb sleep physiology and predisposes to sleep disorders and glossoptosis which can induce sleep-related breathing disturbances may be the cause of sleep problems in these patients. [168, 193]

The incidence of sleep disorders in children from the general population varies between 10% to more than 40%.

Children with intellectual disability have a higher risk of sleep disturbances. [194, 195]

Sleep disorders such as delayed insomnia, disrupted sleep, early awake or a combination of these are frequently reported in cerebral palsy children. Newman et al. found that 44% of the patients presented at least one clinically significant sleep disorder. Epilepsy...
and antiepileptic medication were the principal factors associated with the sleep disturbance. Patients with total body involvement were significantly more affected. Visual impairment or blindness and environmental factors were also associated with disorders of initiation and maintenance of sleep. Svedberg et al. found that 51% of the children with cerebral palsy had a kind of sleep problem. These problems were more often reported in non-walkers (72%) than in walkers (36%).

As mentioned at 2.3.2.3. there might be a relation between sleep and nocturnal enuresis. Further studies are needed to elucidate this relation in the group of intellectually and physically disabled children.
Chapter 4  Evaluation of children with incontinence.

As urinary incontinence in children is often complex in nature, adequate treatment is only possible based on a thorough diagnosis.

History taking and clinical examination are essential diagnostic factors. Monosymptomatic enuresis can be identified based on adequate history taking alone.

Laboratory tests do have a limited value in the work out of urinary incontinence.

Frequency/volume charts and a bladder diary are of utmost importance to determine the degree of urinary and faecal incontinence, to evaluate the drinking and voiding habits and to illustrate the characteristics of the bladder. Urinary flow and ultrasound are non-invasive sources of additional information on bladder function and anatomy of the urinary tract.

Invasive techniques like (video)-urodynamics and cystoscopy should be reserved for selected cases of complex urinary incontinence.[196]

4.1. History taking

History taking in children is always challenging. It is often very difficult for the investigator to preserve the fragile balance between the anamnestic data from the child and the hetero-anamnestic data from the parents. In case of developmentally challenged children history taking is even more complicated. The children themselves are often incapable to provide adequate anamnestic data. Generally, especially in Belgium, intellectually and physically disabled children do stay during the week in well specialized institutions. This means that the investigator not only has to get the hetero-anamnestic data from the parents but also from the institution’s staff.

The use of a well structured questionnaire, adapted to the language and possibilities of children, parents and caregivers is useful to gather reliable and comparable information.

This questionnaire should include items on enuresis, urinary incontinence, lower urinary tract symptoms, and bowel function. It should also include questions relevant to mental and motor development, familial disorders, the child’s psychosocial status and its family situation, neurological and congenital anomalies, previous urinary tract infections, relevant medication and surgery. In some cases it is even necessary to ask for sexual functions and to rule out child abuse.
A voiding and drinking diary is essential to determine the child's voiding frequency and voided volumes and to evaluate the quantity and quality of fluid intake. A dry/wet diary has to be kept up, and the same should be done for defecation registering defecation frequency, stool consistency and soiling.

To help children, parents and caregivers in gathering adequate data the Belgian Consensus Working Group of Enuresis composed a structured information booklet, containing general information on enuresis, a clear and restricted questionnaire, a voiding and drinking diary and a frequency volume chart.[197]

Some authors developed validated symptom score systems to identify and evaluate lower urinary tract dysfunction, classify the severity and document the response to treatment.[198-200] Some of these symptom score systems are rather general others more specific. For example Tokgoz et al. developed a symptom scale specifically for Dysfunctional Elimination Syndrome, providing objective assessment for diagnosis and quantification of severity.[201]

The use of a standard symptom score system, which at present not exists, would provide an accurate, objective and scientific based tool to grade the symptoms in comparative research, diagnosis, treatment and follow-up of children with enuresis and urinary incontinence.

### 4.2. Physical examination

A physical examination should be performed in a child suffering enuresis, urinary and faecal incontinence, LUT symptoms and recurrent UTI.

Theoretically physical examination should include the assessment of perineal sensation, the perineal reflexes supplied by the sacral segments S1-S4 and anal sphincter tone and control. Practically, as this is confronting for the child, this part of the physical examination is restricted to those patients suspicious for neuropathy.

Special attention should be paid to signs of neuropathy such as: spine deformity, abnormal gait, abnormal deep tendon reflexes, asymmetric atrophy of feet, high plantar arches, hammer toes, and of occult spinal dysraphism, i.e. skin discoloration, dimples, hairy tufts, subcutaneous lipoma, asymmetrical buttock, legs or feet and oblique gluteal cleft.[202]

The abdomen should be palpated to asses a full bladder, full sigmoid or descending colon and flank masses.

The external genital region has to be inspected for vaginitis and vulvitis, meatal web and a hymen that covers nearly the complete vaginal introitus in girls and for penile anomalies and meatal stenosis in boys.
In motor disabled children the locomotor system has to be evaluated according to muscle power, mobility, stability and spasticity.

In mental retarded children the IQ and the functional autonomy has to be estimated.

In all children a detailed questioning of the parents’ observation of the child’s voiding habits is important to elucidate the toilet position during micturation and defecation and to describe the way they void or defecate. Proper support of the legs and a stable position on the toilet are essential for adequate pelvic floor relaxation, and correction of these factors may ameliorate or even eliminate LUT symptoms.[203]

4.3. Laboratory tests

Urine analysis to exclude pyuria, proteinuria, glucosuria, hematuria, calciuria and bacteriuria has to be done at the first office visit.

Pyuria, hematuria and bacteriuria occur commonly in children with urinary tract infections. Hematuria and calciuria are indicative for urolithiasis. Urinary tract infections and urolithiasis may be the cause of LUTS.

Proteinuria is a symptom of glomerular renal disease such as diabetes mellitus. Diabetes mellitus also causes glucosuria. Polyuria can be due to renal insufficiency and diabetes mellitus.

Hypercalciuria has been claimed to be related to nocturnal polyuria.[204]

Urinary culture should be reserved for those children with a history of previous urinary tract infections.

Urine osmolality and electrolytes should be determined in case of monosymptomatic enuresis with persistent therapy resistant polyuria.

4.4. Non-invasive diagnostic techniques

4.4.1. Frequency/volume charts: bladder diary

The frequency/volume chart is a non invasive record of a child’s urine output over 24-hour periods. The chart gives objective information on the number of voidings, the distribution of day and night voids, along with the voided volumes and episodes of urgency, urinary incontinence and enuresis.

To determine the exact amount of urine loss during the day one has to weigh the sanitary napkins the patient should wear.

Ideally the chart should cover at least 3 complete days.
Bower et al. proved that the frequency/volume chart is a reliable non-invasive tool to measure maximum voided volume and can be used as an outcome measure in children with lower urinary tract symptoms if care is taken to minimise confounding factors and sources of error during chart completion.\[205\]

In order to obtain more complete information it is better to ask for a bladder diary.

The ideal bladder diary indicates 24 hour fluid intake, urine output, and also defecation frequency, soiling and faecal incontinence. In case of nocturnal enuresis and day-and-night urinary incontinence, duration of sleep, nocturia episodes and nocturnal diuresis (net diaper weight + first morning voided volume) are also essential information.

This diary should be kept up for a fortnight.

Although the amount of urine voided by a non-supervised child during the day varies considerably, mainly because of social circumstances, children with LUT symptoms void smaller volumes than may be expected from traditional estimates. \[205-207\]

4.4.2. Urinary flow

The graphic registration of the urinary flow rate during voiding should be preformed in all incontinent children except in that suffering monosymptomatic enuresis.

This non-invasive procedure should be repeated at least 2 times to allow adequate evaluation of the flow pattern and rate. Mattsson et al. illustrated that at the first micturation, more curves are irregular and flow rates are significantly lower than at the second one. \[208\] Flow recordings with a voided volume of less than 50% of the estimated bladder capacity for age are not consistent. Before micturation bladder volume can be assessed with a bladder scan or an ultrasound. If the bladder isn’t yet full enough the child should be asked to drink some more and to wait until the bladder is full enough.

Urinary flow may be described in terms of rate and pattern and may be continuous, intermittent or fluctuating. The normal flow pattern is bell-shaped regardless of sex, age and voided volume. \[208\] Approximately 1% of school children have a voiding that can be labelled abnormal with flattened or intermittent flow curves. The remaining 99% have a normal curve. A normal flow doesn't exclude a voiding disturbance, nor does an abnormal flow pattern automatically mean a bladder emptying disorder.\[209, 210\]

Some uroflow patterns are pathognomonic.

In overactive detrusor the voiding phase is essentially normal, but the detrusor contraction during voiding can be extremely powerful. This may result in a “tower shape” flow curve, with a quickly reached, very high maximum flow rate.
In dysfunctional voiding repeated uroflowmetries demonstrate fluctuating or intermittent uroflow patterns.

Fluctuating (Staccato) voiding is characterized by a continuous flow with periodic reductions in flow rate precipitated by bursts of pelvic floor activity. Voids are commonly prolonged and incomplete.

Interrupted voiding is characterized by unsustained detrusor contractions resulting in infrequent and incomplete voiding, with micturation in separate fractions.

In case of obstructive pathology, such as Moorman ring, mini urethral valves and meatal stenosis, the flow curve is flattened and flow time is prolonged.

Some children feel uncomfortable when voiding in a strange environment. In those children home uroflowmetry can be used successfully.\[211\]

Especially in developmentally challenged children uroflowmetry is often a problem. Mentally disabled children are often too anxious to perform an uroflometry because they can’t be properly explained what is going to happen to them. Motor disabled children are often incapable to perform a non-disturbed void on the uroflow because of their instable position on the flow chair. Therefore uroflowmetry in developmentally challenged children should be performed in their own environment on their personal adapted toilet chair.

### 4.4.3. Ultrasound

Ultrasound-imaging techniques are routinely used in children with urinary incontinence to evaluate the upper and lower urinary tract.

In the upper urinary tract duplex systems, hydronephrosis and gross reflux nephropathy can be readily detected.

In the lower urinary tract ureteroceles, retrovesical dilated ureters and bladder wall thickness can be evaluated. A bladder wall cross-section of more than 3-4 millimetres, measured at 50% of the expected bladder capacity for age, is suspicious for detrusor overactivity.\[139, 212-214\]

Sreedhar et al. described the Bladder Volume/Bladder Wall Thickness Index (BVWI), which is calculated by measuring bladder volume (when the bladder is maximally full) and bladder wall thickness (when bladder emptying is more than 90% of maximally full bladder).\[140\] The bladder wall is defined to be thick with a BVWI of <70, normal with a BVWI from 70- to 130 and thin when the BVWI is more than 130.
The results of the study show a high predictive value of this tool to distinguish between children with enuresis and normal urodynamics and those with various bladder dysfunctions.

Further study by the same group in children with recurrent urinary tract infection confirmed the value of BVWI as a sensitive tool for diagnosing bladder dysfunction. It can be used as a reliable guide for the appropriate choice of further urodynamic studies.[215]

Ultrasound and bladder scan can also be used to measure the post-void residual volume. Theoretically, except in small infants, the normal bladder empties completely at every micturation.[216] To be conclusive measurement of post-void residual volume should be done immediately after voiding. The finding of post void residual volume requires confirmation before being considered significant. The absence of residual urine doesn’t exclude bladder outlet obstruction or dysfunctional voiding.

The combination of ultrasound and uroflowmetry should be the standardised procedure to obtain data on flow rate and pattern and post-void residual volume.

4.5. Invasive diagnostic techniques

4.5.1. (Video)-Urodynamics (VUDE)

(Video)-Urodynamics remain an invasive examination in children. Therefore it should only be considered if the outcome will influence the treatment.

It is of utmost importance that the children and the parents are carefully prepared and given adequate information before the investigation is performed. Transurethral catheterisation, artificial bladder filling and voiding along a catheter are not evident. Especially during the first procedure artefacts can be registered due to anxiety of the child. Therefore it is important that the parents stay with their child and that the child is distracted by reading a book, listening to some music or watching a movie during the procedure. To get reliable information of a VUDE the procedure should be repeated at least twice.[217]

VUDE should not be performed as a routine procedure in all patients suffering LUT symptoms, enuresis or urinary incontinence.[218] In well selected cases, such as patients with dysfunctional voiding in whom initial conventional management has failed, or children suffering recurrent urinary tract infections, urodynamics reveal a high rate of pathological findings.[84, 219]

To minimize the possible negative influence of the VUDE procedure on the bladder behaviour it is important to use a strict VUDE protocol. For retrograde filling by a catheter, the use of saline 0.9%, contrast medium or a mix of both at body temperature is recommended. Especially in young infants bladder capacity and detrusor activity
seem to be influenced by the temperature of the filling fluid. Slow fill cystometry (5-10% of the expected bladder capacity for age/minute, or < 10ml/minute) is recommended in children, as some cystometric parameters, notably changes in compliance and detrusor overactivity, may be provoked by rapid bladder filling.

Important parameters to check for in children are: bladder sensation, although difficult to evaluate in non toilet-trained children, maximum bladder capacity, bladder compliance, detrusor activity, sphincter activity and pelvic floor activity during filling and emptying phase and the flow pattern. The surplus value of video urodynamics is certainly the fluoroscopic visualisation of the lower urinary tract, especially in cases of anatomical obstruction and vesico-ureteral reflux.

Natural fill urodynamics are clearly more physiological than conventional (video) urodynamics, but there are some practical drawbacks with this method. It is certainly more invasive, as a suprapubic catheter has to be inserted under general anaesthesia. Furthermore it is more time-consuming and more expensive than conventional (V) UDE.

Yeung et al. found natural fill urodynamics to be superior to conventional (V)UDE for assessing bladder function in children and infants. Their main arguments were: (1) bladder function being investigated in near to natural conditions, (2) patients being mostly unaffected by this procedure, and (3) the significant differences found between NFU and conventional (V)UDE.

The former and other studies in adults and children revealed that NFU is more sensitive to detrusor overactivity. This increased overactivity seen on NFU is an indication of problems including bladder wall distension (compliance). Compliance is greater and bladder capacity is lower for NFU. Voiding pressure has been shown to be higher during NFU than in conventional (V)UDE.

Detection and interpretation of compliance and leak point pressure are a problem in NFU. The study by Jorgensen et al. demonstrated a correlation between parameters from NFU and parameters, such as leak point pressure and bladder compliance, from conventional UDE.

NFU provides more reliable data than conventional (V)UDE because it avoids anxiety and other patient compliance problems. On the other hand, due to its invasiveness, it should be reserved for children who do not respond to treatment based on standard (V)UDE findings, and for those suffering LUTS which are not reflected on conventional (V)UDE.
4.5.2. Cystoscopy

Cystoscopy is rather seldom indicated in children suffering LUT symptoms, enuresis and urinary incontinence. Only in case of therapy resistant incontinence in boys with an obstructive flow pattern, high detrusor pressure during micturation and an image on VUDE suspicious for infra-vesical obstruction, a cystoscopy is indicated to rule out and treat anatomical obstructions such as urethral valves, Moorman ring, syringocoele, urethral stricture etc. It has to be mentioned that a voiding cystourethrography not always shows these abnormalities.[229]

In girls meatal abnormalities causing an anterior deviation of the flow, causing vaginal reflux and dysfunctional voiding have been described. A simple meatoplasty may solve the problem.[83]
5.1. Treatment of urinary incontinence in children

5.1.1. Non pharmacological treatment

5.1.1.1 Urotherapy

Anna Helena Hellstrom introduced the terms “urotherapy” and “urotherapist”. [230]

The term urotherapy is not strictly defined. Urotherapy means nonsurgical, nonpharmacological treatment of lower urinary tract function. It can be defined as a bladder re-education or rehabilitation program aiming at correcting of filling and voiding function of the bladder-sphincter unit. [231] It is synonymous with the term LUT rehabilitation frequently used in adults. [232]

To achieve the normalization of the micturation pattern and to prevent further functional disturbances, a combination of patient education, cognitive, behavioural and physical therapy methods is used.

Hoebeke et al. developed an outpatient training in which bladder regimens: individual adapted voiding-drinking schedule and adequate toilet posture, pelvic floor biofeedback and biofeedback uroflowmetry were combined. [233] Immediate success in 92% and a long-term effect of 82% was reported.

In girls suffering urinary incontinence due to vesicovaginal reflux correction of the toilet position, treatment of the labial adhesions and meatal anomalies and diet may help to resolve the problem. [83]

The Utrecht group reported on inpatient training, using a cognitive training program that combines voiding and drinking charts, biofeedback uroflowmetry and wetting alarm and reported a success rate of 80%. [234]

Bower et al. reported on a half-day urotherapy program consisting of teaching the child about bladder function, bladder regimen, biofeedback uroflowmetry, and learning how to relax the pelvic floor muscles. A success rate of 90% was mentioned. [235]

Similar success rates were described by other authors using either short course urotherapy or more sophisticated computer games related urotherapy. [236, 237]

As mentioned by Hoebeke in his editorial on urotherapy in children, the major problem with most of the urotherapy modalities is that there are no randomized controlled trials on the effect of each treatment modality. Furthermore, most centres combine treatments like voiding and drinking charts, instructions on toilet position, pelvic floor
biofeedback, and uroflow feedback, which makes it impossible to evaluate the effect of each modality.\textsuperscript{[231]} Despite this lack of randomized controlled data one can state that, whatever the type, urotherapy works.

Even the term urotherapist is somewhat vague. Nurses, physiotherapists, psychologists and even doctors can be urotherapists as long as they teach the child to correct the malfunction leading to lower urinary tract symptoms.

\subsection*{5.1.1.2 Biofeedback}

Biofeedback was first reported by Maizels et al.\textsuperscript{[238]} It is a technique in which physiological activity is monitored, amplified and conveyed to the patient as visual or acoustical signals, thereby providing the patient with information about unconscious physiological processes.

Biofeedback may consist of pelvic floor relaxation through proprioceptive exercises of the pelvic floor by visualisation of the electromyographic registration of relaxation and contraction of the pelvic floor: “relaxation biofeedback”, observation of the flowcurve during voiding: “uroflow biofeedback”, or a combination of both. Schulman et al. found that both types of biofeedback were equal successful in reducing daytime wetting and urinary tract infections.\textsuperscript{[239]}

Biofeedback may be utilized for the management of both filling phase (detrusor overactivity) and voiding phase (dysfunctional voiding due to pelvic floor muscle overactivity) disorders.

Biofeedback can help children to identify how to relax their pelvic floor muscles or recognize involuntary detrusor contractions.

Commonly pelvic floor muscle relaxation is taught through the use of EMG biofeedback. An anal plug or surface electrodes can be used to register the muscle activity.\textsuperscript{[233]}

This can be extended with real-time uroflow. Interactive computer games are commonly used to make biofeedback training more attractive to the children.\textsuperscript{[237, 240]}

Kaye and Palmer compared animated and nonanimated biofeedback programs in treating two identical groups of girls with documented dysfunctional voiding. They found a similar cure rate using either method, but fewer sessions (3.6) were needed with animated biofeedback as compared with 7.6 sessions with the nonanimated form.\textsuperscript{[241]}

Combs et al. on the other hand found the same results in their nonanimated biofeedback population as the previous group found in the animated form.\textsuperscript{[242]} This suggests that although the type of biofeedback equipment used may facilitate therapy for patients, it is the experience of the therapist that may impact treatment response most.\textsuperscript{[243]}
Biofeedback can be used as a single treatment, or combined with a comprehensive rehabilitation program. Klijn et al. reported successful treatment with home uroflowmetry biofeedback.

The results of biofeedback are generally positive but overall may not be superior to high quality standard urotherapy. Vasconcelos et al. found that the group receiving adjunctive biofeedback did not achieve greater continence rates at the end of the study, although more patients achieved earlier dryness. Furthermore, the post void residual volumes were significantly reduced in the biofeedback group compared to the standard urotherapy group.

Recently, Richardson et al. found that biofeedback techniques were successfully used in the treatment of giggle incontinence. The children were taught to identify the external sphincter muscles and to recruit them more rapidly and forcefully to decrease incontinence.

5.1.1.3 Neuromodulation

Neuromodulation has been used to treat a variety of lower urinary tract symptoms in adults. The use of transcutaneous electrical nerve stimulation (TENS) of the S3 region with surface electrodes made this technique also more applicable in children.

Transcutaneous and percutaneous neuromodulation delivered over either the sacral outflow or peroneal region of the ankle at a frequency between 10-25 Hz, has proven (level of evidence is low) a useful adjunctive treatment in children with a lower urinary tract symptoms.

Recent studies indicate that sacral neuromodulation is effective in children with severe dysfunctional elimination syndrome refractory to maximum medical treatment.

Bower et al. illustrated that home application of TENS in children is successfully feasible in children.

The neuromodulation technique is based on the principle that electrical current directly affects the central nervous system by artificially activating neural structures, facilitating both neural plasticity and normative afferent and efferent activity of the lower urinary tract.

Electrical stimulation of S3 activates the pelvic floor and modulates innervation of the bladder, sphincter and pelvic floor, restoring the balance and coordination of sacral reflexes. Changes in urodynamic parameters during stimulation have been reported with TENS, suggesting that this therapy is useful for inhibiting detrusor contractions.
The reported changes with neuromodulation include: significantly increased bladder capacity, decreased severity of urgency, improved continence, and decreased frequency of urinary tract infections. Significant improvement in urodynamic parameters of bladder compliance, number of uninhibited contractions, and bladder volume at first detrusor contraction have also been noted.[258]

These studies however were non prospective and uncontrolled and have low level of evidence.

Hagstroem S. et al were the first to perform a prospective randomized placebo controlled study on the effect of TENS for refractory daytime urinary urge incontinence in children. In this rather small population, 27 patients, they found TENS to be superior to placebo (sham treatment) for refractory daytime incontinence in children with overactive bladder. The effect does not seem to be the result of improved bladder capacity but might be related to improved sensory mechanisms.[259]

Intravesical stimulation can be used in underactive detrusor in which it can lead to a potentially improvement of the detrusor contractility and enhancement of bladder emptying.[260]

Recently reports on successful sacral nerve stimulation with implantable electrodes in children have been published.[253-255] The authors consider this treatment in children with severe dysfunctional elimination syndrome refractory to maximum medical treatment.

In summary, there is an adjunctive role for the use of neuromodulation in children with LUTS. However larger, controlled and randomized studies on neuromodulation in children are necessary.

5.1.1.4 Alarm treatment
The use of alarm therapy has been well documented in children suffering enuresis, but has rarely been used for the treatment of urinary incontinence during the day.

Halliday et al. reported of a randomized clinical trial comparing a contingent alarm which sounded when the child was wetting, with a noncontingent alarm that sounded at intermittent intervals to remind the child to void.[261] Therapy was considered to be successful when the patients remained without daytime wetting for 6 consecutive weeks. With the non-contingent alarm the success rate was 68% and 80% in the contingent group, which was not significant different. Twenty three percent of those who responded to treatment relapsed up to two years after completion of the trial.

Hvistendahl et al. found in contrast with a previous study from the same group that the use of an alarm system during the night in enuretic children increased significantly the maximal voided volume during the day.[262,263]
In our retrospective study we reviewed the files of 63 children, treated with a daytime alarm for therapy-resistant urinary incontinence during the day. All patients had a proven overactive detrusor. They were treated with the alarm for a fortnight. At a follow-up of 12 months 35% were successfully treated, 33% had a partial success and in 32% treatment failed.\[264\]

Recently the use of a daytime alarm has been advocated as an effective option for toilet training young healthy children. According to the authors it offers parents and day-care providers clear guidelines and limits the time to complete toilet training in many children.\[265, 266\]

5.1.2. Pharmacological treatment

5.1.2.1 Antimuscarinic treatment

Parasympathetic mediated, acetylcholine-induced stimulation of post-ganglionic muscarinic receptors on detrusor smooth muscle is involved in both normal and involuntary detrusor contraction. The latter causing bladder overactivity. Muscarinic receptors are heterogeneous in nature and widely distributed throughout the body. Five molecular distinct subtypes are known to be exist (M1-M5), and tissues may contain a number of different subtypes. M2 and M3 receptors are the main muscarinic receptors involved in bladder control.\[267\] The M2 receptor is the predominant subtype in the bladder (80% of the total muscarinic receptor population), but mediation of bladder contraction by the minor population of M3 is well reported.\[268, 269\]

Stimulation of M3 receptors by acetylcholine leads to phosphoinositol hydrolysis, and ultimately to accumulation of intracellular calcium and smooth muscle contraction. Activation of M2 receptors leads to inhibition of adenylate cyclase. This is thought to cause smooth muscle contraction by indirect inhibition of sympathetically (β-adrenoreceptor)-mediated augmentation of cyclic adenosine monophosphate (cAMP) levels and bladder relaxation. During micturition, it has therefore been suggested that activation of M3 receptors by acetylcholine evokes direct smooth muscle contraction, while stimulation of M2 receptors reverses sympathetically mediated smooth muscle relaxation.\[267\]

Anticholinergic agents are substances that block the neurotransmitter acetylcholine in the central and peripheral nervous system. They are administered to reduce the effects by acetylcholine on acetylcholine receptors in neurons through competitive inhibition.

Antimuscarinic agents may not only interfere with the postjunctional effects of acetylcholine on the detrusor, but also with acetylcholine release from parasympathetic nerves. Presynaptic muscarinic receptors have been identified in various tissues, including the bladder. Activation of these receptors facilitates (M1) or inhibits (M2/M4) the release of acetylcholine, according to the frequency of nerve stimulation. It is thought that activation of the presynaptic facilitating M1 receptor may serve as an
amplification mechanism during micturation, when intense parasympathetic activity occurs. In contrast, the inhibitory M2/M4 receptors appear to be preferentially activated at low frequencies of nerve stimulation.\[267\]

Antimuscarinic agents might block acetylcholine binding at more than one muscarinic receptor subtype. Furthermore, receptor-selective agents might block muscarinic receptors outside the bladder and cause adverse effects. Blockade of M3 receptors in the salivary gland, lower bowel and ciliary smooth muscle are the most frequently reported, associated with dry mouth, constipation and blurred vision.\[270\]

Currently, oxybutinin IR and oxybutinin ER are the only antimuscarinics approved by the FDA for the treatment of overactive bladder symptoms in children. Therefore oxybutinin is the most widely used pharmacological therapy in children with detrusor overactivity. The recommended daily dose is 0.3 mg/kg body weight.

Dry mouth through reduced saliva production is the most commonly reported adverse effect of antimuscarinic therapy. The incidence of dry mouth in patients taking oxybutinin IR was 17-97%, oxybutinin ER 23-68% and transdermal oxybutinin 4-39%.\[270\] It doesn’t only cause discomfort for the patient but it also induces tooth decay.\[271\] Transdermal oxybutinin circumvents “first-pass” metabolism and results in lower concentrations of the active metabolite N-desethoxybutinin, a metabolite that has a greater affinity than oxybutinin for muscarinic receptors in the parotid gland and might contribute to dry mouth.\[272\]

Constipation is generally the second most common adverse effect. It is reported in 4-50% of the patients receiving oxybutinin IR and in 1-21% of those on transdermal Oxybutinin.\[270\]

Constipation might cause or exacerbate urinary symptoms.

Abnormal vision was found in 3-24% of the patients taking oxybutinin IR and 18% of those using transdermal oxybutinin.\[270\]

As oxybutinin crosses the blood brain barrier it may cause CNS effects, such as psychological and personality changes.

Facial flushing, heat stroke, tachycardia, drowsiness and headache are other well known adverse effects of antimuscarinic drugs. The frequent occurrence of side effects causes up to 10% of the children using oxybutinin to stop treatment.\[271\] A study by Jonville et al. reported that side effects with oxybutinin occur 4 times more frequently in children than in adults.\[273\]

Oxybutinin ER utilizes a novel delivery system, which results in absorption in the large intestine, thereby bypassing the first pass metabolism in the liver. This leads to a
decrease in the amount of active metabolite, which is produced in the liver, resulting in a more favourable tolerability profile. Another way to avoid the first pass effect is intravesical therapy. As there is a need for catheterization it should be reserved for the treatment of the neuropathic bladder. Several studies illustrated that intravesical administration of oxybutinin doesn’t decrease the adverse events, resulting in 25% of the patients stopping therapy.

There are only a few studies, none randomized and double blinded, assessing the efficacy of oxybutinin in detrusor overactivity in children. Some other data do even suggest that oxybutinin is no more effective than non-pharmacologic therapy in increasing bladder capacity in monosymptomatic enuretic children.

In some countries the antimuscarinic agent with additional calcium channel-modulating properties, propiverine is approved for use in children. The recommended daily dose is 0.8mg/kg body weight. Marschall-Kehrel et al. studied in a multicenter placebo-controlled double-blind study the efficacy of propiverine for the treatment of overactive bladder in children aged 5-10 years. The trial demonstrated significant superiority of propiverine over placebo and good tolerability. Madersbacher et al. studied the effect of propiverine versus oxybutinin for treating neurogenic detrusor overactivity in children and adolescents. They found propiverine to be at least as effective as oxybutinin, but distinctly better tolerated. The overall clinical effectiveness was found to be better for propiverine.

Currently some new antimuscarinics have been introduced for the treatment of detrusor overactivity in adults. Not one of them has been approved for use in children.

Tolterodine is a so called “bladder selective” antimuscarinic agent designed specifically for use in detrusor overactivity. The chemical nature of tolterodine makes it less likely to penetrate the blood brain barrier, which is supported by EEG studies. The safety, efficacy and dosing of tolterodine in the adult population have been extensively studied in controlled clinical trials and reported. These results demonstrated that tolterodine at a dosage of 2mg twice daily has a favourable pharmacological profile reflected by equal effectiveness but significantly fewer side-effects than oxybutinin.

As adverse effects are one of the main reasons to discontinue a treatment with oxybutinin in children, new “bladder selective” antimuscarinic agents may become important alternatives in future.

Goessl et al. published the first study of tolterodine in children. They reported tolterodine to be equally effective and better tolerated than the standard drug oxybutinin chloride in children with detrusor hyperreflexia.
Christoph et al. studied a paediatric population treated with tolterodine because of neurogenic detrusor overactive for five years. The data of this study demonstrated the efficacy and tolerability over a long follow-up period.

Munding et al. retrospectively reviewed their experience with 30 patients treated with tolterodine at adult doses, for a primary diagnosis of dysfunctional voiding. Wetting episode were cured in 33%, improved in 40% and failed to show improvement in 27%. Side effects were reported in 13.3%. They concluded that tolterodine can be safely and effectively used in children at an adult dose.

The study by Bolduc et al. demonstrated that tolterodine is well tolerated by children. In the group of patients who couldn't tolerate oxybutinin, 78% were able to continue tolterodine treatment with no significant side-effects.

Hjalmas et al performed an open, unrandomized, dose-escalating study to determine the safety, efficacy and pharmacokinetics of tolterodine in children with overactive bladder. They found a dose-response for adverse events. There were more adverse events and more severe events at 2mg than at the 0.5mg and 1mg dosages. Furthermore, adverse events possibly related to the drug only became prevalent with the 2 mg dosage. These results, coupled with the lack of differences in efficacy between 1 mg and 2 mg dosages, and that the AUC of active moiety of the 1 mg dosage in children aged 5-10 years was comparable to the 2 mg dosage in adults, supported the use of 1mg twice daily as the preferred dosage for children.

Raes et al. preformed a retrospective analysis of efficacy and tolerability of tolterodine in 256 children with video-urodynamically proven overactive bladder. The results suggested that tolterodine is well tolerated and offers effective treatment for urinary symptoms due to overactive bladder. It is superior to non-selective antimuscarinic drugs, with respect to adverse events, allowing more compliance and more effective treatment.

Reinberg et al. compared therapeutic efficacy of extended release oxybutinin chloride, and immediate release and long acting tolterodine in children with diurnal urinary incontinence. They found extended release oxybutinin and long acting tolterodine being more effective than immediate release tolterodine in decreasing diurnal urinary incontinence. Extended release oxybutinin chloride is more effective than either immediate or long acting tolterodine for control of daytime urinary incontinence and urinary frequency.

More recent studies in children with neurogenic detrusor overactivity reported that tolterodine extended release and tolterodine instant release were as effective and well tolerated. The instant release formulation was found to be more effective in terms of urodynamic parameters. The extended release formulation is less expensive and has
the advantage of a single dose. Long-term treatment with extended release tolterodine was found to be well tolerated by children.

5.1.2.2 **Botulinum toxin**

Botulinum toxin (BTX) is a potent neurotoxin that inhibits acetylcholine release at the presynaptic cholinergic junction, inducing muscle relaxation. It is produced by Clostridium botulinum, a gram-positive anaerobic bacterium. Six additional strains of botulinum producing neurotoxins have been identified. Several subtypes of botulinum toxin exist, identified as "A" through "G".

A and B are commercially available. A as Dysport® (Ipsen) and Botox® (Allergan), B as Myobloc® (Elan Pharmaceuticals). A has been FDA approved for the treatment of strabismus, blepharospasm, disorders of the 7th nerve, cervical dystonia and moderate to severe frown lines. B has been FDA approved for the treatment of cervical dystonia. Up to now botulinum toxin has not been FDA approved for therapeutic use in urology.

In spite of this BTX-A toxin is used in adult urology to treat neurogenic detrusor overactivity, chronic urinary retention, detrusor-sphincter dyssynergia, non-neurogenic detrusor overactivity and chronic prostatic pain.

In children BTX-A toxin has been mainly used to treat urinary incontinence in children with a neurogenic bladder.

In vivo, type A appears to be the most potent subtype with the longest duration of action as an injection.

Botulinum neurotoxin interferes with presynaptic release of acetylcholine from nerve endings and interrupts neuromuscular transmission. It cleaves the synaptosomal-associated protein with a molecular weight of 25kD (SAP-25) in addition, it exerts a blocking action on the parasympathetic nervous system and may inhibit other neurotransmitters, such as noradrenalin, dopamine, serotonin, g-amino-butyrate, glycine and peptide methionine-enkephaline, glutamate, substance P, calcitonin gene-related peptide or affect transmission of afferent neuronal impulses.

There is increasing evidence that BTX has an antinociceptive effect separate from its neuromuscular action, which may explain its efficacy in reducing urgency.

Recent research has focussed on the function of the myofibroblast cell in the suburotheleum and its relation to the mechanism of action of botulinum toxin. It is proposed that the myofibroblasts show functional similarity to the interstitial cells of Cajal in the gastrointestinal tract, and may also be arranged within a plexus that acts as a sensory organ in the suburothelium.
The effect is temporary and most of the recovery of neuromuscular function is due to the recovery of the “mother” neuron and not from the sprout “touchdown”. Contrary to reports on striated muscles, axonal sprouting within the detrusor is very limited after BTX-injections, indicating pathophysiological different reactions to the toxin between striated and smooth muscles. Eventually, regeneration of the original neuromuscular junction takes place.\[305\] No changes in the ultrastructure of the detrusor have been found after BTX-A injection.\[306\]

In the bladder, the action of BTX-A at presynaptic cholinergic junction induces detrusor muscle relaxation, and potentially affects afferent sensory receptors in the urothelium.\[307\]

Only a few studies documented the use of BTX in children. Investigators administered doses varying between 5 and 12 U/kg body weight (similar to doses used in the I.M. treatment of cerebral palsy) with a total dose of 50-360U Botox, reflecting a higher dose/kg body weight than is used in adults.\[300, 308-310\] The number of injection sides was 20-50 which is similar to adult protocols. It is not known whether submucosal injection or restricting the injection to the detrusor muscle is more efficacious.

Based on mounting evidence that BTX-A may also affect sensory nerves, investigators have advocated injecting the trigone or the suburothelial space. No evidence of new or worsening of pre-existing vesico-ureteric reflux was found following trigonal injections.\[311\]

The maximum benefits are reached within 2-6 weeks of injection.\[300, 301, 312\]

The results last about 6-9 months and there is now evidence of its maintained efficacy with repeated injections.\[65, 301, 312, 313\]

BTX-A treatments are well tolerated. Most studies reported no systemic adverse effects after treatment with Botox. Urinary retention (5%) and the need for CIC in up to 16% of patients with detrusor overactivity were reported.\[301\] Muscle weakness was not reported in any of the studies in children.\[312\]

There is no study that assesses the impact of repeated injections on the bladder wall, and on the risk of fibrosis and of bladder compliance alteration in time.\[312\]

BTX-A antibodies can develop after injection of BTX-A for urologic disorders. These antibodies may cause therapy failure.\[314\] To minimise the small risk of BTX resistance, most investigators currently recommend waiting at least 3 months between treatments, avoiding the use of booster injections and using the smallest dose that achieves the desired clinical effect.\[315\]
Until now botulinum toxin A has been used mainly in the treatment of children with neurogenic detrusor overactivity, mainly due to myelomeningocele. Considerable improvements in urinary continence, maximal cystometric capacity, Pdetmax, bladder compliance and incidence of urinary tract infections were reported as well as resolution of vesico-ureteral reflux. [300, 308, 311, 312, 316-322]

In his review article, Xavier Gamé, illustrated the efficacy of BTX-A in children with neurogenic detrusor overactivity. The mean reduction from baseline of urinary incontinence score varied between 40 and 80%. Between 65% and 87% of patients became completely continent, between CICs, after Botox treatment.[312]

According to the use of botulinum toxin A as a treatment of idiopathic detrusor overactivity in children there’s only our own publication on 21 patients illustrating the successful treatment in 70% of the patients.[310]

External urethral sphincter injections can be used to treat dysfunctional voiding in children. Only 3 full studies and 1 case report have been published about this topic, demonstrating improvement of the maximum flow-rate, post-void residual and leak-point pressure. [300, 323-325]

5.1.2.3 Alpha blockers

In the genitourinary system, alpha-adrenergic receptors are predominantly located in the bladder outlet and detrusor body, with their stimulation resulting in contraction of the outlet and increased bladder tone.

Alpha-receptors have been found to modulate voiding function at the level of the parasympathetic ganglia, resulting in decreased bladder compliance and increased detrusor instability.

Central nervous system micturitional pathways are under alpha-adrenergic modulation with alpha stimulation causing bladder contractions.

Alpha-adrenergic receptors are present in the bladder urothelium with stimulation increasing the release of nitric oxide. Elevated intravesical nitric oxide concentrations results in increased urinary frequency, urinary urgency, and sense of incomplete bladder emptying.

Anatomic outlet obstructions and/or neurologic injury will result in alterations of the supratrigonal alpha-adrenergic receptors in both receptor subtype and density. There is also evidence that reorganization of the CNS alpha-adrenergic regulation of bladder activity also occurs. These changes result in increased alpha-adrenergic responsiveness to neural stimulation and directly correlate with a decrease in detrusor compliance and increased detrusor instability.
Due to these findings, alpha blockers are no longer believed to relieve lower urinary tract symptoms by an effect directed strictly at the bladder outlet. Alpha-blockers will help relieve irritative bladder symptoms by its action on the receptors in the bladder urothelium (by decreasing sensation to void and feeling of incomplete bladder emptying), parasympathetic ganglia (by inhibiting detrusor contractility, improving bladder compliance, increasing bladder capacity), and central nerve system (by inhibiting detrusor contractility, increased bladder capacity, delaying voiding intervals).

The use of alpha-adrenergic antagonists in paediatric urology is still in progress.

Austin et al. were the first to report the successful use of a selective alpha-1-blocker, doxazosin, in the treatment of children with neuropathic and nonneuropathic voiding difficulties and OAB.[327]

Kramer et al. performed a double-blind placebo controlled study to determine whether the alpha-adrenergic antagonist doxazosin could be used as primary therapy in children with voiding dysfunction. Compared to placebo, doxazosin did not demonstrate a significant objective benefit. A significant subjective benefit, improvement of the patient’s dysfunctional voiding symptom score and of the parent’s perception that the children had improved urinary continence, was found.[328]

According to this results, alpha blockers are of little, if any use as primary therapeutic agent in the treatment of voiding dysfunction.[326]

Yucel et al. illustrated with a randomized study that alpha antagonist therapy as secondary therapy for recalcitrant voiding dysfunction is a viable alternative to biofeedback techniques.[329] Cain et al. stated that it can be used as a replacement or in addition to biofeedback.[330]

Donohoe et al. found alpha-adrenergic antagonists to be a clinically effective therapy for primary bladder neck dysfunction in children.[331]

Selective alpha blocker therapy appears to be effective for improving bladder emptying in children with an overactive bladder, wetting, recurrent infections and increased post voiding residual urine. Several studies demonstrated symptomatic relief in more than 50% of the patients receiving a selective alpha-blocker.[332-334]

Doxazosin (starting dose 0.5mg/day, maximum at 4mg/day), tamsulosin (starting dose 0.2mg/day, maximum at 0.8 mg/day) and terazosin (starting dose 0.5mg daily increasing up to 5mg/day) are the three most common alpha antagonists used in children at present. The safety and efficacy of tamsulosin and terazosin have not been established in children.[326-329, 331, 335]
Irrespective of the type of alpha-antagonist used, the medication is best tolerated if given at night. This will reduce greatly the symptoms of hypotension and asthenia (fatigue and muscle weakness) that can be noticed with morning ingestion of the medication.\cite{326,334}

Major side effects (i.e. postural hypotension, syncope or palpitations) of alpha-blockers have not been reported in children. Donohoe et al. found that 75% of their patients receiving terazosin or doxazosin had mostly central nervous system side effects such as mild degrees of headache, somnolence and nausea.\cite{331} VanderBrink et al. studied the effect of tamsulosin on systemic blood pressure. No patient experienced a clinically significant alteration in systemic blood pressure.\cite{334} At present it seems that selective alpha-adrenergic blockers can be used safely in children.

5.2. **Treatment of nocturnal enuresis in children**

5.2.1. **Non pharmacological treatment**

5.2.1.1 **Enuresis alarm**

Alarm therapy is the most effective treatment option of monosymptomatic nocturnal enuresis.\cite{113,336} It is more effective than any other form of treatment, and lasting cure rate appears to be twice as high.\cite{337,338}

A meta-analyses by Butler et al. showed success rates across all studies ranging from 30% to 87%.\cite{339} The average success rate is nearly 68% with efficacy increasing with the duration of therapy. Intervention with an alarm is associated with a nine time less likelihood of relapse than antidiuretic therapy. Relapse rates in the 6 months following treatment are between 15 and 30%. Meta-analysis showed a 43% lasting cure rate.\cite{65,337,340} Success rate is influenced by the type of enuresis, the treatment duration and the success criteria adopted.

The exact mechanisms for alarm therapy are not known. The effects are not due to classical conditioning as stimulus awakening occurs after and not before wetting. Instead it is an operant type of behavioural approach, i.e. a learning program with positive reinforcement that includes aversive elements.

Dryness is achieved either by waking up, leading to nocturia in 35% of the children or by sleeping through the night with a full bladder in 65%.

Body worn alarms are as effective as bedside alarms\cite{339}

The best results occur in optimal motivated children and parents. Lack of concern shown by the child, lack of supervision, inconsistent use, technical failures, family stress, abnormal scores on behaviour checklists, psychiatric disorders of the child, failure to awaken in response to the alarm, unsatisfactory housing conditions and more than one wetting episode per night are negative predictive factors of a successful treatment.
with the alarm. The more frequent the wet nights a week the better the results of the
treatment and the lower the relapse rate. Treatment shouldn’t be considered to be
ineffective before 6 to 8 weeks of treatment.

Relapse after successful treatment occurs in 42% of the children. Intensified
treatment, involving the consumption of large quantities of fluid during the evening to
provoke enuresis after primary success has been achieved, may reduce this risk.

Several studies showed that the nocturnal bladder capacity, but also the maximum
voided volume and the mean day-time voided volume in enuretic children with an
initially small bladder, increased significantly during alarm treatment. This
possible explains why some children, after successful alarm treatment, are able to sleep
dry without nocturia. Normalization of the bladder capacity doesn’t lead to complete
dryness in all enuretic children. A higher nocturnal urine production on nocturia
nights explains why some children have nocturia and others do not.

Despite the fact that the enuresis alarm is clearly the most effective treatment option
in monosymptomatic nocturnal enuresis, it remains rather unpopular in patients
and physicians because of the demanding preconditions for successful treatment,
i.e. lengthy instructions, high compliance needed, close co-operation among family
members, and the slow onset of action of this treatment.

In an attempt to increase the success rate of the enuresis alarm, alarm therapy has been
combined with dry bed training and arousal training. The dry bed training incorporates
the enuresis alarm, cleanliness training and specific waking schedules. Arousal
training entails reinforcing appropriate behaviour, i.e. waking and toileting, in response
to alarm triggering.

High success rates and low drop out have been reported for both methods.

Bollard et al. found that the enuresis alarm accounted for most of the success achieved
through dry bed training.

Van Kampen et al. introduced the full-spectrum therapy for nocturnal enuresis. It
consists of enuresis alarm, bladder training, motivational therapy and pelvic floor muscle
training. The initial success rate was 87%. The relapse rate during the first year was 50%,
and after one year 16%. In a current study they showed that pelvic floor muscle exercise
has no beneficial effect in the treatment of children with enuresis.

5.2.1.2 Acupuncture
Several studies illustrated the efficacy of acupuncture in the treatment of nocturnal
enuresis. Bower et al. performed a meta-analysis of 11 studies. All the trials were of
low methodological quality. The review provided tentative evidence for the efficacy
of acupuncture for the treatment of nocturnal enuresis. The study by Serel et al.
concerned a fairly large population of 50 patients suffering primary persistent nocturnal enuresis. Within 6 months 86% of the patients were completely dry, which is a rather spectacular result.[358] This positive effect may be due to the increased nocturnal bladder capacity.[359]

In line with traditional acupuncture, electro-acupuncture and laser-acupuncture have been advocated for enuresis.[360-362] The study by Radmayr et al., a prospective randomized trial using laser acupuncture versus Desmopressin in the treatment of nocturnal enuresis in children with a proven normal voiding pattern and a high nighttime urine production, illustrated both treatments to be as efficacious.[361]

5.2.2. Pharmacological treatment

5.2.2.1 Desmopressin

Desmopressin acetate (dDAVP) is a synthetic analogue of arginine vasopressin (AVP). AVP, also known as antidiuretic hormone (ADH), is produced in the hypothalamus and released from the pituitary gland, principally in response to hyperosmolality or a low effective circulating blood volume. Vasopressin receptors have been identified in the kidney, liver, brain, pituitary gland, aortic smooth muscle and on platelets. These receptors are divided into three subtypes: V1, V2 and V3. AVP acts on V2 receptors in the collecting ducts and distal tubules to enhance water reabsorption. By virtue of its V1 receptor agonistic properties, AVP is also a potent vasoconstrictor.

Desmopressin (or dDAVP) is an analogue of vasopressin created by removing an amino group from the cysteine molecule in position 1 and substituting D-arginine for L-arginine at position 8. These structural modifications result in significant increase in antidiuretic activity (2000-3000 times superior to that of AVP), extended half-life (1.5-3.5 hours) and markedly diminished vasopressor and smooth muscle activity.[65]

Since the late seventies dDAVP was found to be successful in the treatment of enuresis.[363]

The use of dDAVP in the treatment of nocturnal enuresis increased markedly in most parts of the world since Norgaard et al. demonstrated that a significant proportion of children with monosymptomatic nocturnal enuresis lack the normal circadian rhythm of AVP, producing large quantities of dilute urine at night.[118, 364] Subsequently the WHO has supported dDAVP as the prime medication for use in enuresis therapy. Desmopressin is the only pharmacological treatment given a level 1, grade A recommendation for use in primary nocturnal enuresis by the ICI and ICCS.[365] In Europe and the United States the drug has been approved for intranasal, sublingual and oral administration in the treatment of enuresis.

Desmopressin is easy to administer and the clinical effects appear almost immediately. The usual dose is 0.2-0.4mg orally, 120-240μg for the melt formulation or 20-40
micrograms intranasal at least one hour before bedtime, as the mean maximum plasma concentration is reached within 1 hour of administration.\textsuperscript{[366]}

The intranasal form is no longer recommended for nocturnal enuresis in many places around the world, because of the increased risk for accidental overdosage and inherent risk for water intoxication.\textsuperscript{[65]}

It can be orally administrated as a tablet or as a melt formula. The latter consists of a freeze-dried structure that disintegrates instantaneously into the saliva and then is swallowed.\textsuperscript{[367]}

The bioavailability of the melt formulation is approximately 60% greater than that observed for the tablet formulation.

Lottmann et al. found a statistically significant preference for desmopressin melt in children aged 5-11 years. Compared with the tablet, the Melt formulation requires no intake of water and is associated with higher compliance. Meanwhile, it retains similar levels of efficacy and safety at lower dosing levels than the tablet. Significantly, desmopressin Melt was well accepted by all ages, and facilitates the early initiation of treatment in children with primary nocturnal enuresis.\textsuperscript{[368]}

The efficacy of desmopressin in the treatment of enuresis is well documented. Success rate varying from 25 to 70% have been published. A Cochrane analysis confirmed desmopressin rapidly reducing the number of wet nights per week, but there was some evidence that this was not sustained after treatment was stopped.\textsuperscript{[369]}

With long-term treatment, between 50-80% of patients showed a decrease of at least 50% in wet nights over 6-12 months and 40-70% became almost completely dry.\textsuperscript{[370, 371]} Cure rate in most studies was higher, up to 30%, than the annual spontaneous cure rate of approximately 15%.\textsuperscript{[371-373]}

The efficacy of desmopressin may not be maintained on discontinuing treatment. Recurrence of symptoms after cessation of therapy varies between 50 and 95%.\textsuperscript{[374]} This is especially true after short-term treatment, while long-term treatment yields cure rates up to 71%.\textsuperscript{[370, 375]}

If desmopressin treatment is successful, a one-week interruption is recommended every 3 months to see if the problem has been cured.\textsuperscript{[372]}

Marschall-Kehrel et al. illustrated that structured desmopressin withdrawal improves response and treatment outcome in children with monosymptomatic enuresis. They compared abrupt termination and structural withdrawal, leaving the dose constant and increasing daily treatment intervals to every second evening for 2 weeks, twice weekly for 2 weeks and once weekly for 2 weeks. The abrupt termination group had a 51%
response whereas the structured withdrawal group had a 72% response. According to the authors this might be due to the fact that structured withdrawal of desmopressin stimulates maturation of the innate production of antidiuretic hormones. On the other hand it also supports the idea that desmopressin might have more than one centre of action, and also works in the central nervous system.[376]

Treatment with desmopressin is generally well tolerated, even during long term treatment (≥ 1 year), and side effects are rare, provided that the patient does not consume large amounts of liquids while taking the drug. Reported side effects are generally described as mild and include headache, abdominal pain, nausea, nasal congestion, rhinitis and epistaxis. Hyponatremia with convulsions or unconsciousness, resulting from water retention due to the potent antidiuretic effect, is the single most concerning potential adverse effect of desmopressin.[377] Two review studies, investigating the risk of desmopressin-associated hyponatremia, showed that the occurrence of water intoxication during desmopressin treatment is rare and that most of these cases were secondary to excessive fluid intake or other conditions (e.g. cystic fibrosis) contributing to this complication.[377, 378] Dehoorne et al. illustrated that a prolonged desmopressin bioactivity may increase the risk of water intoxication. [379] The incidence of mild asymptomatic hyponatremia is reported to be 1-10% in short term trials and around 1% in long-term treatment trials.[377, 380, 381] The over-all incidence of adverse effects in long-term clinical trials is low (0.8-5%).[370, 371]

The risk of hyponatremia can be minimised by starting the treatment at the lowest dose, counselling the patients regarding evening fluid restriction (stop fluid intake one hour before bedtime until the next morning) and potential warning signs of hyponatremia (headache, nausea, vomiting, weight gain and in severe cases convulsions).

Studies showed that some patients do have a delayed, a partial or an absent response to desmopressin.[370]

Clinical experience in partial responders showed that increasing the dose may lead to higher response rates.[382]

Nocturnal bladder instability, increased nocturnal osmotic excretion, intermittent inadequate desmopressin bioavailability, and a disorder in circadian rhythm of renal glomerular and/or tubular functions have been mentioned as causal factors for desmopressin resistant nocturnal enuresis. [120, 121, 383-386]

5.2.2.2 Antimuscarinic treatment
In those children who have nocturnal enuresis due to detrusor overactivity during the night, and certainly in those with combined nocturnal enuresis and diurnal incontinence, treatment with antimuscarinic drugs should be considered.[387-389]
Evidence however is low on the value of antimuscarinics in becoming dry. In a Cochrane review no evidence was found that oxybutinin was more effective than placebo in the treatment of nocturnal enuresis.\[390\]

5.2.2.3 **Tricyclic antidepressants**

Tricyclic drugs act on the central nervous system by blocking the synaptic alpha-receptors' re-uptake of noradrenalin and serotonin into the neurons, thus prolonging their effects due to an accumulation and increased availability of neurotransmitter substance at the postsynaptic membrane. Other pharmacological effects are an anticholinergic effect in the central and peripheral nervous system, and a direct decrease in smooth muscle contractile activity.\[391\]

Their usual clinical use is as antidepressants.

Imipramine also has a vasopressin independent antidiuretic effect due to increased alpha-adrenergic stimulation in the proximal tubules with a secondary increased urea and water reabsorption more distally in the nephron.\[391\]

Tricyclic antidepressants, such as imipramine, amitriptyline, nortriptyline and clomipramine, as well as some drugs related to tricyclics (viloxazine, desipramine, mianserin and maprotiline) have been used in the treatment of nocturnal enuresis.

A Cochrane review of 58 randomized trials that included 3721 children concluded that both imipramine and other tricyclic medications have been proved effective in reducing bed-wetting.\[392\] Treatment with tricyclic agents, as compared with placebo, reduced bed-wetting by about 1 wet night per week. About a fifth of the children became dry. The lasting cure rate was only 17 percent, which restricts the use of these drugs.\[393\]

However, owing to the unfavourable adverse event profile, which includes association with mood changes and sleep disturbances, and the risk of death with an over dosage, due to the potential cardiotoxic side effects, the ICCS recommends that imipramine be used only when all therapies have failed.\[393, 394\]

Reboxitine, a novel selective norepinephrine reuptake inhibitor, with a minimal affinity to the reuptake serotonin site, without an effect on the dopamine reuptake, and a minimal affinity to the adrenergic (alpha 1) and muscarinic (M1) receptors, has been effectively used as a non-cardiotoxic alternative to imipramine in the treatment of nocturnal enuresis.\[395-397\]

5.2.2.4 **Inhibitors of prostaglandin synthesis**

In some patients nocturnal polyuria is due to an increase in nocturnal excretion of sodium.\[386, 398-401\] High urinary prostaglandin E2 levels found in these children point toward a role for increased prostaglandin synthesis in the pathogenesis of enuresis-
related polyuria. In those cases prostaglandin synthesis inhibitors, such as diclofenac and indomethacin, proved to be effective. Prostaglandin synthesis inhibitors possess antinatriuretic, antidiuretic and bladder relaxing properties.

A Cochrane analysis showed indomethacin and diclofenac to be better than placebo. Compared to desmopressin, indomethacin was less effective.

Although no adverse effects were reported with the use of prostaglandin synthesis inhibitors in children with enuresis, careful use of these drugs is necessary because of their side effects such as gastrointestinal toxicity and acute renal failure.

5.2.2.5 Combination therapy

The two most commonly combined therapies are the enuresis alarm and desmopressin. It was found to be more effective than alarm treatment alone.

Antimuscarinic drugs combined with desmopressin have been used successfully in cases of limited response to desmopressin.
Chapter 6  Objectives of this thesis and background of the research performed at our centre.

The literature review in part 1 clearly demonstrates the complexity of urinary incontinence and nocturnal enuresis.

A lot of children referred to a tertiary urinary incontinence centre suffer day and night urinary incontinence. Even in children referred with so called refractory monosymptomatic enuresis, thorough examination often reveals a combination of day and night problems.\([196]\)

This is even more the case in children with an intellectual and/or physical disability.

In our treatment philosophy we first deal with the daytime problem, and secondarily focus on nocturnal enuresis.

Up till to date, in “normally developed” children suffering urinary incontinence, the therapeutical approach consists of urotherapy whether or not combined with biofeedback and/or antimuscarinics. The latter are still recommended as first choice treatment of overactive bladder.

As illustrated in part 1 a lot of supplementary therapeutical options have been studied in literature. Our own group illustrated the value of transcutaneous and percutaneous nerve stimulation in the treatment of urinary incontinence.\([249, 251]\)

This large variation of treatment modalities, often with low evidence, illustrates that a real successful golden standard therapy for urinary incontinence doesn’t exist.

As mentioned antimuscarinics are of major importance in the treatment of overactive bladder. At start of our research for this thesis, oxybutinin was the only antimuscarinic drug, FDA approved to be used in children. The level of evidence of the studies with oxybutinin is rather low.

One of the major concerns using oxybutinin is the numerous side effects reported in literature. Moreover, the results of oxybutinin are often deceiving.

Because of these restrictions there is an ongoing search for more selective, more potent, more effective and safer anti-muscarinics in adults. Unfortunately there is rather no interest from industry for the urinary incontinent paediatric population. This prompted us, tertiary paediatric incontinence centres, to use this “adult” medication off label in our paediatric patients.
Based on the promising results of the use of, a so called “bladder selective”, extensively studied anti-muscarinic, tolterodine in adults and the sparse studies in children we evaluated the efficacy and the tolerability of tolterodine in a non-selected paediatric population.

The results of this retrospective analysis of efficacy and tolerability were promising. Further studies considered tolterodine to be safe in children, but efficacy results were rather disappointing. [297]

Tolterodine was certainly not the solution for all our patients. From our experience with the use of tolterodine we found that some children are not treated sufficiently, probably due to a faster metabolisation of drugs in children than in adults or because of changed pharmacokinetics when tablets were broken.

Some remained refractory urinary incontinent despite adequate followed therapy. Others failed because of low compliance.

Based on our experience with tolterodine we started to use off label another new potent, selective anti-muscarinic, once daily oral agent: solifenacin succinate. We reviewed the charts of children with therapy resistant overactive bladder treated with solifenacin. The results of this retrospective study are very promising according to efficacy and tolerability.

As mentioned before the use of antimuscarinics, even the more bladder selective, is sometimes deceiving because of side effects and ineffectiveness. Therefore we started to look for non-antimuscarinic alternatives.

Botulinum-A toxin had already been used successfully as treatment of neurogenic and idiopathic detrusor overactivity in adults, and of neurogenic bladder in children.

The main advantage of a treatment with Botulinum-A toxin is that the results of a single treatment last for about 6-9 months independent of the patients’ compliance. There are three main disadvantages of the use of Botulinum-A toxin in children: 1. it is invasive as complete anaesthesia is required, 2. the exact dose is still unknown and 3. the long term safety has never been proven. Because of these disadvantages Botulinum-A toxin can, in our opinion, only be used as a treatment of refractory, therapy resistant urinary incontinence in children. Therefore we started a prospective, uncontrolled pilot study to evaluate the tolerability and effectiveness of Botulinum-A toxin in children with therapy resistant overactive bladder. The results of this study illustrated Botulinum-A toxin to be a valid alternative in the treatment of overactive detrusor in children.

In some cases of refractory, therapy resistant daytime incontinence, medication is insufficient, not well tolerated or simply fails. In some patients parents do refuse the use of further medication. Many of these children are no longer aware that incontinence
happens and wet pants are simply ignored. We wondered if a cognitive training with a daytime alarm could increase their awareness and as such could offer a supplementary solution in some of these cases. In a retrospective study we reviewed the files of 63 children suffering refractory daytime incontinence. We found a full response in 35% of the patients and a partial response in another 35%, which is certainly encouraging considering that all of them were “hard core day-wetters”.

Another group suffering refractory urinary incontinence, rarely studied, are the intellectually and physically disabled children. Urinary incontinence is often thought to be a minor, inevitable, untreatable and even unimportant part of their often complex pathology.

The majority of studies in these children were performed on small, very heterogeneous populations. Therefore results are often inconclusive.

We first set up a prospective pilot study to look for pathophysiologic factors, such as dysfunctional voiding, reduced maximum voided volume and restricted fluid intake. This study illustrated the importance of restricted fluid intake.

In a more recent study we prospectively evaluated the importance of adequate fluid intake in the treatment of urinary incontinence in these children. It turned out to be a very important factor.

In some of these children urotherapy alone will be insufficient to treat the urinary incontinence. Overactive detrusor is also in this population an important causal factor.

Children with an intellectual and/or physical disability often show behavioural problems, reduced concentration and hyperactivity. Also the incidence of constipation and faecal incontinence is higher than in “normal” children. This means that these patients are more prone to the side effects of anti-muscarinics, and that the advantages of the use of more selective anti-muscarinics are even more important.

Even the use of Botulinum-A toxin and the daytime alarm might offer therapeutical perspectives in this population. To our knowledge no studies on these topics have been performed yet.

As mentioned many of our patients do not only suffer diurnal incontinence but also have nocturnal enuresis. Once the daytime problem is nearly completely solved, our attention has to be focussed on the nighttime problem.

Also enuresis is very complex in origin. This, sometimes underestimated, heterogeneity is certainly one of the most important reasons for the large number of different treatment options described in literature.
This thesis is part of a full research line on pathogenesis, pathophysiology and treatment of urinary incontinence and nocturnal enuresis.

Our group performed studies on genetics \(^{[151]}\), treatment of monosymptomatic enuresis\(^{[17, 113, 367]}\), and desmopressin resistant nocturnal polyuria.\(^{[116, 120, 121, 123, 384]}\)

We also studied the irrefutable importance of co morbidity factors, such as ADHD and psychological disturbances, in nocturnal enuresis and urinary incontinence.\(^{[146, 161, 162, 164, 166, 167, 410-414]}\)

Non-monosymptomatic nocturnal enuresis and urinary incontinence in children is less evidence based documented in literature. Hoebeke et al. illustrated the importance of bladder dysfunction in children with NMNE and urinary incontinence.\(^{[84]}\)

Our group performed several studies on urotherapy \(^{[231]}\) and especially pelvic floor therapy in the treatment of dysfunctional voiding.\(^{[84, 233, 415-417]}\)
Retrospective Analysis of Efficacy and Tolerability of Tolterodine in Children with Overactive Bladder

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In this paper the efficacy and tolerability of tolterodine in children with an overactive bladder is evaluated.

The results of this retrospective study suggest tolterodine to be a well tolerated and effective treatment for urinary symptoms due to overactive bladder.
Retrospective Analysis of Efficacy and Tolerability of Tolterodine in Children with Overactive Bladder

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Abstract

Objective: To evaluate the efficacy and tolerability of tolterodine in children with an overactive bladder, treated in a single incontinence centre.

Materials and methods: A retrospective analysis of a database of a total of two hundred and fifty-six patients (175 boys and 81 girls, age range 3 years to 17 years, mean age 8.33 years) with urodynamically confirmed bladder overactivity was performed. All children received tolterodine tartrate (dose range of 0.5–4 mg orally). In group I (n = 205) tolterodine tartrate replaced anticholinergic drugs (AC) (oxybutinin chloride or oxyphencyclimine hydrochloride). A subgroup of patients switched because of intolerance due to serious adverse events (60.4%) or because of lack of improvement in micturition variables (39.6%). In group II tolterodine was prescribed as initial therapy (n = 51). Tolerability was assessed by a standardised questionnaire on adverse events at every outdoor clinic visit. Efficacy assessment was based on micturition diary variables, mean change of maximum bladder capacity and number of incontinence episodes/24 h.

Results: The mean treatment time was 9.32 months with a range from 1.5 months to 23.4 months. The final dose was 0.1 mg/kg orally daily divided into two doses. In group I central nervous system disorders (81%) were the most common adverse events, 26.2% showed flushing, 12.2% accommodation problems and 25.2% had gastrointestinal complaints (constipation, encopresis, abdominal pain). Withdrawal of the non-selective antimuscarinic drug resulted in total recovery from adverse events.

Introduction of tolterodine in group I and II caused no serious adverse events. Nine patients (3.5%) reported side-effects and only two discontinued treatment. There were no reports of flushing, troubles of visual accommodation, hyperpyrexia. In group I we observed a mean decrease in urgency by 38.7%, a mean increase in maximal bladder capacity by 33.6% and the number of incontinence episodes decreased by 64.8%. In group II we observed equivalent values with a significant (p < 0.001) change in maximal bladder capacity (49.7%), incontinence episodes (64.8%) and micturition episodes/24 h.

Conclusions: The results of this retrospective analysis suggest that tolterodine is well tolerated in children and offers an effective treatment for urinary symptoms due to overactive bladder. Tolterodine is superior to non-selective antimuscarinic drugs, with respect to adverse events, allowing more compliance and more effective treatment in children.

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Keywords: Tolterodine; Overactive bladder; Antimuscarinic drugs; Children; Tolerability; Efficacy

1. Introduction

Detrusor hyperactivity in childhood is a common phenomenon and these children may suffer day- and nighttime wetting, urinary tract infections and
associated vesicoureteral reflux [1–3]. Treatment options for children with symptoms of overactive bladder range from simple behavioural measures such as bladder training and biofeedback techniques through medical treatment with drugs [5,6]. Among the drugs used for the treatment of the overactive bladder, antimuscarinic agents are still regarded as first-line therapy. Since 1972 oxybutinin chloride (OC) is the reference standard antimuscarinic [4]. This type of drug is effective, but its use is limited by systemic adverse events, in a significant proportion of children, which may result in poor compliance or even discontinuation of treatment. Tolterodine is a potent antimuscarinic agent specifically developed for the treatment of urinary incontinence and other symptoms related to the overactive bladder. The safety, efficacy and dosing of tolterodine in the adult population have been extensively studied in controlled clinical trials and reported [7–11]. These results demonstrated that tolterodine at a dosage of 2 mg twice daily has a favourable pharmacological profile reflected by equal effectiveness but significantly fewer side-effects than OC. To date, only three reports are published about the use of tolterodine in children. Goessl et al. published the first study of tolterodine in children with detrusor hyperreflexia and demonstrated that the drug improved the bladder compliance in these children [13]. Munding et al. showed that tolterodine may be efficacious in 30 children with dysfunctional voiding to reduce wetting episodes without severe adverse effects [12]. Hjalmars published pharmacokinetic data [14]. However the published data are always on a limited number of selected patients, with a short-term follow-up. Specific information regarding the response to use of tolterodine in a non-selected population of children with overactive bladder remains sparse. The aim of our study was to evaluate the efficacy and the tolerability of tolterodine in a non-selected paediatric population through a retrospective analysis of the files. The ethical committee at the University Hospital of Ghent approved this study.

2. Materials and methods

All the files of children treated with tolterodine at the University Hospital of Ghent between November 1999 and August 2001 were analysed. At least 6 weeks follow-up was required for inclusion. Patients with a neuropathic bladder, anatomical abnormality of the lower urinary tract and recurrent urinary tract infections were excluded. 256 files were identified. All patients had evidence for an overactive bladder. The majority presented with symptoms of nocturnal enuresis associated with daytime wetting, frequency, urgency and/or small bladder volume. At our institution all the patients undergo a standardised initial evaluation, which includes a complete clinical history, clinical examination, urine analysis, ultrasound of the kidney, bladder and residual volume, uroflowmetry and micturition diary. If there is evidence for a small bladder, without abnormal uroflow and/or residual urine, anticholinergics are the treatment of choice. In the case of a completely failing urodynamic investigation and treatment and instructions on drinking and voiding. Because tolterodine is not yet registered in children, it is still not the first-choice therapy and we do not prescribe the drug without documentation of the underlying bladder dysfunction, which is often overactive bladder had been confirmed by videocystomanometry in 237 patients. The other 19 children showed symptoms (urge, frequency) suggesting unstable bladder and received anticholinergic treatment without urodynamic investigation.

Before starting tolterodine, patients and parents were informed that the drug was not registered for children in Belgium and that international available data are limited. The patients were started on a regimen of tolterodine in a dose range from 0.5 to 2 mg. In group IA oxybutinin hydrochloride or oxyphencyclimmin hydrochloride was replaced by tolterodine due to adverse events and in group IB tolterodine was introduced due to completely failing to respond to treatment. In group II tolterodine was started as initial therapy when a risk to develop side-effects was suspected. Most of these patients had a clinical history of behavioural disorders (hyperactivity or attention disorders). When only partial improvement was noted, the dose of tolterodine was gradually increased to a total of 3 or 4 mg/day. The children who received concurrent biofeedback training continued with this therapy. Patients’ follow-up consisted of standardised evaluation at the outdoor clinic every six weeks, with registration of the data on maximal bladder capacity, voiding chart variables, a questionnaire on adverse events due to antimuscarinic treatment and subjective symptoms. In addition, uroflowmetry was performed at every visit, consequently followed by ultrasoundographic assessment of residual volume and collection of these data in the file. All adverse events regarding the intensity, seriousness and therapeutic interventions were recorded.

Medical records are then used to collect data on their demographic data, primary diagnosis, previous treatments, compliance with the medications, side-effects and voiding variables on the tolterodine treatment. Efficacy assessment was based on micturition diaries collected by the patient at each visit. Efficacy was measured by comparing the values at the end of the follow-up period to baseline. Efficacy measures included the number of micturitions/24 h, the number of incontinence episodes/24 h, urgency and the mean change of maximum bladder capacity. Efficacy was also evaluated through patients’ perception of their bladder condition. Tolerability was assessed from adverse events through an explicit questionnaire about adverse effects. Adverse events were classified as mild, moderate or severe with respect to therapeutic intervention. Appropriate parametric statistical methods were used for analysis, and significance was set at the 5% level.

3. Results

A total of 256 patients (175 boys and 81 girls; age range of 3 years to 17 years; mean age 8.33 years) were included for data analysis. The follow-up ranged from 6 weeks to 23.4 months with a mean of 9.32 months. We excluded 3 files from further analysis due to inadequate follow-up in 2, and subsequent anatomical abnormality in 1.

Patients were divided in two groups.
Group I consisted of 205 children (142 boys and 63 girls) between 4.1 years and 18.1 years of age (mean age of 8.4 years), previously treated with an anticholinergic medication (oxybutinin hydrochloride or oxyphencyclimin hydrochloride) but switched to tolterodine because of significant adverse events (subgroup A) or lack of improvement in micturition variables (subgroup B) during anticholinergic therapy. All patients had previously been treated with anticholinergics for a minimum of 6 months. Hundred and eight patients received concomitant biofeedback training, which was continued during this episode. In forty-six patients desmopressin (10–20 µg intranasal) was associated.

Group II consisted of 51 children between 3.1 years and 6.9 years (mean age 6.6) who had received no anticholinergic medication before the initiation of tolterodine treatment, but almost all children had a clinical history of ADHD. Analysis of baseline demographics, disease characterization, micturition charts and urodynamic variables revealed no significant differences between the two groups. The dose of tolterodine ranged from 0.5 mg to 4 mg, but the final dose used was approximately 0.1 mg/kg orally, divided into two gifts.

For both groups we observed a significant increase \( (p < 0.001) \) in maximal bladder capacity. In group I we found a mean change of 57 ml (33.6%) of maximal bladder capacity from baseline value, without difference between the two subgroups. The second group showed a greater increase in maximal bladder capacity (mean of 73 ml (49.7%)) (Fig. 1).

There was a progressive decrease in the mean frequency of micturitions in both groups. The treatment with tolterodine reduced the mean daily micturition episodes with 0.3 (subgroup A) and 0.89 (subgroup B) in group I. For the second group there was a significant reduction \( (p < 0.001) \) with a mean daily reduction of 1.1 micturition episodes (Fig. 2). In total 215 had diurnal incontinence episodes at baseline. These patients showed significant decrease from baseline in both groups. The mean daily incontinence episodes were reduced by 64.8% \( (n = 2.3) \). In group I, 50% of the patients reached diurnal continence and 27.4% had a 50% reduction in wetting episodes, with no statistically difference between the subgroups. Those patients who were completely continent with OC remained so under tolterodine. In group II, 54% reached diurnal continence and 24% had a 50% reduction in wetting episodes. For the variable, urgency we observed a reduction with 38.7% in the first group and of 28.9% in the second group (Fig. 2).

Concerning the variable, residual urinary volume, we observed a decrease of residual volume to normalisation in 35 of 48 patients previously treated with antimuscarinic drugs. Serious adverse events during treatment with tolterodine were not reported. During treatment with oxybutinin and oxyphencyclimin hydrochloride central nervous system disorders (81%) were the most common adverse events (cognitive impairment, headache, behavioural abnormalities), 26.2% showed flushing, 12.2% had abnormal accommodation and 25.2% had gastrointestinal complaints (constipation, soiling, diarrhoea). Withdrawal of the non-selective antimuscarinic drug resulted in total recovery from adverse events and introduction of tolterodine caused no serious adverse events. Only 1 patient suffered from behavioural disorder (aggressiveness) and 2 had mild

![Fig. 1. Mean change from baseline in maximal bladder capacity and residual volume under treatment with tolterodine in group I (■) and group II (□).](image1)

![Fig. 2. Mean (± S.D.) change from baseline in number of micturitions, incontinence episodes and urge/24 h during treatment with tolterodine in group I (■) and group II (□).](image2)
gastrointestinal complaints. In the whole treatment group we observed 3 patients with behavioural disorders (1 attack of fear, 1 trouble with concentration, 1 aggressiveness) and 6 with mild gastro-intestinal complaints (1 soiling, 2 diarrhoea and 3 mild complaints), leading to treatment withdrawal in only two. There were no reports of flushing, hyperpyrexia, abnormal accommodation, or dry mouth. Three patients withdrew the tolterodine treatment due to the high price.

4. Discussion

Our data support that tolterodine might offer an interesting and safe therapeutic alternative in children with an overactive bladder. Antimuscarinic drugs are generally regarded as the standard therapy for symptoms attributable to bladder overactivity. However their utility is often limited by their adverse effects (dry mouth, flushing, central nervous dysfunctions). Tolterodine, a new potent and selective antimuscarinic drug was specifically developed for the treatment of detrusor hyperactivity. Until now, controlled studies of tolterodine are only available for adults and tolterodine has been shown to be equally effective and to result in significantly fewer adverse effects than oxybutinin. However paediatric experience with tolterodine is limited. Munding et al. reported that tolterodine in conjunction with behavioural modifications can improve incontinence due to dysfunctional voiding to reduce wetting episodes without severe adverse events in children. Our data are the largest published for the paediatric population until now. Despite limitations, this study has several advantages. Limitations are not only because it is a retrospective study, but also because there is no control-group nor randomisation and some patients have combined therapies. We are aware of an ongoing large multi-centre prospective double-blind randomised study with tolterodine (extended release) in children. However high risk patients (hyperkinetic children, patients with history of severe side-effects on anticholinergic drugs, children with history of urinary tract infections, residual urine and/or abnormal uroflow) might be excluded, resulting in a highly selected population. Association with other therapies such as bladder volume training, psychological coaching, pelvic floor relaxation therapy as treatment for uroflow abnormalities and/or residual urine, and the introduction of DDAVP and/or alarm therapy once daytime continence is achieved, is not allowed in this prospective study. We, among others, do believe that monotherapy results only in an extremely poor success rate in this study population, resulting in full day- and nighttime continence in only 10–25% at 1 year of therapy, with important negative psychological effects on the child, and very high drop-out rates during therapy.

Therefore we are convinced that there is definitely need for data in a non-selected, probably high risk population, but this kind of studies will probably never be performed in a prospective randomised way. Such data can only be obtained from retrospective data of patients with compassionate use of this drug.

In our analysis we stratified results for children previously treated with a non-selective antimuscarinic drug (divided in a group who had prior adverse events and a group without adequate improvement on therapy) and children who had no prior therapy. Introduction of tolterodine resulted in a significant difference of the micturition variables in both groups. We observed a marked increase in bladder capacity and a significant decrease in other micturition variables: number of micturitions/24 h, number of incontinence episodes/24 h, compared with baseline values for both groups without statistical differences between the groups. In only 4 children we observed a worsening of the incontinence. It could be argued that the high response in the first group reflect a selection bias, as improvement on previous anticholinergics failed due to reduction of the dose or poor compliance. However comparing the results from the patients previously treated with antimuscarinic drugs and those without prior therapy, we were not able to detect a significant difference. Association with pelvic floor therapy could be an explanation for this observation. Therefore analysis of both groups, for treatment with tolterodine alone and for combination therapy of tolterodine and pelvic floor therapy, was performed and data showed no significant difference. The improvement was equally divided between the two groups. Although this study is a retrospective analysis, these results show that tolterodine has therapeutic efficacy in children with an overactive bladder of different ages, comparable with other anticholinergic drugs. This confirms the results of Munding and Goessl and findings in adults, in whom controlled studies tolterodine is an effective treatment in patients with an overactive bladder and is equally potent as the reference drug oxybutinin chloride. Goessl et al. showed that one of 22 patients suffered from a side-effect, transient flushing. In the study by Munding et al. 4 of 24 children had mild side-effects. Our study was designed to evaluate the tolerability of tolterodine and to compare it with other antimuscarinic drugs. The most frequent side-effects under treatment with oxybutinin are central nervous disorders and gastrointestinal complaints. In a total of 256 patients...
we observed only 9 patients with side-effects (3 behavioural disorders, 6 gastrointestinal complaints). None of the children had dry mouth, flushing or abnormal accommodation. The side-effects were not gender- or age-related. From the 122 patients who had been switched to tolterodine due to adverse events on previous treatment only 3 showed mild side-effects and one discontinued due to inadequate improvement. These results demonstrate an excellent tolerability of tolterodine in children. Tolterodine is better tolerated than oxybutinin, particularly with respect to the frequency and intensity of side-effects, behavioural disorders, accommodation abnormalities and other side-effects. It is envisioned that the comparable efficacy and significantly better tolerability would manifest itself in improved quality of life for children treated with tolterodine and allows more children to remain on effective therapy than the current most commonly prescribed agent for the treatment of the overactive bladder [15].

5. Conclusions

These findings suggest that tolterodine offers a safe and effective therapy for children with an overactive bladder. Tolterodine enables children to continue treatment with a minimum of adverse effects, resulting in improved compliance and more effective therapy than the standard therapy. A tolterodine dose of 1–2 mg twice daily combined favourable efficacy and tolerability in this retrospective analysis. Further evaluation of this medication in controlled trials in children is necessary to confirm both parameters.

References

**Publication 2**

**Solifenacin for Therapy Resistant Overactive Bladder**

Piet Hoebeke, Jan De Pooter, Karel De Caestecker, Ann Raes, Joke Dehoorne, Erik Van Laecke, Johan Vande Walle


Solifenacin, as a once daily oral agent, was used in therapy resistant children with overactive bladder.

An uncontrolled, retrospective study was performed in 138 children suffering therapy resistant overactive bladder.

The results according to efficacy and side effects are given in this paper.
Solifenacin for Therapy Resistant Overactive Bladder

Piet Hoebeke,* Jan De Pooter, Karel De Caestecker, Ann Raes, Joke Dehoorne, Erik Van Laecke and Johan Vande Walle

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Abbreviations and Acronyms

EN = nocturnal enuresis
ID = diurnal incontinence
OAB = overactive bladder

Purpose: With the availability of the once daily oral antimuscarinic agent solifenacin (5 mg), we started to use it for therapy resistant overactive bladder. We evaluate side effects and efficacy.

Material and Methods: We reviewed the charts of children treated with solifenacin succinate between August 2005 and August 2008 for therapy resistant OAB. Incontinence was compared at study entry and study end.

Results: During the study period 84 boys and 54 girls with a mean age of 9 years 2 months received solifenacin. Mean follow-up was 22.59 months. While on solifenacin, side effects were observed in 9 of 138 patients (6.5%). Efficacy evaluation included only 99 patients after 3 months of therapy. Mean voided volume after treatment was 253.5 ml, showing a significant 25% increase compared to the mean value before therapy (50.5 vs 203.0 ml, p < 0.01). Of the patients 84 (85%) were considered responders, including 45 who were completely dry (full response) and 39 who had fewer nocturnal enuresis or diurnal incontinence symptoms (partial response). Of these 39 patients 17 became dry during the day, 1 became dry during the night and 21 had more than a 50% decrease in nocturnal enuresis and diurnal incontinence symptoms. In 15 patients the outcome was unchanged or worse (no response).

Conclusion: In this group of children with OAB we noted favorable results with solifenacin with few side effects. Despite the uncontrolled, retrospective study design the effect is attributable to solifenacin intake.

Key Words: urinary bladder, overactive; anticholinergics; urinary incontinence; nocturnal enuresis; drug resistance

Children with idiopathic OAB are initially treated with urotherapy, a nonsurgical, nonpharmacological treatment consisting of lower urinary tract rehabilitation using drinking and voiding charts, lifestyle changes and some specific interventions such as physiotherapy, neurostimulation and alarm therapy.¹ When urotherapy fails, antimuscarinic drugs can be used. Oxybutynin is the only antimuscarinic drug licensed for use in the pediatric age group. Tolterodine, a newer antimuscarinic drug, has been tested in children and was considered safe but efficacy results were disappointing.² Newer antimuscarinic drugs, such as solifenacin, darifenacin and fesoterodine, have not been evaluated in children. In nonresponding children some of these treatments are off label options.

Solifenacin succinate, a once daily oral antimuscarinic agent developed for OAB, significantly decreased urgency episodes in a pooled analysis of 4 pivotal trials in more than 2,800 adults.³ The side effect profile of this drug with a high affinity for the M3 muscarinic receptor is much more favorable than that of some unsp-
specific antimuscarinics. Since we treat so many children with OAB who do not respond to therapy and due to the availability of solifenacin succinate (5 mg), we started to use it in children. Because solifenacin is not licensed for use in children this was off label use, for which parental consent was obtained. The hospital ethical committee approved this study. We retrospectively evaluated the side effects and efficacy of solifenacin succinate in children with idiopathic OAB.

PATIENTS AND METHODS

We reviewed the charts of children treated with solifenacin succinate for therapy resistant OAB between August 2005 and August 2008. The Appendix shows the data that were collected, entered into an Excel® database and subsequently analyzed. Preceding antimuscarinic therapy was stopped 4 weeks before the start of solifenacin. All patients were included in the side effect evaluation. For efficacy evaluation only patients who received the drug for at least 3 months were included. Patients with neurogenic bladder were excluded from this analysis. Efficacy was measured based on incontinence during the day and/or night, and by measuring voided volume. Incontinence and voided volume at study entry were compared to incontinence and voided volume at study end. Treatment outcome definitions used were those proposed by the International Children’s Continence Society, including nonresponse—0% to 49% decrease, partial response—50% to 89% decrease, response—90% or greater decrease and full response—100% decrease in incontinence or less than 1 incontinence incident monthly. The paired Student t test was used for statistical analysis.

RESULTS

During the study period 84 boys and 54 girls with a mean age of 9 years 2 months (range 4.50 to 16.59) were identified who received solifenacin. Mean followup was 22.59 months. Mean therapy duration was 6.61 months (range 0.40 to 27.93). Patients were divided into 3 study groups by incontinence pattern, including group 1—86 with EN and ID, group 2—30 with ID without EN and group 3—17 with monosymptomatic EN. Three patients with neuropathic bladder were excluded from the efficacy evaluation. No patients were dry before starting solifenacin. Mean voided volume at study entry in the whole study group was 201.4 ml. No patient had post-void residual urine after voiding at study entry.

The main indication for study inclusion was nonresponse to previous treatment. All patients had been previously treated for OAB for more than 24 months. Treatment consisted of standard therapy—behavior therapy, bladder training, physiotherapy and medical therapy. All study patients underwent videourodynamics in the period before the study. In all patients detrusor overactivity was observed during filling. Six patients had recurrence after former successful anticholinergic therapy and 16 changed to solifenacin because of side effects on other anticholinergic therapy. The solifenacin dose was 5 mg.

Side Effects

Of the patients 108 received another anticholinergic before starting solifenacin, of whom 42 (39%) experienced side effects due to that therapy. On solifenacin side effects were observed in 9 of 138 patients (6.5%), including behavior problems (hyperactivity) in 2, drowsiness in 1, insomnia in 1 and gastrointestinal problems in 5, that is constipation (3), gastrointestinal pain (1) and fecal impaction (1). Five of these 9 patients reported side effects during previous anticholinergic therapy. Except for fecal impaction the side effects were considered mild. In 5 patients solifenacin was discontinued because of adverse effects. No patient had post-void residual urine while on treatment.

Efficacy

Overall study group. Efficacy evaluation was performed in 99 of 138 patients. Of the patients 14 were lost to followup, 17 could not be evaluated due to less than 3 months of therapy, 5 stopped treatment because of adverse effects and 3 diagnosed with neuropathic bladder were excluded from efficacy evaluation. Of the 84 patients (85%) considered responders, 45 were completely dry (full response) and 39 had fewer symptoms of EN or ID (partial response). Of the 39 patients 17 became dry during the day, 1 became dry during the night and 21 had more than a 50% decrease in ID and EN symptoms. In 12 patients the outcome was unchanged and in 3 the outcome was worse (no response) (fig. 1). Mean voided volume after treatment was 253.5 ml, representing a significant 25% increase compared to the mean value before therapy (50.5 vs 203.0 ml, p <0.01, fig. 2). The response was observed after 1 month at followup visit 1. Most responders reported improvement after 1 week of treatment.

Group 1 (ID + EN). Efficacy evaluation was performed in 63 of 88 patients. Eight patients were lost to followup, 14 could not be evaluated due to less than 3 months of therapy and 3 stopped therapy due to side effects. Of the patients 53 (84%) were considered responders, of whom 24 became completely dry (full response) and 29 had fewer EN or ID symptoms (partial response). Of the 29 patients 17 became dry during the day, 1 became dry during the night and 11 had more than a 50% decrease in ID and EN symptoms. In 7 patients the outcome was unchanged and in 3 the outcome...
was worse (no response) (fig. 3). Mean voided volume after treatment was 233.6 ml, representing a significant 21% increase compared to the mean value before therapy (40.2 vs 193.4 ml, p <0.01, fig. 2).

**Group 2 (ID).** Efficacy evaluation was performed in 21 of 30 patients. Five patients were lost to followup, 2 could not be evaluated due to less than 3 months of therapy and 2 stopped therapy due to side effects. Of the patients 19 (90%) were considered responders, of whom 14 became completely dry (full responder) and 5 had fewer EN or ID symptoms (partial response). In 2 patients the outcome was unchanged (no response) (fig. 4, A). Mean voided volume after treatment was 297.1 ml, representing a significant 29% increase compared to the mean value before therapy (65.9 vs 231.2 ml, p <0.01, fig. 2).

**Group 3 (EN).** Efficacy evaluation was performed in 15 of 17 patients. One patient was lost to followup and 1 could not be evaluated due to less than 3 months of therapy. Of the patients 12 (80%) were considered responders, of whom 7 became completely dry (full response) and 5 had fewer EN or ID symptoms (partial response). In 3 patients the outcome was unchanged (no response) (fig. 4, B). Mean voided volume after treatment was 283.3 ml, representing a 39% increase compared to the mean value before therapy (79.8 vs 235.1 ml, p <0.01, fig. 2).

**Group comparison.** We compared mean voided volume in all study groups. The increase in voided volume is expressed as the percent of voided vol-
volume before therapy (table 1 and fig. 2). The EN group had the highest increase (32%). We also compared response rates in the different groups (table 2).

**DISCUSSION**

OAB may lead to a disturbed detrusor filling phase, characterized by urgency, frequency and at times urge incontinence. Girls present with OAB symptoms more often than boys. In addition to urinary symptoms, children with OAB may also have recurrent urinary tract infections and constipation. Antimuscarinic therapy remains a common OAB therapy. Its use is based on the concept that parasympathetic mediated stimulation of muscarinic receptors in the bladder causes detrusor overactivity, which is responsible for OAB symptoms. Antimuscarinic agents increase bladder capacity and bladder compliance, and decrease detrusor contractions in cases of neurogenic detrusor overactivity. Detrusor overactivity is believed to have a role in many children with functional incontinence, vesicoureteral reflux and urinary tract infections.

Despite the frequent use of anticholinergic therapy the outcome of medical therapy for OAB in children is unpredictable and inconsistent, and few randomized studies have assessed drug safety and efficacy. Currently the most widely used pharmacological therapy in children with detrusor overactivity is oxybutynin. Historically oxybutynin has been limited by its adverse effect profile with side effects such as dry mouth, constipation and central nervous system effects. The incidence of side effects seems to be dose related for oral and intravesical administration. The central nervous system effects are related to the ability of oxybutynin to cross the blood-brain barrier. Newer, more selective anticholinergic drugs are currently available for use in adults. Due to higher specific receptor affinity (predominantly M3) these drugs are associated with a lower side effect rate.

We retrospectively evaluated the effect of 5 mg solifenacin succinate for OAB in children. Its side effect profile is excellent. Children who received previous anticholinergic treatment can be considered their own control group for side effect evaluation. While 39% of the children had side effects on other anticholinergics only 6.5% had side effects on solifenacin. Five of the 9 patients with side effects on solifenacin also had side effects on

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<th>Table 1. Voided volume</th>
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<td>ID + EN</td>
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* p <0.01.

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the previous anticholinergic therapy, which could indicate that side effects were related to the patients. Some patients are likely to have higher sensitivity to anticholinergic side effects than others. This is only clinical safety based on side effects. To our knowledge no pharmacokinetic or dose finding studies have been performed so that to date we can only report clinical safety and not pharmacokinetic or pharmacodynamic profiles. With the new safety regulations for drugs in children in the United States and Europe pharmacokinetic studies are needed before registration.

Solifenacin seems to be effective for OAB symptoms with an overall 85% response rate and a full response in more than 50% of responders. Specifically the effect on daytime incontinence seems to be more pronounced than the effect on nighttime incontinence. Due to the significant increase in voided volume this effect was to be expected. However, in our study the highest increase in voided volume was seen in the EN group and the highest response rate was seen in the ID group. The response in children with EN depends less on voided volume since many of them need further alarm treatment to become dry at night even when voided volume is normalized.

The study limitation is its uncontrolled, retrospective design. Since this series was initially designed as a prospective, observational study of the effects of an off label drug, it was decided at the start of the study to have no control group. Due to the off label availability of these new drugs this is the only way to investigate their use in children.

CONCLUSIONS
In this group of children with OAB we report favorable results with solifenacin. Despite the uncontrolled, retrospective study design the effect is attributable to solifenacin intake. However, since no pharmacokinetic or pharmacodynamic data were obtained on this study group, we should be careful when promoting this treatment. Only after prospective, controlled studies with pharmacokinetic and pharmacodynamic data may the drug be used. Until then off label application with informed consent is the only way to use it.

APPENDIX
Data From Charts

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<th>Patient identification</th>
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<td>Symptoms at entry</td>
<td>Voided volume after solifenacin therapy (ml)</td>
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<td>Treatment with other anticholinergics before (yes/no)</td>
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REFERENCES
The Effect of Botulinum-A Toxin in Incontinent Children with Therapy Resistant Overactive Detrusor.

P. Hoebeke, K. De Caestecker, J. Vande Walle, J. Dehoorne, P. Verleyen, E. Van Laecke


In this paper the results of the first prospective study with botulinum-A toxin in a paediatric population of therapy resistant children with a nonneurogenic overactive bladder are illustrated.

Botulinum-A toxin injection in this population is a safe, excellent treatment adjunct, leading to long-term results in 70% after 1 injection.
The Effect of Botulinum-A Toxin in Incontinent Children With Therapy Resistant Overactive Detrusor

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Purpose: We determined the effect of detrusor injection of botulinum-A toxin in a cohort of children with therapy resistant nonneurogenic detrusor overactivity. This prospective study included therapy resistant children with overactive bladder.

Material and Methods: During the study period of 19 months 10 boys and 11 girls were included. All patients showed decreased bladder capacity for age, urge and urge incontinence. Main treatment duration before inclusion was 45 months. A dose of 100 U botulinum-A toxin (Botox®) was injected in the detrusor.

Results: Side effects were evaluated in all 21 included patients. The side effects reported were 10-day temporary urinary retention in 1 girl and signs of vesicoureteral reflux with flank pain during voiding in 1 boy, which disappeared spontaneously after 2 weeks. No further examinations were done since the boy refused. Two girls experienced 1 episode each of symptomatic lower urinary tract infection. Eight girls and 7 boys with a minimum followup of 6 months represent the study group for long-term evaluation. In this study group after 1 injection 9 patients showed full response (no more urge and dry during the day) with a mean increase in bladder capacity from 167 to 271 ml (p <0.001). Three patients showed a partial response (50% decrease in urge and incontinence) and 3 remained unchanged. Eight of the 9 full responders were still cured after 12 months, while 1 of the initially successfully treated patients had relapse after 8 months. The 3 partial responders and the patient with relapse underwent a second injection with a full response in the former full responder and in 1 partial responder.

Conclusions: Botulinum-A toxin injection in children with nonneurogenic overactive detrusor is an excellent treatment adjunct, leading to long-term results in 70% after 1 injection.

Key Words: bladder; urinary incontinence; botulinum toxin type A; muscle, smooth; child

Botulinum-A toxin is a potent neurotoxin that blocks neuronal acetylcholine secretion by binding to pre-synaptic nerve endings. Intramuscular injection of botulinum-A toxin blocks the neuromuscular junction at the site of injection until new presynaptic nerve sprouts occur. Initially used to treat striated muscle overactivity, increasing data in the literature are available on its effectiveness for acetylcholine stimulated smooth muscle overactivity, as in the lower urinary tract.

Botulinum-A toxin is used in adult urology to treat neuromuscular overactivity in the bladder. Chronic overactivity and chronic prostatic pain. Recent studies show high short-term effectiveness for idiopathic detrusor overactivity in adults. In children it has been safely used to treat strabismus, muscular hypertonia due to cerebral palsy and neurogenic detrusor overactivity in those with myelomeningocele. Due to the high prevalence of overactive detrusor in the pediatric population, the known effect on overactivity in adults and safety in a pediatric population we designed a prospective study. We report the results of what is to our knowledge the first experience with botulinum-A toxin in a pediatric population with nonneurogenic overactive bladder.

MATERIALS AND METHODS

A prospective protocol was designed for the use of botulinum-A toxin in children with urodynamically proven detrusor overactivity without overt neuropathy or uropathy. Urodynamics considered for inclusion had to be performed within 2 months before inclusion. Methods conform to the standards and recommendations for urodynamic studies of the International Continence Society. Children who had previously been treated without success were considered for inclusion. Children with dysfunctional voiding or post-void residual urine were excluded. The study was approved by the ethics committee of the Ghent University Hospital. Subjects and their parents provided informed consent.

Treatment was done with the patient under general anesthesia. A dose of 100 U botulinum-A toxin (Botox®) was diluted in 15 ml normal saline. Under cystoscopic guidance the detrusor was injected at 15 sites with 1 ml injected per site. A 3.7Fr Deflux® injection needle was used. Injection was started above the superior edge of the trigone and a line of 5 injections was given with each injection 1 cm apart. Two more lines 1 cm cranial from the former line were injected subsequently. The ventral bladder wall was avoided due to its close relationship with the peritoneal cavity. After injection the bladder was emptied. After spontaneous voiding the patient was sent home.
The intent was to repeat urodynamics after injection. However, we encountered strong patient and parent obstruction. Most patients had undergone urodynamics during former treatments and just before study inclusion. Especially when the result was favorable, they refused followup urodynamics. Therefore, we excluded this from the protocol and considered a less invasive evaluation.

Patients were seen after 1 week for uroflowmetry and post-void residual urine measurement. After 6 weeks patients were seen for clinical evaluation. A voiding diary was supposed to be kept for a few days. Six and 12 months after injection they were reevaluated. At each visit they were questioned about side effects and the effects of treatment.

Outcome was measured by measuring bladder capacity and documenting urge and urge incontinence in the voiding diary. Nighttime continence was not used as an outcome measure. We called the result a complete response when no more daytime symptoms (urge and urge incontinence) were observed. A 50% decrease in urge and urge incontinence was called a partial response. No clinical improvement was termed failure. Functional bladder capacity was documented and evaluated. However, it was not used as an outcome measure.

RESULTS

During a study period of 19 months starting May 2003, 10 girls and 11 boys were included. Mean age at study inclusion was 10.8 years (range 8 to 14). Based on voiding diaries all patients showed decreased bladder capacity for age, urge and urge incontinence before inclusion. All patients experienced nighttime incontinence. Constipation was seen in 7 patients.

The diagnosis was overactive bladder in all cases. None of the patients showed dysfunctional voiding. The diagnosis was confirmed by urodynamics before treatment. None of the patients showed post-void residual urine.

Main treatment duration before inclusion was 45 months. Former treatment consisted of capacity training with antispasmodics or anticholinergics and urotherapy. All included children had been treated without success at the voiding school, which is a 2-week in-hospital bladder training.

A dose of 100 U botulinum-A toxin (Botox®) was injected in the detrusor with the patient under general anesthesia. The side effects reported were 10-day temporary urinary retention in 1 girl, temporary vesicoureteral reflux in 1 boy and lower urinary tract infection in 2 girls. No other side effects were seen.

Eight girls and 7 boys with a minimum followup of 6 months formed the study group for long-term evaluation. After 1 injection 9 patients showed a full response (no more urge and dry during the day) with a mean increase in bladder capacity from 167 to 271 ml (61%) (p < 0.001). Three patients showed a partial response (decreased urge and incontinence) and 3 remained unchanged. Eight of the 9 full responders were still cured after 12 months. One patient had relapse after 8 months.

The 3 partial responders and the patient with relapse underwent a second injection with a full response in the former full responder and in 1 partial responder. No further response was observed in 2 partial responders.

On postoperative uroflowmetry no differences were seen except voided volume in most patients. Three girls and 1 boy had temporary dysfunctional characteristics on postoperative uroflowmetry. In 1 of these girls post-void ultrasound showed significant residual urine (greater than 50% of capacity). Minimal post-void residual urine (less than 5% of detrusor capacity) was seen in another 4 patients. After 6 weeks all patients voided to completion.

DISCUSSION

To our knowledge we report the first experience with botulinum-A toxin in a pediatric population with nonneurogenic detrusor overactivity. The first difference in the current data compared to results in the literature is the longer duration of the effect. In studies in adults it has been shown that the effect of botulinum-A toxin injection is temporary. In the current study a long-term effect of more than 12 months was seen in 8 of 15 patients. Former reports of use in children with neurogenic bladder demonstrate an effect that lasted 10 months.4,46 Perhaps the fact that the treatment was used for a disorder that is an expression of a maturation delay of detrusor function rather than a structural anomaly can account for this longer and better effect. Overactivity inhibition can allow detrusor function to mature.

The dose of botulinum-A toxin used in the current study was selected rather arbitrarily. Concerning the dose, no clear guidelines are found in the literature. In children with neuropathic overactive bladder higher doses are used. Riccabona et al used 10 U/kg body weight to a maximum of 360 U,4 while Schulte-Baukloh et al preferred 12.5 U/kg body weight to a maximum of 300 U.5 Important and misleading for determining the dose is the fact that the different brands of botulinum-A toxin have different units. The 100 U used in the current study are only applicable to Botox®.

As long as the dose does not exceed 300 U, it is unlikely that systemic weakness or paralysis would occur. Muscle weakness has been described in urological procedures in adults by some groups4,6 but to our knowledge it has never been mentioned in the treatment of children to date. Temporary autonomic side effects have been described but they mainly disappear after some weeks.6

In this study no systemic side effects were noted. It seems to be important to keep the injected volume as low as possible because the risk of systemic absorption and generalized weakness seems to be related more to the volume than to the quantity of botulinum-A toxin.5,6

In the current study no serious side effect was seen in 1 girl with a post-void residual urine volume of more than 50% of functional bladder capacity. She needed intermittent catheterization for 10 days, after which voiding normalized. It is even questionable if this retention was due only to the autonomic side effect of botulinum-A toxin or rather the result of a combination of detrusor-sphincter dyssynergia and the botulinum-A toxin effect. In our study we found that some children had a dysfunctional uroflow pattern some weeks after injection, which later disappeared. One boy had clinical vesicoureteral reflux with pain at the kidney site during voiding. The patient refused voiding cystography, so the diagnosis was not confirmed. The symptom disappeared after 2 weeks. Furthermore, 2 girls had a lower urinary tract infection after injection. These girls had normal uroflowmetry and emptied the bladder completely. Therefore, the infections might have been unrelated to botulinum-A toxin treatment.
After this pilot study, which proves safety and long-term efficacy, some further studies are needed, especially in regard to the botulinum-A toxin dose. Possibly some children may need multiple injection and, therefore, defining the dose is important. With repeat injections it is known that resistance develops to the toxin in some patients. Humans may form antibodies to botulinum-A neurotoxin or to associated nontoxin proteins.\textsuperscript{5,6} It has been shown that shorter intervals between doses and higher doses contribute to the development of resistance.\textsuperscript{7,8} Therefore, it is recommended to avoid booster injections, leave at least a 3-month interval between 2 treatments and use the smallest clinically effective dose.\textsuperscript{9} The latter is probably the most challenging factor because the dose used today in children is still determined rather empirically.

In our view the clinically effective dose is less influenced by the body weight of the child than by bladder properties, such as bladder mass and detrusor compliance. We postulate that the thicker the bladder wall, as estimated on ultrasound, the more muscle mass and the higher the dose needed to have a long lasting effect.

As in the treatment of neuropathic overactive bladder but probably also in some children with nonneuropathic overactive bladder, several repeat injections are necessary. An adequate method of determining the clinically effective dose should be developed to avoid elimination of this valuable treatment due to resistance.

In the current study it seems that a partial response was a poor prognostic factor for repeating the injection. Three partial responders underwent repeat injection but only 1 responded. One full responder who had relapse showed a new full response after a second injection. Thus, probably a full response after the first injection is a good prognostic factor for further injection therapy. Repeat injections seem to be as safe and effective as the first injection.\textsuperscript{10}

Before botulinum-A toxin injection therapy can be used as a primary therapy for overactive detrusor in childhood further research is necessary. Most evidence could be gathered in a placebo controlled study. However, to our knowledge the industry shows no interest in the development of nontoxin proteins.\textsuperscript{5,9} It has been shown that shorter intervals between doses and higher doses contribute to the development of resistance and antibody production, the primary risk is that injection of the toxin may create irreversible long-term side effects, eg ultrastructural and functional changes of the detrusor. This would probably only be revealed after a longer period of use. Reports of long-term followup with repeat injections in the bladder of children through puberty are nonexistent and a few short-term reports are based on retrospective studies.

Schulte-Baukloh et al recently reported a study of repeat injections of botulinum-A toxin in children with neurogenic bladder in children who are resistant to common treatments is a safe and effective treatment modality. Standardization of this therapy, especially concerning the optimal clinical effective dose, must be done if we want to keep this therapeutic tool effective in the long term.

REFERENCES


EDITORIAL COMMENT

The use of botulinum-A toxin was pioneered by Schurch et al in 2000 by applying the toxin into the neurogenic overactive detrusor and by that achieving increased bladder capacity and decreased pressures.\textsuperscript{1} The first child to receive botulinum-A toxin for a neurourological condition was a 7-year-old girl with upper tract dilatation.\textsuperscript{2} Since then, the overall use in children with a urological condition has concentrated on treating neurogenic overactive bladder. In adults the indications for treatment with botulinum-A toxin have now expanded to other urological conditions, eg urinary incontinence and voiding disorders. Evidently this trend will be reproduced in children. Therefore, it is important to bear in mind that overactive bladder in most children is a dynamic condition, as opposed to the static overactive bladder in adults. This fact should be taken into account when considering this treatment.

At this point no major short-term or long-term adverse effects have been described in children. Besides the generalised effect and antibody production, the primary risk is that injection of the toxin may create irreversible long-term side effects, eg ultrastructural and functional changes of the detrusor. This would probably only be revealed after a longer period of use. Reports of long-term followup with repeat injections in the bladder of children through puberty are nonexistent and a few short-term reports are based on retrospective studies.

Schulte-Baukloh et al recently reported a study of repeat injections of botulinum-A toxin in children with neurogenic overactive bladder.
detrusor overactivity. As in similar studies, this study shows increased capacity, decreased pressure and increased bladder compliance. The current series is the first to explore the effectiveness of injecting botulinum toxin into the detrusor in children with nonneurogenic overactive bladder. They observed impressive results in a select, hard core group of children with continuing incontinence after what modern combined therapy could offer. The investigators injected a standard dose of 100 U botulinum-A toxin into the detrusor. This is interesting since the recommended dose in children is 10 to 12 U/kg body weight (maximum 300 U). Since this is not based on evidence but taken from the dose used in pediatric neurology, this should be further evaluated.

Unfortunately, as in many other studies in children, intent to treat has replaced the randomized, controlled clinical trial. Future studies including randomization, controls and long-term followup are mandatory before this treatment for nonneurological bladder dysfunction is taken into daily clinical use.

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The Daytime alarm: A useful Device for the Treatment of Children with Daytime Incontinence

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In this paper we present the results of a daytime wetting alarm as treatment for therapy resistant daytime incontinence in children with an overactive detrusor.

Complete cure was attained in 35% of patients, another third had a clear improvement in their complaints and training failed in a third.
The Daytime Alarm: A Useful Device for the Treatment of Children With Daytime Incontinence

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Purpose: We present the results of the use of a daytime wetting alarm as treatment for therapy resistant daytime wetting in children with an overactive detrusor.

Material and Methods: In a retrospective study we reviewed the files of 63 children treated with a daytime alarm because of persistent daytime wetting. Results were considered a complete success when the children were completely dry after treatment, a partial success when there was greater than 50% improvement in daytime wetting and a failure when no change was observed in daytime symptoms.

Results: During a study period of 25 months 63 children were treated with a daytime alarm at the department of pediatric urology. The mean treatment period was 14 days. At a followup of 12 months treatment failed in 20 children (32%), 21 (33%) had partial success and 22 (35%) were successfully treated.

Conclusions: In children with therapy resistant daytime wetting and an overactive detrusor the daytime alarm may be a useful treatment tool. Complete cure of daytime incontinence can be attained in 35% of patients, almost a third have improvement in their complaints and training fails in a third.

Key Words: urinary incontinence, bladder, awareness, treatment failure

O veractive detrusor is a frequently observed problem in children. Urge and urge incontinence are the typical symptoms. Treatment consists of providing insight into and knowledge of the problem, keeping voiding diaries to increase this insight, bladder capacity training and pharmacological treatment. Although good results are reported with this treatment, some children are therapy resistant.1 Awareness is an important part of this therapy resistance. Many children are no longer aware that incontinence happens and wet pants are ignored. Especially when attention is focused to a demanding activity, such as watching television or playing a computer game, incontinence happens without awareness.

Therefore, it was postulated that increasing awareness could improve the problems. To increase awareness treatment with daytime wetting alarms was started. Drawing the attention of a child to bladder behavior by a daytime alarm can contribute to a larger awareness of the bladder and teach them to anticipate the incontinence problem by going to the toilet on time. The results of this treatment were reviewed retrospectively.

PATIENTS AND METHODS
The files of children treated with a daytime alarm for therapy resistant daytime wetting between June 1998 and August 2000 were retrospectively reviewed. The inclusion criterion for this retrospective study was persistent daytime wetting with a frequency of 1 to 5 times daily. Children with constipation were excluded from study. The duration of therapy and concomitant treatments were noted.

The Charco® daytime alarm consists of an alarm device with an auditory or a vibratory buzzer alarm. A wire connects a sensor strip fixed inside the underwear to the alarm device. The alarm is carried around the waist, supported by a waist belt.

During the 2-week home program the children wore the alarm during the whole day. The alarm was activated the moment a drop of urine wet the sensor strip. The children were taught by the physiotherapist to stop voiding and perform a withholding maneuver at the moment that the alarm went off. They then went to the toilet and emptied the bladder in a proper way.

Treatment was considered a complete success when the child became dry while on treatment, a partial success when there was greater than 50% improvement in daytime incontinence and a failure when no change was observed in daytime symptoms. The results of treatment were evaluated immediately after training. They were reevaluated 6 weeks later and finally 1 year after training was started.

RESULTS
The files of 63 children with a minimal followup of 1 year were reviewed. A total of 34 boys and 29 girls were identified. Mean age in the study group was 8 years (range 5 to 14). Of the children 15 (25.4%) experienced pure daytime wetting, 2 boys (3.2%) had a history of posterior urethral valves and daytime wetting, and 45 children (71.4%) experienced daytime and nighttime wetting. All children had a proven diagnosis of overactive bladder on videourodynamic examination. The previous failed treatment period was 21.6
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months. Bladder capacity training failed in children while on pharmacotherapy.

During the pre-alarm training period all children were trained with a strict drinking and voiding schedule. A total of 38 participants (60%) underwent pelvic floor therapy. All children were initially treated with pharmacotherapy, including 5 (7.9%) with 1 anticholinergic (oxybutynin HCl), 50 (47.6%) subsequently with 2 anticholinergics (oxybutynin HCl and oxyphenycyclim HCl) and 8 (12.7%) with 3 anticholinergics (oxybutynin HCl, oxyphenycyclim HCl and tolterodine). Eight patients (12.7%) subsequently underwent treatment with 2 anticholinergics (oxybutynin HCl and oxyphenycyclim HCl) and an α-mimetic (imipramine). Nine children (14.3%) were treated with a combination of anticholinergics (oxybutynin HCl in 4 and oxyphenycyclim HCl in 5) and an α-mimetic (imipramine). Three children subsequently received treatment with oxybutynin HCl, oxyphenycyclim HCl and an α-lytic (terazosin).

All children used the alarm for 2 weeks. According to the anamnestic results of the children and the hetero-anamnestic results of the parents all children were highly motivated and showed high compliance during the 2-week home program.

At the moment that the daytime alarm was started 15 children (23.8%) were on no concomitant treatment, 39 (50.6%) were being treated with anticholinergics (oxybutynin HCl and oxyphenycyclim HCl), 3 (4.8%) were on α-mimetics (imipramine), 1 (1.6%) was on an α-lytic (terazosin) and 5 (7.9%) were on a combination of anticholinergics and α-mimetics. Children remained on medication because they had an initial positive if partial result, namely increased bladder capacity, decreased urge and decreased wetting frequency. This partial result was durable while on this therapy and it could only be changed when therapy was stopped. None of the children became completely dry during the pre-alarm treatment period.

Results were evaluated separately in patients with and without concomitant treatment. The table shows an evaluation of the results in the 15 children who were on no concomitant therapy at the moment that the daytime alarm was started.

| Results in children with and without concomitant therapy when alarm was started, and in entire study population |
|---|---|---|---|
| No. Failure (%) | No. Success (%) | No. Partial Success (%) |
| No concomitant therapy | | |
| After 2 wks of training | 6 (40) | 7 (47) | 2 (13) |
| 6 Wks after training | 6 (40) | 6 (40) | 3 (20) |
| 1 Yr after training started | 6 (40) | 4 (27) | 5 (33) |
| Concomitant therapy: | | |
| After 2 wks of training | 13 (27) | 32 (66) | 3 (6) |
| 6 Wks after training stopped | 13 (27) | 16 (53) | 19 (59) |
| 1 Yr after training started | 14 (28) | 18 (36) | 16 (33) |
| Entire population: | | | |
| After 2 wks of training | 19 (38) | 36 (62) | 8 (16) |
| 6 Wks after training started | 19 (38) | 22 (35) | 22 (35) |
| 1 Yr after training started | 20 (32) | 22 (35) | 21 (33) |

Immediately after the 2-week training period 7 children (47%) had complete success, 2 (13%) had an incomplete result and in 6 (40%) treatment failed. Reevaluation 6 weeks after training was started showed that 63% of those who were initially dry had a partial relapse. One year after therapy was started another 2 children, who were still successful after 6 weeks, had a partial relapse. None of the children who had a complete relapse the 6 patients who were initially unsuccessful remained without a result after 1 year.

The table also shows the results in 48 children on concomitant treatment. The immediate complete success rate after 2 weeks of training was 66%, 6% of children had a partial result and 27% were unsuccessful. Six weeks after treatment was stopped 50% of those who were initially dry had a partial relapse. One year after therapy was started we found that 1 girl who was completely dry after 6 weeks, and 1 boy and 2 girls who had an incomplete result after 6 weeks had a complete relapse. Two girls who did not become dry and 1 girl with an incomplete result at 6 weeks became completely dry within a year after starting daytime alarm training. After 1 year 18 patients (38%) were successful, 16 (33%) had a partial result and 14 (29%) remained without a result.

Comparing results in children on pharmacological treatment at the moment that the daytime alarm was started with results in those not on concomitant therapy showed that the initial success rate was higher in the group on drug therapy (66% vs 47%). Six weeks after the alarm was started the success rate was decreased to 33% in the group with concomitant treatment and to 40% in the group without medication. Evaluation of the situation 1 year after starting the daytime alarm showed that in the end a higher relapse rate was found in the group without concomitant therapy than in the group on concomitant medication. One year after starting the alarm 27% of the children who had no concomitant therapy remained dry, in contrast to those with concomitant therapy, of whom up to 38% were successfully trained to be dry.

Evaluation of the global study population showed that the complete success rate immediately after the alarm training session was high, in that 62% of the children were successfully trained, 8% had a partial result and about 30% remained without a result (see table). Six weeks after training was stopped the complete success rate had decreased to 35%, 30% of the children remained unsuccessful and another 35% had partial success. Those who relapsed still had a partial result. Evaluation 1 year after therapy was started showed that study results remained almost unchanged. Of the children 35% were completely dry during the day, 33% had partial success and 32% were without any success.

Of the 29 girls 11 (38%) were completely successful 1 year after therapy was started, 13 (45%) had a partial result and 5 (17%) remained untreated. Of the boys 11 (32%) were completely successful, 8 (24%) had a partial result and up to 44% (15) had no result 1 year after starting alarm training.

According to the results in the global group we conclude that in the long term (1 year) training failed in about a third of the children, a third had an incomplete result and a third seemed completely cured. Girls seemed to have a better complete and partial training result than boys, although this was not proved statistically.
DISCUSSION

Overactive detrusor is a frequent underlying condition in children with daytime incontinence without underlying neuropathy or uropathy. In many of these children awareness of the incontinence period is decreased or even absent. There exists an adaptation to the feeling of wearing wet clothes or neglect is a defense mechanism against the condition.

This lack of awareness seems to be an important factor in the therapy resistance of some children. Indeed, before being able to respond to an involuntarily event the patient must recognize the signs that accompany the event. In cases of overactive detrusor wetting occurs at the time of an overactive detrusor contraction. Relearning to recognize the feeling of urge preceding urge incontinence enables the patient to prevent wetting by going to the toilet on time or by central inhibition of the overactive detrusor contraction. With this in mind the daytime wetting alarm was introduced as a treatment tool for daytime incontinence.

The daytime alarm is derived from the nighttime wetting alarm. It consists of an alarm device with an auditory alarm or a vibratory buzzer alarm. A wire connects a sensor strip fixed inside the underwear to the alarm device. Although the classic nighttime wetting alarm has been used successfully to treat patients with persistent diurnal enuresis, it is preferable that the device has an adapted size and does not interfere with the normal activities and normal behavior of the child.²,³

It is important that the function and meaning of the device be explained in detail to the child. At our department this task is performed by a urotherapist. The child must learn to react adequately to the alarm. After 1 drop the alarm is activated. The child must try to stop the loss of urine, go to the toilet and empty the bladder appropriately.

Many children with persistent diurnal incontinence demonstrate a lack of awareness or ignorance of bladder function. It is important to teach these patients to react adequately to bladder instability and prevent them from wetting by going to the toilet on time or by central inhibition of the overactive detrusor contraction. Vijverberg et al described a similar setting during an inpatient treatment program for persistent urge incontinence.⁴

In contrast to the belief that the daytime alarm alerts patients to bladder behavior and enables them to stay dry, Halliday et al stated that a noncontingent alarm that rings unrelated to wetting events produces as good a response as a contingent alarm.⁵ The results achieved in their study with the contingent alarm were comparable to the results in our study population. In our opinion, certainly in children with difficult to treat, persistent daytime wetting, it is preferable and certainly more physiological to use a wetting alarm that sounds when wetting occurs. It makes the children aware of bladder function, leading to better control and better continence.

The success of this therapy is certainly influenced by motivation and compliance with the training program by participating children. Motivation and compliance during the 2-week home program was high in this group. This is because this was a highly select subgroup of children with multiple failed treatments in the past who looked forward to participating in this study with what was completely new therapy for them.

The good results found after 2 weeks of training are certainly due to this fact. Although an inpatient daytime alarm treatment with professional coaching by trained physiotherapists, nurses and psychologists may result in an increase in training compliance and success, this procedure may be hardly acceptable because of psychological and economic reasons.

Decreases in patient motivation and attention in this study population is certainly a reason for the high relapse rate 6 weeks after training was completed. However, after 6 weeks the results seemed to be permanent since there was almost no difference between results after 6 weeks and after 1 year. After a child has learned to cope with bladder dysfunction a positive, lasting continence result may be achieved.

Other factors, such as the natural resolution of wetting, which are undoubtedly important for the outcome of treatment in the whole population of children with daytime wetting, were far less important in this highly selected group of children with persistent daytime wetting who showed no progress while on common therapy during a mean of 21.6 months. As such, they do not really influence the results of our study. Also, because overactive bladder in childhood is considered a maturation delay, it is postulated that this treatment enhances the further maturation of detrusor function.

The results of this study are not stated in statistical data because no reliable statistical analysis could be performed. We were dealing with a heterogeneous group of patients considering pathogenesis, age, sex, the number of previous treatments and the duration of therapy.

CONCLUSIONS

The daytime alarm is a useful device in children with severe, often drug resistant daytime wetting. Complete results were found in 35% of the patients and another 33% showed an important improvement in their complaints. Outpatient use is preferable not only for psychological, but also for economic reasons.

REFERENCES

Voiding Disorders in Severely Mentally and Motor Disabled Children

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In this paper the voiding and continence pattern in severely mentally and motor disabled children is presented.

A remarkably high incidence of urinary incontinence, 52.7% was found in the studied population.

No correlation could be found between the uroflow pattern and the continence pattern. Restricted fluid intake was correlated with an important bladder capacity deficit.

Continence seemed to be rather influenced by motor disability than by mental development.
ABSTRACT

Purpose: We evaluated the voiding and continence patterns in severely mentally and motor disabled children.

Materials and Methods: The hetero-anamnestic, uroflowmeter and morning urine concentration profile results of 17 girls and 21 boys with severe mental and motor disability were evaluated in a prospective study.

Results: Of the children 20 (52.7%) suffered daytime and/or nighttime wetting and 18 (47.4%) were continent. Daytime and nighttime wetting occurred in 85.7% of children with tetraparesis and in 66.6% of those with an IQ between 46 and 55, representing the highest incidence rates. Bladder capacity was too small for age (mean deficit 145 ml.) in 92% of the children. Uroflowmetry demonstrated a dysfunctional pattern in 60.7% of patients. Dysfunctional voiding occurred in 100% of children with coordination disorders and in 87.5% of those with an IQ between 46 and 55, representing the highest incidence rates. The morning urine concentration profiles showed an osmolality of at least 1,021 mOsm./kg. in all cases.

Conclusions: Although we found a remarkably high incidence of dysfunctional voiding, no correlation between the uroflow and continence patterns could be found. Restricted fluid intake, due to swallowing problems and insufficient hydration, causes an important bladder capacity deficit in most patients. Becoming continent is determined by motor disability, especially the degree of mobility, rather than by mental development.

KEY WORDS: urination disorders; disabled, mentally; paresis; flowmetry

Daytime and nighttime wetting by severely mentally and motor disabled children is too often considered an inevitable fact, and literature on this underestimated problem is limited. Better insights into voiding and continence patterns of these children can lead to better solutions or even treatment of incontinence.

MATERIALS AND METHODS

The hetero-anamnestic, uroflowmeter and morning urine concentration profile results of 17 girls and 21 boys with a mean age of 10.5 years (range 6 to 16) were evaluated in a prospective study. The patients live in the same medical pedagogical institution at which they are treated by classified medical and paramedical staff. All patients suffered severe mental and spastic motor disability. IQ was 36 to 45 in 4 girls, 46 to 55 in 2 girls and 1 boy, 56 to 70 in 6 girls and 10 boys, and 71 to 90 in 5 girls and 10 boys. Of the patients 3 girls and 4 boys were quadriparetic, 8 girls and 6 boys were diparetic, and 1 girl and 5 boys were hemiparetic. Three girls and 1 boy had ataxia, 1 girl and 3 boys had athetosis, 1 girl had severe coordination disorders and 2 boys had myopathy.

Hetero-anamnestic information about continence was gathered from parents and institution staff. A gravimetric uroflowmeter and adapted toilet chair were placed at the institution. All children performed 1 to 6 (mean 3) recordings, the number of which for each patient was determined based on local organizational possibilities of the paramedical staff. Osmolality was measured by the same laboratory on a sample of morning urine from each child.

RESULTS

Based on the history of parents and staff members, 20 children (52.6%) had daytime and/or nighttime wetting, including 5 (13.2%) with nighttime wetting, 2 (5.3%) with daytime wetting and 13 (34.2%) with daytime and nighttime wetting. The remaining 18 (47.4%) patients were continent. The incidence of wetting according to motor disability is shown in table 1. The highest incidences of daytime and nighttime wetting were in children with myopathy (100%) and tetraparesis (85.7%), while the lowest incidences occurred in those with coordination disorders (0%) and ataxia (25%). The incidence of nighttime and daytime wetting according to mental development is also shown in table 1. The highest incidence of nighttime wetting, 75%, was found in children with an IQ of 36 to 45 (75%), and the highest incidence of daytime and nighttime wetting, 66.7%, was found in the group with an IQ of 46 to 55 (66.7%).

Mean voiding frequency was 6 times a day (range 4 to 10). Of the children 35 (92.1%) had a bladder capacity too small for age compared with the estimated capacity formula. Mean bladder capacity deficit, determined as bladder capacity—estimated bladder capacity for age, was 145 ml. (range 23 to 345). Only 1 girl with diparesis had a normal bladder capacity, and 1 boy with a hemiparesis and 1 girl with diparesis had a capacity too large (mean +189.5 ml.). The child with a normal bladder capacity and the girl with a large capacity had no incontinence problems, while the boy with a large capacity had nighttime wetting infrequently.

Swallowing problems were severe in 1 tetraparetic girl, and 1 girl and 1 boy with athetosis, and moderate in 2 diparetic boys, 1 diparetic girl and 1 girl with ataxia. The remaining 31 (81.6%) children had no swallowing problems.
Mean bladder capacity deficit was 214.7 ml. in children with severe swallowing problems, 207 ml. in those with moderate problems and 127.6 ml. in children without swallowing problem. The children performed 112 uroflow recordings (mean 3 per patient, range from 1 to 6). Every uroflow recording was evaluated by the same investigator. The pattern was normal on only 39 uroflow recordings (34.8%), dysfunctional, staccato or fractionated in 68 (60.7%), and purely obstructive in 1 (0.9%). Four uroflow recordings (3.6%) were pathognomonic for straining. The results of the uroflowmetry according to the type of motor disability are listed in table 2. The highest incidences of dysfunctional uroflowmetry were in patients with dyscoordination disorders (100%) and ataxia (78.6%), while the highest incidence of normal uroflowmetry was in those with hemiparesis (47.6%). The uroflow patterns according to mental development are also given in table 2. The highest incidence of dysfunctional voiding was in the group with an IQ of 46 to 55 (87.5%).

The correlation between the uroflow pattern and continence or incontinence pattern is shown in table 3. The pattern was considered normal if more than 50% of the recordings were normal, dysfunctional if more than 50% were dysfunctional and mixed if 50% were normal and 50% dysfunctional. In table 4 the uroflow and continence patterns of each patient are related to the mental and motor disability. No statistical significance of the correlation among the continence pattern, voiding pattern and type of mental and motor disability could be obtained due to the small study population. The concentration profiles of the morning urine of our population. The concentration profiles of the morning urine showed an osmolality of 1,021 mOsm./kg. or more in all cases.

**DISCUSSION**

Severely mentally and motor disabled children often present with symptoms of dysfunctional voiding. More than half of our population (52.6%) had daytime and/or nighttime wetting, which is comparable to the incidence reported in the literature (range 30% to 74%). McNeal et al studied 50 patients with cerebral palsy, of whom 30% had 1 or more symptoms indicative of a neuropathic bladder. Decter et al reported almost the same incidence (about 33%) of dysfunctional voiding symptoms in children with cerebral palsy. Vezina et al studied 17 children with spastic ataxia of whom 53% presented with urinary symptoms of urgency and urgent incontinence. Also Houle et al found that nearly 50% of children with cerebral palsy presented with dysfunctional voiding symptoms. In contrast to the findings of Reid and Borzyskowski, and according to the results of Brodak day-time and nighttime wetting was the most common presenting symptom of our study population (65%) and not daytime incontinence.

To our knowledge there have been no studies of the voiding pattern of this population evaluated by uroflowmetry performed in their own environment, as all information in literature about bladder function has been based on videourodynamic investigations. Reid and Borzyskowski reported that 85% of their patients had 1 or more problems and 50% of these patients had an abnormal videourodynamic study, and almost the same incidence (83%) was mentioned by Deeter et al. The most commonly diagnosed problems were hyperreflexic detrusor contractions with reduced bladder capacity (87%) and detrusor hyperreflexia. Both reports mentioned that detrusor-sphincter dyssynergia was found rather infrequently in children with cerebral palsy. Vezina et al stated that 41% of their patients with spastic ataxia showed a lack of detrusor inhibition on cystometric evaluation. In contrast to the aforementioned reports, they found a higher incidence (37.5%) of abnormal electrical hyperactivity of the external sphincter.

Of our children 25 (65.8%) had a disturbed uroflow pattern, the most common of which was dysfunctional voiding, staccato or fractionated (94%). No correlation between the uroflow and continence patterns could be found. In fact the incidence of daytime and/or nighttime wetting was higher in patients with a normal (69.2%) than a disturbed (48%) uroflow pattern. No clear correlation could be found among continence pattern, uroflow pattern, mental development and motor disability. It is clear that mobility has an important role in continence. Nearly all children with tetraparesis and myopathy had daytime and nighttime wetting. The more mobility, especially children with diparesis, ataxia and coordination disorders, the higher the incidence (71.4%), 75%, 100% respectively of being continence. Mental development is less correlated with the degree of continence. Although the fact that 75% of children with an IQ of 36 to 45 and 66.6% of those with an IQ of 46 to 55 were incontinent may make us believe that mental capability has an important role in continence, further evaluation showed that these children with inconti-
nence also had a severe mobility problem. The children with a low IQ but reasonable degree of mobility were continent. On the other hand, nearly all children with a higher IQ but a high degree of immobility were incontinent.

Bladder capacity deficit was found in nearly all children (92.1%), and it was neither influenced by mental development or type of motor disability. In children with severe and moderate swallowing problems the mean capacity deficit was higher than in those without swallowing problems. The high osmolality suggested that fluid intake was too low in all children. Restricted fluid intake because of swallowing problems but certainly more often because of insufficient hydration of the patients due to their environment, was the main cause. Being continent is one of the factors determining survival. Thus, achieving it by toilet training or alternative options remains a priority in the treatment of patients with severe mental and motor disability.

CONCLUSIONS

Children with severe mental and motor disability often suffer from bladder dysfunction and daytime and nighttime wetting are the most frequent symptoms. The possibility to become continent is determined by the motor disability rather than mental development. The more mobile the higher the incidence of continence. Although most children have abnormal uroflowmetry no correlation could be found between the uroflow pattern and continence problem. A major problem, in nearly all of these children is the often extreme small bladder capacity. Insufficient fluid intake, because of swallowing problems and insufficient hydration, remains the main cause. Being continent is one of the factors determining survival. Thus, achieving it by toilet training or alternative options remains a priority in the treatment of patients with severe mental and motor disability.

REFERENCES

Adequate Fluid Intake, Urinary incontinence, and Physical and/or Intellectual Disability

Erik Van Laecke, Ann Raes, Johan Vande Walle and Piet Hoebek


In this paper the value of adequate fluid intake as a part of urotherapy for urinary incontinence in mentally and/or motor disabled children is illustrated.
Adequate Fluid Intake, Urinary Incontinence, and Physical and/or Intellectual Disability

Erik Van Laecke,* Ann Raes, Johan Vande Walle and Piet Hoebeke

From the Departments of Paediatric Urology and Nephrology (AR, JVW), Ghent University Hospital, Gent, Belgium

Purpose: Urinary incontinence in physically and/or intellectually disabled children is a common problem. Literature on therapy is sparse. In these patients we prospectively studied the effect of urotherapy, particularly adequate fluid intake.

Materials and Methods: In a prospective study 66 boys and 45 girls with a mean age of 9.1 years were included, of whom 22 were motor disabled, 16 were mentally disabled and 73 had mental and motor disability. All patients were put on a fluid intake schedule of 1,500 ml/m² body surface. Mean followup was 22.9 months (range 12 to 30). Patients were evaluated using a diary, uroflowmetry and bladder scan.

Results: Of the children 44 (39.6%) were dry at study inclusion, 41 (46.9%) had daytime and nighttime urinary incontinence, 11 (9.9%) had daytime urinary incontinence and 15 (13.5%) had nocturnal enuresis. Anticholinergics were started in 18 children, of whom 11 became dry. The other children received only an adequate fluid intake schedule. Eight patients (7.2%) withdrew from study. At study end 69 children (67%) were completely dry during the day and night, 14 (13.6%) remained urinary incontinent during the day and night, 5 (4.9%) had daytime urinary incontinence and 15 (14.6%) had nocturnal enuresis. Of the children 73 (65.8%) drank at least 25% less than the physiologically necessary quantity. Initially 62 children (55.9%) had a small age related expected maximum voided volume, which decreased to 24 (21.6%) at end of study.

Conclusions: Adequate fluid intake is an important part of urotherapy for urinary incontinence in mentally and/or motor disabled children.

Key Words: urinary bladder, urinary incontinence, drinking behavior, disabled children, questionnaires

MATERIALS AND METHODS

Groups at 4 institutions for mentally and motor disabled children participated in the study. Children between 4 and 15 years old with a mental, motor or mental and motor disability were included in analysis, and those with proven neuro-pathic bladder were excluded. Approval of the University Hospital Ghent ethical committee was obtained. Informed consent was provided by all patient families and informed assessment was obtained from mentally capable children. A questionnaire was used to collect data on urinary continence problems, in-
including nocturnal enuresis, urinary incontinence during the day, and during the day and night, stool problems, constipation and fecal incontinence. This questionnaire was completed by parents and institution staff. Maximum voided volume, fluid intake quantity and urinary incontinence were recorded in a voiding and drinking diary. Maximum voided volume was calculated from the voided volumes recorded during a day. The children received no extra water load. Mental status was evaluated by measuring IQ, mental age and verbal capacity. Motor disability was scored based on mobility and postural stability. The global handicap was evaluated as a degree of functional autonomy.

All children underwent clinical examination done by 1 investigator. A uroflowmeter was installed at the institution. At least 3 recordings were made before and after therapy, spread over several days. A personal adapted toilet chair was used. Post-void residual urine was measured at least once with bladder scan. Clinical evaluation, uroflowmetry and bladder scan were repeated regularly during the entire 6-week study period. A bladder diary was used to record maximum voided volume, fluid intake quantity and incontinence.

After documenting maximum voided volume, fluid intake and the degree of incontinence a personally adapted fluid intake schedule was started. A mean fluid intake of 1,500 ml/m² body surface was recommended equally divided during the day in 4 to 6 portions.1 Guidelines on fluid quality and quantity were given to parents and caregivers. No specific voiding regimen was started. Children indicated spontaneously when they wanted to visit the toilet. No patients were placed on a timed voiding regimen.

The toilet was adapted to the individual needs of the children to optimize a stable toilet position and maximum pelvic floor relaxation. The effect on maximum voided volume, anticholinergics and a wetting alarm were only started after a minimum of 6 weeks of treatment with adapted fluid intake. In select patients, including those with urinary incontinence plus normal or disturbed uroflow and recurrent post-void residual urine, and those with persistent urinary incontinence with no change in maximum voided volume despite adequate therapy for longer than 3 months, videourodynamic was performed if parents provided consent. Results were analyzed using the chi-square test with p <0.05 considered statistically significant.

RESULTS

Included in the study were 45 girls and 66 boys with a mean age of 9.1 years (range 4 to 15). Ten girls and 12 boys were only motor disabled, 9 girls and 7 boys were only mentally disabled, and 26 girls and 47 boys were intellectually and physically disabled. Table 1 lists underlying pathological conditions. Of children with mental retardation 45 (50.6%) were mildly, 32 (35.5%) were moderately, 9 (10.1%) were severely and 3 (3.4%) were profoundly mentally retarded. Of the 95 motor disabled children 48 (50.5%) had a certain degree of spasticity. The gender distribution was 1.5 boys and 1 girl with mental retardation, and 1.6 boys and 1 girl with motor disability. Mean follow-up was 22.9 months (range 12 to 30). Eight patients (7.2%) withdrew from the study, including 1 who died, 2 who moved to an institution that did not participate in the study and 5 at the time that strict fluid intake was started.

Continenace

At the time of study enrollment according to International Children’s Continence Society definitions2,3 39.6% of children were continent of urine, 36.9% had daytime and nighttime urinary incontinence, 9.6% had daytime urinary incontinence and 13.5% had nocturnal enuresis. No significant difference was noted among the 3 subgroups, ie mentally disabled, motor disabled, and mentally and motor disabled (p >0.05, table 2). At the end of the study period a significant change in the continence pattern was observed (p <0.001). Of the children 67% were completely continent and the incidence of urinary incontinence decreased from 46.9% at the study start to 18.4% at the end (table 3).

Fluid Intake

At the study start only 11 patients (9.9%) had a normal fluid intake of 1,500 ml/m² body surface while 73 (65.8%) had an intake of less than 75% and 27 (24.3%) had an intake of less than 50% of the expected normal fluid requirement. A significant difference in fluid intake was found between the group with mental and motor disability, and the 2 other groups (p <0.005). No significant difference was

Table 1. Underlying pathological conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>12</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>61</td>
</tr>
<tr>
<td>Duchenne’s disease</td>
<td>5</td>
</tr>
<tr>
<td>Encaphalopathy</td>
<td>4</td>
</tr>
<tr>
<td>Prematurity</td>
<td>3</td>
</tr>
<tr>
<td>Microcephalia</td>
<td>2</td>
</tr>
<tr>
<td>Pierre Robin syndrome</td>
<td>2</td>
</tr>
<tr>
<td>Encaphalitis</td>
<td>1</td>
</tr>
<tr>
<td>Dysmaturity</td>
<td>1</td>
</tr>
<tr>
<td>Posttraumatic</td>
<td>1</td>
</tr>
<tr>
<td>Langehan’s syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Metabolic disorder</td>
<td>1</td>
</tr>
<tr>
<td>Chromsome q13</td>
<td>1</td>
</tr>
<tr>
<td>Fragile X syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Congenital glycoprotein disorder-Jacken syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Prader-Will syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Myoclonic encephalopathy-myotonic dystrophy</td>
<td>1</td>
</tr>
<tr>
<td>Leigh syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Sjogren-Larsson syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Werdning-Hoffman type II</td>
<td>1</td>
</tr>
<tr>
<td>Spinal muscular atrophy myotonic dystrophy</td>
<td>1</td>
</tr>
<tr>
<td>Charcot-marie-Tooth disease</td>
<td>1</td>
</tr>
</tbody>
</table>
found between mentally and motor disabled patients (p >0.05, table 4).

Swallowing Problems
Of the children 71 (64%) had no swallowing problems while 22 (19.8%) had moderate and 8 (7.2%) had severe swallowing problems. In 2 children the available information was inadequate. No significant difference was found in the fluid intake deficit between children with vs without swallowing problems (p >0.05). Almost all children had a deficient fluid intake. Of the patients with severe, moderate and no swallowing problems 50%, 72.7% and 73.2%, respectively, had an intake of less than 75% of the expected normal fluid intake (see figure).

Maximum Voided Volume
A total of 12 children (10.8%) had an age related expected maximum voided volume but 62 (55.9%) had a maximum voided volume of less than 65% of the age related expected maximum. Of those with a normal maximum voided volume 83.3% were continent and 16.7% had nocturnal enuresis at study enrollment. Of children with a maximum voided volume of less than 65% of the age related expected maximum only 35.5% were continent, 41.9% had daytime and nighttime urinary incontinence, 9.7% had daytime incontinence and 12.9% had nocturnal enuresis, significantly different vs those with a normal maximum voided volume (p <0.01).

Increased Fluid Intake Influence
At the study start no significant difference was observed in the continence rate when correlated with the degree of fluid intake (p >0.05, table 2). After adequate fluid intake a 19.2% increase in continence was observed in the group with normal drinking (p >0.05). In the group with a fluid intake of less than 75% of the expected intake a significant change in the continence pattern was found with a 26.4% increase in continence (p <0.01). Increased fluid intake resulted in a significant increase in continence and maximum voided volume in those with an important decreased fluid intake at the study start (table 5). Of the patients 58 (56.3%) gained more than 25% of maximum voided volume and 45 (43.7%) gained more than 50%. An increase in maximum voided volume resulted in significant amelioration of continence (p <0.0001, table 5). No significant difference in the incidence of normalization of maximum voided volume after treatment with adequate fluid intake was seen among the 3 subgroups, including 53.4% in mentally and motor disabled, 43.8% in mentally disabled and 68.1% in motor disabled children (p >0.05).

Constipation/Fecal Incontinence
According to Rome III criteria fecal incontinence and constipation were reported in 37 (33.3%) and 30 patients (27%), respectively. Only 5.4% of the children with fecal incontinence and 26.7% with constipation were continent of urine, significantly less than the 56.8% without fecal incontinence and the 50.7% without constipation (p <0.001 and <0.05, respectively).

Additional Therapy
At study enrollment 3 patients on anticholinergics were continent, of whom 1 became incontinent again during the study and 2 remained dry. In 18 children

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**Table 2. Continence at study enrollment, fluid intake and continence patterns**

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Continent</th>
<th>Urinary Incontinence</th>
<th>Nocturnal Enuresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pts (%)</td>
<td>111</td>
<td>44 (39.6)</td>
<td>41 (36.9)</td>
<td>11 (9.9)</td>
</tr>
<tr>
<td>No. motor disabled (%)</td>
<td>22</td>
<td>8 (36.4)</td>
<td>6 (27.3)</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>No. mentally disabled (%)</td>
<td>16</td>
<td>6 (37.5)</td>
<td>6 (37.5)</td>
<td>0</td>
</tr>
<tr>
<td>No. motor + mentally disabled (%)</td>
<td>73</td>
<td>30 (41.1)</td>
<td>29 (39.7)</td>
<td>7 (9.6)</td>
</tr>
<tr>
<td>% Fluid intake change:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 or Less</td>
<td>11</td>
<td>36.4</td>
<td>36.4</td>
<td>0</td>
</tr>
<tr>
<td>Greater than 25</td>
<td>63</td>
<td>39.7</td>
<td>38.4</td>
<td>9.6</td>
</tr>
<tr>
<td>Greater than 50</td>
<td>50</td>
<td>40.7</td>
<td>40.7</td>
<td>11.1</td>
</tr>
</tbody>
</table>

**Table 3. Continence pattern at study end**

<table>
<thead>
<tr>
<th></th>
<th>% Study Start/End (change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continence</td>
<td>Urinary Incontinence</td>
</tr>
<tr>
<td>Overall</td>
<td>39.6/46.9 (27.4)</td>
</tr>
<tr>
<td>Mentally disabled</td>
<td>37.5/46.7 (28.2)</td>
</tr>
<tr>
<td>Motor disabled</td>
<td>45.5/10.5 (−35.5)</td>
</tr>
<tr>
<td>Mentally + motor disabled</td>
<td>41.1/19.2 (25.1)</td>
</tr>
</tbody>
</table>

**Table 4. Fluid intake pattern**

<table>
<thead>
<tr>
<th></th>
<th>No. Fluid Intake (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Overall</td>
<td>10</td>
</tr>
<tr>
<td>Mentally disabled</td>
<td>4</td>
</tr>
<tr>
<td>Motor disabled</td>
<td>5</td>
</tr>
<tr>
<td>Mentally + motor disabled</td>
<td>1</td>
</tr>
</tbody>
</table>

---
Anticholinergics were started during the study due to persistent urinary incontinence despite adequate urotherapy, ie an individual fluid intake scheme, a personally adapted toilet chair, and a voiding and drinking diary. Of the patients 11 became continent on combined anticholinergics and continued adequate fluid intake. In 2 severely mentally and motor disabled children a daytime alarm was started to make them more alert to the bladder. Initially a positive reaction was noted but after 2 weeks the children did not want to cooperate further and even became angry with the device. This therapy was cancelled. In another 2 patients with only nocturnal enuresis a wetting alarm was started successfully.

DISCUSSION

Although urinary incontinence is a common feature in intellectually and physically disabled children, it remains poorly documented. The literature is sparse and mainly limited to prevalence and urodynamic findings in children with cerebral palsy. Reports of pathophysiology, prevention and treatment are rare and often restricted to case reports.

We performed a prospective, uncontrolled study in a population living in an institution for developmentally challenged children. The limitation of this study is that it was uncontrolled and done in a rather heterogeneous population according to the underlying pathological condition.

According to prevalence a wide variation in incidence is reported (between 23% and 86%),5–15 most likely because many studies were performed in a small population and included patients were inadequately categorized according to underlying pathological condition, age, mental and motor development, and incontinence type.

In our study 39.6% of the population achieved continence spontaneously. There were no significant differences in the continence pattern among the 3 subgroups. Achieving continence is a multifactorial process in which mental and motor development has an important role. In the pathophysiology of nocturnal enuresis and daytime urinary incontinence detrusor overactivity with or without decreased voided volume is often noted. Nocturnal polyuria and a disturbed arousal mechanism are the other main causative factors of nocturnal enuresis.16

According to the literature the prevalence of overactive detrusor in children with an intellectual and/or physical disability may be as high as 97%.17 Insufficient fluid intake and decreased voided volume are major problems in developmentally challenged children. Our results are comparable with those in the literature.13,14,18,19

Fluid intake is clearly influenced by pathological condition severity. Patients with a motor handicap have significantly lower fluid intake than patients with a single disability, mainly because they depend more on caregivers for help with normal daily activities such as eating, drinking and visiting the toilet. Swallowing problems are often thought to be a main reason why intellectually and physically disabled children have insufficient fluid intake. Our results do not sustain this theory. It seems that regardless of swallowing problems most of these children do not drink enough. We noted a

<table>
<thead>
<tr>
<th>Change</th>
<th>No. Pts</th>
<th>% Contience</th>
<th>% Day + Night Urinary Incontinence</th>
<th>% Day Urinary Incontinence</th>
<th>% Nocturnal Enuresis</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Fluid intake:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 or Greater</td>
<td>9</td>
<td>19.2</td>
<td>−36.4</td>
<td>11.1</td>
<td>6.0</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>25 or Greater</td>
<td>68</td>
<td>26.4</td>
<td>−20.8</td>
<td>−5.2</td>
<td>−0.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>50 or Greater</td>
<td>25</td>
<td>31.3</td>
<td>−20.7</td>
<td>−7.1</td>
<td>−3.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% Max voided vol:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greater than 25</td>
<td>58</td>
<td>11.1</td>
<td>−28.5</td>
<td>6.3</td>
<td>−8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Greater than 50</td>
<td>45</td>
<td>28.0</td>
<td>−34.0</td>
<td>6.0</td>
<td>8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
correlation between the severity of the swallowing problem, and voided volume and the degree of continence. The more severe the swallowing problem, the worse the therapeutic outcome.

A third of the patients had fecal incontinence and 27% had constipation. These data are somewhat lower than expected from the literature, probably because many parents and caregivers do not recognize these problems and only mentioned more severe cases. As described by many groups, we also found a strong correlation between fecal problems and urinary incontinence. Furthermore, a clear correlation between urinary incontinence and constipation is documented in the literature. Adequate fluid intake has a direct positive influence on urinary incontinence and is indirectly combined with a healthy diet for constipation.

This study clearly proves that increasing the fluid intake results in increased voided volume and significant amelioration of the continence pattern during the day and during the night. Increased fluid intake during the day causes improvement in voided volume, and a decrease in nocturnal diuresis and osmotic excretion because of increased daytime osmotic excretion. Although adapting fluid intake to a normal level is often time-consuming, it is probably one of the most important therapeutic factors for incontinence in physically and intellectually disabled children. A standard drinking protocol according to fluid intake quantity (1,500 mL/m² body surface), beverage quality and drinking time schedule (4 to 6 times daily) is the cornerstone of treatment and probably also of the prevention of urinary incontinence in developmentally challenged children. These children are often limited in their reaction to stimuli, such as full bladder sensation. Increased maximum voided volume and decreased nocturnal diuresis enable them to interpret and react more adequately to the desire to void, allowing them to reach the toilet in time. This contributes to achieving continence.

In some patients adequate fluid intake, toilet adaptation and toilet position amelioration as urotherapy are insufficient to achieve continence. In those cases when no contraindications exist, anticholinergics can be used successfully. Careful follow-up is needed, especially considering side effects such as concentration and behavioral problems. A wetting alarm during the day and night was used in some cases but because of low participation its value could not be determined. Further studies in larger series are necessary.

Urinary incontinence in developmentally challenged children is a multifactorial problem. Adequate therapy starts with a thorough diagnosis. Optimal fluid intake together with other urotherapies, such as toilet adaptation to achieve a stable toilet position, keeping a voiding and drinking diary, and constipation treatment, are the basics of therapy. In cases of persistent incontinence additional diagnostic investigations such as urodynamics and videourodynamics may lead to extra information and a change in therapy.

CONCLUSIONS

Developmentally challenged children are amenable to continence rehabilitation. Although urinary incontinence is a common, multifactorial problem, treatment is often not that complex. Adequate fluid intake has a major role in the treatment strategy in urinary incontinence, developmentally challenged children. It has a major impact on bladder capacity and constipation, which are 2 important comorbidity factors of urinary incontinence. Therapy starts with simple measures such as environment adaptation, adequate fluid intake and a healthy diet. These measures are often time-consuming and demanding but results often exceed expectations. Therapists must learn to adapt their attitudes to children needs instead of trying to adjust children attitudes to their needs.

REFERENCES


Approach to refractory urinary incontinence in children, with special emphasis on children with intellectual and/or physical disability.
Part 3.
General Discussion
Further research
General discussion

Treatment of urinary incontinence in children remains challenging. Urinary incontinence in children is a complex, multifactorial disease for which no golden standard therapy exists.

Treatment of incontinence in children feels like completing a puzzle in which some pieces are missing.

In this thesis some new “pieces” are presented.

For medical treatment of the overactive bladder, anti-muscarinic agents are still regarded as first-line therapy. Oxybutinin chloride is the standard antimuscarinic drug. This drug is effective, but its use is limited by systemic adverse events, in a significant proportion of children, which may result in poor compliance or even discontinuation of treatment.

Is tolterodine an effective and better tolerated alternative for oxybutinin in the treatment of urinary incontinence due to overactive bladder in children? (paper 1)

Tolterodine, a potent and selective anti-muscarinic drug was specifically developed for the treatment of detrusor overactivity. At the moment of this study, controlled studies of tolterodine were only available for adults. These studies showed tolterodine to be equally effective and to result in significantly fewer adverse events than oxybutinin.

Despite limitations of this study, the fact that it is retrospective, non-controlled, and non-randomized, our study has some advantages. The major advantage is the fact that it includes a non-selected, general population of urinary incontinent children with an overactive detrusor.

According to efficacy we found tolterodine to be very effective in the treatment of symptoms, i.e. increase in maximum voided volume, and decrease in number of micturations/24 hours and number of incontinence episodes / 24 hours, of overactive detrusor in children. The effect was independent of previous treatment with a non-selective antimuscarinic, and was not significantly influenced by associated pelvic floor therapy.

Results of our study illustrate that tolterodine is better tolerated than oxybutinin, particularly with respect to the frequency and intensity of side-effects, behavioural disorders, accommodation abnormalities and other side-effects.
Currently published studies do confirm our findings. Bolduc et al. found that in the subgroup of patients who couldn't tolerate oxybutinin, 77% were able to continue tolterodine treatment with no significant side effects. [291] Christoph et al. performed a study on long-term efficacy of tolterodine and patient compliance in children with neurogenic detrusor overactivity. [289] They found that regular tolterodine application significantly improved bladder volume, maximum detrusor pressure and detrusor compliance. The 17% mild side effects they found was higher than the 3% we observed. These mild side effects were well tolerated by the patients. Similar results were found by Reddy et al. [296] Ellsworth et al. didn't find a relationship between dose and adverse events. [419]

The only double-blind, placebo-controlled studies of tolterodine ER in children suffering urgency urinary incontinence by Nijman et al., confirmed that short-term (12 weeks) as well as long-term treatment (12 months) with tolterodine ER is well tolerated in children. [297, 420]

Is there a place for Solifenacin in the treatment of therapy resistant overactive bladder? (paper 2)

Solifenacin succinate is a specific antimuscarinic drug with a high affinity for the M3 muscarinic receptor. The efficacy and long-term safety of this once daily oral antimuscarinic agent developed for OAB in adults was illustrated in the review paper of Basra et al. [421]

Since a lot of children with OAB do not or insufficiently answer to standard therapy, we started to use solifenacin off label in a group of children with therapy resistant urinary incontinence. In a retrospective study we reviewed the results of 138 children treated with solifenacin. Due to the higher specific receptor affinity (predominantly M3) we expected solifenacin to be associated with a lower side effect rate. Especially central nervous system effects, which are related to the ability to cross the blood-brain barrier, were expected to be less present. While 39% of the children had side effects on other anticholinergics only 6.5% had side effects on solifenacin. Except for faecal impaction (1 patient) the side effects were considered mild. Only 2 patients had behaviour problems, 1 suffered drowsiness, 1 insomnia and 5 gastrointestinal problems. So the side effect profile of solifenacin in children may be considered excellent despite the retrospective design of the study. Remarkably 5 of the 9 patients with side effects on solifenacin also had side effects on the previous anticholinergic therapy. This might suggest that some patients are likely to have higher sensitivity to anticholinergic side effects than others. The restriction of this study is that it only documents clinical safety based on side effects. Further pharmacokinetic studies are needed to proof the safety of this drug in children.

The overall efficacy was 85%. More than 50% of the responders were full responders, and 46% were partial responders.
Due to the significant increase (25%) in voided volume, the effect on daytime incontinence seems to be more pronounced than the effect on nighttime incontinence. The response in children with EN depends less on voided volume since many of them need further alarm treatment to become dry at night even when voided volume is normalized.

According to our findings, solifenacin seems to be a good if not superior alternative for oxybutinin. As long as there are no prospective, controlled studies with pharmacokinetic and pharmacodynamic data available, solifenacin can only be used off-label in children.

**What about Botulinum-A toxin? Can it be used in the treatment of children with therapy resistant overactive detrusor? (paper 3)**

Botulinum-A toxin is a potent neurotoxin that has been successfully used in the treatment of neurogenic detrusor overactivity and recently also in idiopathic detrusor overactivity in adults. Until our study the urological application in children was restricted to limited experience with the treatment of neurogenic detrusor overactivity in patients with meningomyelocoele.

Due to the high prevalence of OAB in the paediatric population, which is often hard to treat, we are looking for safe alternative treatment options. As Botulinum-A toxin was safely and efficiently used to treat overactivity of the detrusor in adults and children with neurogenic overactivity of the detrusor, we designed a prospective uncontrolled pilot study to evaluate the safety and efficacy of Botulinum-A toxin in children with a nonneurogenic overactive bladder.

Although the effect of a Botulinum-A toxin is temporary, we found it to last longer in our population than in adults and children with neurogenic overactive detrusor. Perhaps the fact that the treatment was used for a disorder that is an expression of a maturation delay of detrusor function rather than a structural anomaly, can account for this longer and better effect. Overactivity inhibition can allow detrusor control to mature.

In the long-term follow up group (≥ 6 months) 9 of the 15 patients showed a full response, 3 a partial response and 3 remained unchanged.

The side effects reported were temporary urinary retention in 1 girl, temporary vesicoureteral reflux in a boy and lower urinary tract infection in 2 girls. No other side effects were seen. On postoperative uroflow, 4 patients showed temporary dysfunctional voiding characteristics. In 1 girl post-void ultrasound showed significant residual urine and 4 other patients had minimal post-void residual urine. After 6 weeks all patients voided spontaneously to completion.
Other side effects, such as systemic weakness or paralysis are unlikely to occur if the dose does not exceed a maximum of 300 U. In this study no systemic side effects were noted. It seems to be important to keep the injected volume as low as possible because the risk of systemic absorption and generalized weakness seems to be related more to the volume than to the quantity of Botulinum-A toxin.\[422, 423\]

According to the safety of this therapy, at this point no major short-term and long-term adverse effects have been described in children. The concern raised by Bettina Jorgensen according to the risk that the toxin may create irreversible long-term side effects, e.g. ultrastructural and functional changes of the detrusor, is questionable as long as no long term studies have been performed.

The question about optimal dosage in children remains unanswered. We used a dose of 100 U Botulinum-A toxin. This dose, which was selected rather arbitrarily, is lower than the dosages used by other authors in children with neuropathic overactive bladder.

Possibly some children may need multiple injections. It is known that repeat injections may induce resistance to Botulinum-A toxin. It has been shown that shorter intervals between doses and higher doses contribute to the development of resistance. Therefore, it is recommended to avoid booster injections, leave at least a 3-month interval between 2 treatments and use the smallest clinically effective dose.

In our view the clinically effective dose is less influenced by the body weight of the child than by the bladder properties, such as bladder mass and detrusor compliance. We postulate that the thicker the bladder wall, as estimated on ultrasound, the more muscle mass and the higher the dose needed to have a long lasting effect.

Therefore it is of utmost importance to develop an adequate method of determining the clinically effective dose, to avoid booster and quick repeat injections, which induce resistance and inevitably will lead to elimination of this valuable treatment. Dose response studies are absolutely needed in order to establish this issue.

In the current study it seems that partial response was a poor prognostic factor for efficacy after repeat injection. Three partial responders underwent repeat injection but only one responded. One full responder who had relapse showed a new full response after a second injection. Thus, probably a full response after the first injection is a good prognostic factor for further injection therapy. Repeat injections seem to be as safe and effective as the first injection.

The results of our study are very promising, but it is clear that before Botulinum-A toxin can be used as a primary therapy for overactive detrusor in childhood, further research and placebo controlled studies are necessary.
Does it make sense to use a daytime alarm as cognitive training in the treatment of therapy resistant children with daytime incontinence? (paper 4)

In some children suffering therapy resistant urinary incontinence, lack of awareness is an important part of the persistent problem. Many of these children are no longer aware of incontinence and wet pants are ignored. Therefore, it was postulated that increasing awareness, by drawing the attention of the child to bladder behaviour could improve the problem by teaching them to go to toilet in time.

Indeed, before being able to respond to an involuntary event the patient must recognize that signs that accompanies the event. In cases of overactive detrusor wetting occurs at the time of an overactive detrusor contraction. Relearning to recognize the feeling of urge proceeding urge incontinence enables the patients to prevent wetting by going to the toilet on time or by central inhibition of the overactive detrusor contraction.

The daytime alarm method was first described by Vijverberg et al. in an inpatient setting. Our patients were trained on an outpatient basis.

Halliday et al. stated that a noncontingent alarm produces as good response as a contingent alarm. In our opinion, certainly in children with persistent, therapy resistant urinary incontinence during the day, it is preferable and certainly more physiological to use a contingent alarm. This is the only method to make these children aware of bladder function, leading to adequate bladder control and better continence. Certainly motivation and compliance are important factors in the success of this treatment modality. This explains the good results after 2 weeks of training: 62% full response, 8% partial response and 30% failure. Decreases in patient motivation and attention are certainly a reason for the high relapse rate 6 weeks after training was completed: 35% full response, 35% partial response and 30% failure. Almost no difference was found between the results after 6 weeks and after 1 year. This made us believe that once a child has learned to cope with bladder dysfunction a positive, lasting continence result may be achieved.

We believe that other factors, such as natural resolution of wetting, which are undoubtedly important for the outcome of treatment in the whole population of children with daytime incontinence, were far less important in this highly select group of children with persistent daytime incontinence who showed no progress while on common therapy during a mean of 21.6 months.

Also, because overactive bladder in childhood is considered a consequence of maturation delay, it is postulated that this treatment enhances the further maturation of detrusor function.
This theory is consolidated by the recent findings by Vermandel et al. who advocated the use of a daytime alarm as an effective option for toilet training young healthy children to limit the time to complete toilet training in many children.\[265, 266]\]

Daytime alarm is certainly a useful device in children with therapy resistant urinary incontinence during day. Outpatient use is preferable to inpatient treatment not only for psychological, but also for economic reasons.

**Urinary incontinence in physically and/or intellectually disabled children is a common problem. What is the importance of dysfunctional voiding in this population? Does restricted fluid intake play an important role in incontinence? And if so does adequate fluid intake contribute to the treatment of urinary incontinence in these patients? (paper 5 and 6)**

Urinary incontinence in physically and intellectually disabled children is a common yet poorly investigated problem. Far too often urinary incontinence is considered normal, unavoidable and even a minor problem in this group of patients.

In our first prospective pilot study we found an incidence of 52.7%. In our more current prospective study performed in 111 patients, 39.6% achieved continence spontaneously, 36.9% had daytime and nighttime urinary incontinence, 9.6% had daytime incontinence and 13.5% had nocturnal enuresis. No significant difference was found among the 3 subgroups. Both studies showed that urinary incontinence during day and night was the most common presenting symptom. The overall incidence of urinary incontinence is clearly higher in the study group than in a normal paediatric population.

To our knowledge there have been no studies of this population on the voiding pattern evaluated by uroflowmetry performed in their own environment. In paper 5 we described the results of uroflowmetry. A disturbed uroflow pattern, the most common of which was dysfunctional voiding, staccato or fractionated, was found in 65.8%. Remarkably, no correlation between the uroflow and continence patterns could be found. In fact the incidence of daytime and/or nighttime incontinence was higher in the patients with a normal uroflowmetry than in patients with a disturbed uroflow pattern. No clear correlation could be found among continence pattern, uroflow pattern, mental development and motor disability.

In paper 5 the influence of mobility and mental development on continence was evaluated. The more mobile and the higher the IQ the higher the continence rate. In this study population mobility seems to play a major role in achieving continence compared to mental development. Children with a low IQ but reasonable degree of mobility were continent, where as children with a higher IQ but a high degree of immobility were incontinent.
In both studies about 90% of the children had an insufficient maximum voided volume. This was neither influenced by motor development nor by type of motor disability.

In children with severe and moderate swallowing problems the mean maximum voided volume deficit was higher than in those without swallowing problems.

In the pilot study (paper 5) the urinary osmolality was measured in all children. The general too high osmolality suggested that fluid intake was too low in all children. In the current study specific attention was paid to the fluid intake. Only 9.9% had a normal fluid intake. According to our results fluid intake is clearly influenced by severity of the underlying pathology. Patients with mental and a motor handicap have significantly lower fluid intake than patients with a single disability, mainly because they depend more on caregivers for help with normal daily activities such as eating, drinking and visiting toilet.

Swallowing problems are often thought to be the main reason why intellectually and physically disabled children have insufficient fluid intake. The results of paper 6 do not sustain this theory. It seems that regardless of swallowing problems most of these children do not drink enough. We noted a correlation between the severity of the swallowing problem, and voided volume and the degree of continence. The more severe the swallowing problem, the worse the therapeutic outcome.

Inadequate fluid intake is mainly because of insufficient hydration of the patient due to their environment.

Increased fluid intake to a normal level of 1500ml/m² resulted in a significant increase in continence and maximum voided volume in those with important decreased fluid intake at start of study. Adequate fluid intake has a direct positive influence on urinary incontinence, and is indirectly influencing urinary incontinence combined with a healthy diet for constipation. This study clearly proves that increasing the fluid intake results in increased voided volume and significant amelioration of the continence pattern during the day and the night. An increase in continence of 27.4% was found.

Although adapting fluid intake to a normal level is often time-consuming, it is probably one of the most important therapeutic factors for incontinence in physically and intellectually disabled children. A standard drinking protocol according to fluid intake quantity, beverage quality and drinking time schedule is the cornerstone of treatment and probably also of the prevention of urinary incontinence in developmentally challenged children. These children are often limited in their reaction to stimuli, such as a full bladder sensation. Increased maximum voided volume and decreased nocturnal diuresis enables them to interpret and react more adequately to the desire to void and allows them to reach the toilet in time. This contributes to achieving continence. In some patients adequate fluid intake, toilet adaptation and toilet position amelioration
are insufficient to achieve continence. In those cases when no contraindications exist, anticholinergics can be used successfully.

Developmentally challenged children are amenable to continence rehabilitation. Although urinary incontinence is a common, multifactorial problem, treatment is often not that complex. Adequate fluid intake has a major role in this treatment strategy.

**Consequences of these studies.**

Based on the results of these studies we developed a therapeutical strategy in the treatment of urinary incontinence in children.

In the normally developed children urotherapy still remains the basic intervention. Urotherapy alone often fails in the treatment of urinary incontinence due to OAB. In case of proven OAB and after exclusion of neurogenic bladder, obstructive uropathy and underactive detrusor, antimuscarinics are started. The side effects of oxybutinin are well explained to the parents and the existence of the alternatives tolterodine and solifenacin is mentioned. As the safety of solifenacin in children has not been proven in literature the use of the latter is restricted to children with a bodyweight of more than 25 kg.

The main disadvantage of tolterodin and solifenacin is the fact that they are expensive and not reimbursed in contrast to oxybutinin. This is probably the main reason why oxybutinin is still the first choice of a lot of parents. In case of important side effects or inefficacy tolterodin or solifenacin are started with a clear preference for solifenacin due to the promising results and the fact that it is a once daily dosage.

Neuromodulation can be started as mono-therapy or additional therapy in those patients who prefer this treatment, in those who refuse medication, and in those whom anti-muscarinics are insufficient or have to be stopped because of side effects.

If therapy fails because of lack of motivation and low compliance of parents and child, additional psychotherapy and even an inpatient treatment in the voiding school is offered.

In case of refractory urinary incontinence, and urodynamically proven bladder overactivity and reduced bladder capacity, despite good patients’ compliance and adequate followed therapy a treatment with Botulinum-A toxin is proposed.

The daytime alarm remains the ultimate treatment for the hard core daytime wetters.

In children with an intellectual and/or physical disability suffering urinary incontinence adequate fluidintake is the major urotherapeutical step. A fluidintake of 1500ml/m²
bodysurface spread over the day should be achieved. A stable toilet position is also of utmost importance.

If anti-muscarinics are necessary, tolterodin and solifenacin are preferably prescribed because of their favourable spectrum of side effects.

We tried to use the daytime alarm in a few children without good result.

Until now we have no experience with the use of neuromodulation and Botulinum-A toxin in these patients, and to our knowledge this has not been described in literature.
Further research

Considering the safety and effectiveness of new, more selective anti-muscarinics, prospective, double blind controlled studies in children are needed. Pharmacokinetic and pharmacodynamic and dose response relation should be investigated in order to be able to use these drugs in the first line therapy of OAB.

The same is true for Botulinum-A toxin. Dose finding for this application is more specifically important. These studies will be industry driven but from our academic setting we should be involved in order to have good level of evidence after these studies.

Urinary incontinence in developmentally challenged children remains a poorly investigated problem. Most studies are in small, very heterogeneous populations. Therefore multicentre prospective, large scale studies in well defined subgroups, according to underlying causal pathology, are needed. The methodology developed for this thesis and proven to be effective should be used to explore larger groups of patients.

Finally some more basic research is needed into the pathophysiology of lower urinary tract conditions in both healthy and disabled children. Natural fill urodynamic studies, functional MRI and electrophysiological investigations should be planned in patients next to basic research in animal models.
Approach to refractory urinary incontinence in children, with special emphasis on children with intellectual and/or physical disability.
Part 4. Dutch Summary
In deze thesis wordt de geactualiseerde aanpak van moeilijk te behandelen, vaak therapieresistente urinaire incontinentie bij kinderen weergegeven.

Urinaire incontinentie bij kinderen is een complex probleem, dat door multipel factoren beïnvloed wordt en waarvoor geen gouden standaard therapie bestaat.

In het eerste deel van deze thesis wordt de terminologie, de fysiopathologie, de diagnostiek en de gangbare therapie van urinaire incontinentie en enuresis bij kinderen belicht. De problematiek van urinaire incontinentie bij kinderen met een mentale en/of motorische retardatie wordt daarbij apart benaderd.

Antispasmodica en anticholinergica behoren tot de eerstelijns therapie voor urinaire incontinentie en enuresis veroorzaakt door een overactieve detrusor. Oxybutininechloride is in de pediatrische urologie nog steeds het standaard anticholinergicum. Dit medicijn is zeer effectief, maar heeft het grote nadeel bij kinderen een behoorlijk aantal systemische bijwerkingen te veroorzaken, die het gebruik ervan limiteren.

In artikel 1 en 2 wordt het gebruik van twee nieuwere, meer blaasspecifieke anticholinergica, die nog niet geregistreerd zijn voor pediatrisch gebruik, bij kinderen met urinaire incontinentie en/of enuresis bestudeerd.

In artikel 1 wordt retrospectief de effectiviteit en veiligheid van tolterodine bij kinderen met een overactieve blaas nagegaan. In deze studie werden 256 kinderen geïncludeerd. Uit deze studie bleek dat tolterodine zeer effectief was bij de behandeling van symptomen van overactieve detrusor. Er werd een significante toename van het maximum geplast volume, een afname van het aantal micties / 24 uur en een vermindering van het aantal plasaccidenten per 24 uur waargenomen. Slechts bij 3% van de kinderen werden milde bijwerkingen van de medicatie gezien, die slechts in 2 gevallen leidden tot stopzetten van de behandeling.

In het tweede artikel wordt op retrospectieve wijze het gebruik van solifenacine bij kinderen met een overactieve overactiviteit van de blaas bestudeerd. Deze niet-gecontroleerde, retrospectieve studie werd uitgevoerd op een populatie van 138 kinderen met therapie resistente overactieve blaas. Slechts 6.5% van de kinderen hadden bijwerkingen op solifenacine. Behalve fecale impactie, gediagnosticeerd en behandeld bij 1 kind, ging het om milde bijwerkingen. Opvallend was het feit dat 5 van de 9 kinderen met bijwerkingen op solifenacine ook voordien al bijwerkingen hadden op oxybutinine, wat er kan op wijzen dat sommige kinderen meer gevoelig zijn voor anticholinerge bijwerkingen dan andere.

De medicatie leidde bij 50% van de kinderen tot volledige respons, 46% waren partiële responders en bij 4% had de behandeling geen effect. Gezien de significante toename van het geplast volume onder deze medicatie was het effect van solifenacine meer uitgesproken bij kinderen met urinaire incontinentie dan bij kinderen met enuresis.
Gebaseerd op deze resultaten is solifenacine een waardig, misschien wel superieur alternatief voor oxybutine. Verdere prospectieve, gecontroleerde studies met farmacokinetische en farmacodynamische gegevens zijn noodzakelijk. Zolang kan solifenacine enkel off-label gebruikt worden.

In het derde artikel wordt het gebruik van botuline-A toxine (Botox®) in de behandeling van kinderen met therapie resistente overactieve detrusor beschreven.

In deze prospectieve studie werden 21 kinderen met therapie resistente niet-neurogene detrusor overactiviteit geïncludeerd. Al deze kinderen hadden een te beperkte blaascapaciteit volgens hun leeftijd en vertoonden aandrang en aandrangincontinentie.

Bij de groep die langer dan 6 maand na het injecteren van de Botox® gevolgd werd, waren 9 van de 15 kinderen volkomen succesvol behandeld, 3 vertoonden een partieel antwoord op de therapie en bij 3 werd geen verbetering van de klachten waargenomen.

Het gebruik van Botox® in de blaas bleek voor wat de korte termijn opvolging betreft veilig te zijn. Slechts 1 meisje ontwikkelde een tijdelijke retentie, een jongen vertoonde tijdelijk klachten van vesico-ureterale reflux. Vier kinderen hadden een tijdelijk disfunctioneel uroflow patroon. Echografisch werd bij 1 meisje een significant postmictioneel residu waargenomen en 4 kinderen hadden een minimaal residu. Na 6 weken plasten alle kinderen terug spontaan leeg. Systemische bijwerkingen werden in deze studiepopulatie niet waargenomen.

Opvallend was het feit dat de patiënten met een partieel antwoord op de initiële Botox® injectie het ook bij een tweede behandeling niet goed deden. Het patiëntje dat een herval kende na een initieel succesvolle behandeling, was ook na een tweede injectie terug volkomen droog.

Bij alle kinderen werden 100 IE geïnjecteerd in de detrusor. Het gaat daarbij om een vrij arbitrair gekozen dosis, lager dan de dosis gebruikt bij kinderen met neurogeen blaaslijden.

Er is dan ook absolute nood aan het bepalen van de minimaal effectieve dosis. Enkel op die manier kunnen booster injecties en te snel herhalen van de behandeling, die leiden tot resistentie en eliminatie van deze methode, vermeden worden.

De resultaten van deze studie laten het beste verhopen voor het gebruik van Botox® in de behandeling van de overactieve blaas bij kinderen. Verder onderzoek en placebo gecontroleerde studies zijn echter noodzakelijk.

In de vierde publicatie wordt het gebruik van de dagwekker bij kinderen met broekplassen beschreven.
Bij sommige kinderen met therapie resistente urinaire incontinentie speelt een gebrek aan bewustzijn van het probleem een belangrijke rol in het persisteren van de klacht. Een contractie van de overactieve detrusor ligt aan de basis van de urinaire incontinentie bij deze kinderen. Door middel van de dagwekker trachten we de kinderen beter het aandranggevoel te leren interpreteren zodat zij daarop kunnen anticiperen door tijdig naar het toilet te gaan.


In artikel 5 en 6 wordt het probleem van urinaire incontinentie bij kinderen met een mentale en/of motorische retardatie bestudeerd. In publicatie 5 worden de resultaten van een piloot-studie uitgevoerd bij 38 kinderen weergegeven. Slechts 47.4% van deze kinderen was continent. In artikel 6 worden de resultaten van een prospectieve studie bij 111 kinderen beschreven. Slechts 39.6% van de kinderen waren continent bij het begin van de studie.

De piloot-studie is de eerste studie waarin het plaspatroon wordt bestudeerd door middel van een uroflow geplaatst in de leefwereld van de kinderen. Meer dan 65% van de kinderen had een disfunctionele uroflow curve. Opvallend daarbij was dat er geen correlatie kon aangetoond worden tussen het uroflowpatroon en het continentiepatroon. Ook de invloed van de mobiliteit en de mentale ontwikkeling op het verwerven van continentie werd nagegaan. Mobiliteit bleek bij deze populatie een belangrijkere invloed te hebben dan mentale ontwikkeling.

Uit beide studies bleek dat meer dan 90% van de kinderen een te klein blaasvolume hadden.

Uit de eerste studie bleek dat urinaire osmolaliteit bij de meeste kinderen te hoog was. Dit liet vermoeden dat deze kinderen een te beperkte vochtinname hadden. In de tweede studie werd de vochtinname van de kinderen in kaart gebracht. Minder dan 10% van kinderen had een normale vochtinname. De vochtinname werd duidelijk beïnvloed door de ernst van de ontwikkelingstoornis. Patiënten met een gecombineerde motorische en mentale handicap deden het beduidend slechter. Vaak wordt gedacht dat slikproblemen een belangrijke oorzaak zijn van de beperkte vochtinname. De resultaten van studie 6 weerleggen dit ten dele. Onafhankelijk van de graad van slikmoeilijkheden bleken de meeste kinderen te weinig te drinken. Wel was er een correlatie tussen de ernst van de slikstoornis, en het blaasvolume en de graad van continentie. Bovendien bleken kinderen met een ernstig slikprobleem moeilijker te behandelen.
Aanpassen van de vochtinname tot een niveau van 1500 ml/m² resulteerde in een significante toename van de continentie met 27,4%.

Deze studie toont duidelijk aan dat aanpassen van het drinkgedrag, ook al is dit vaak erg tijdrovend, leidt tot een normaliseren van het geplast volume en tot een duidelijke verbetering van de continentie.

Samen met enkele andere maatregelen, zoals aanpassen van het toilet aan de noden van de patiënt, vormt aanpassen van het drankschema een hoeksteen van de urotherapie bij incontinentie kinderen met een ontwikkelingstoornis.

Uit deze studies blijkt dat urinaire incontinentie een complex probleem is waarvoor tot op heden geen standaard therapie bestaat.

Gebaseerd op de resultaten van deze studies hebben wij onze therapeutische strategie voor het behandelen van urinaire incontinentie bij kinderen aangepast.

Bij “normaal” ontwikkelde kinderen blijft urotherapie de basis behandeling. Wanneer overactiviteit van de blaas de incontinentie veroorzaakt, is deze urotherapie als monotherapie vaak ontoereikend. In die gevallen, en pas nadat neurogeen blaaslitten, obstructieve uropathie en een onderactieve detrusor zijn uitgesloten, zal antimuscarine medicatie gestart worden. Oxybutinine blijft daarbij tot vandaag het enige erkende, terugbetaalde middel bij kinderen in België. De bijwerkingen van dit product en het bestaan van alternatieve middelen zoals tolterodine en solifenacine worden uitvoerig met de ouders besproken. Daar de veiligheid van solifenacine bij kinderen nog niet bewezen is, wordt dit product enkel gebruik bij kinderen die meer dan 25 kilogram wegen.

Daar tolterodine en solifenacine duur zijn, verkiezen de ouders vaak eerst een behandeling met oxybutinine. Bij ernstige bijwerkingen of onvoldoende resultaat met oxybutinine wordt tolterodine en solifenacine voorgesteld, met een voorkeur voor solifenacine gezien de veelbelovende resultaten van onze studie en het feit dat patiëntje maar één keer per dag medicatie dient in te nemen.

Neuromodulatie kan als monotherapie of als supplementaire behandeling gestart worden bij die patiënten die deze therapie verkiezen, bij hen die medicatie weigeren en bij diegene waar antimuscarine middelen onvoldoende werken of te veel bijwerkingen veroorzaken.

Wanneer de therapie faalt door gebrekkige medewerking of motivatie van het kind en/of de ouders wordt psychotherapie en soms zelfs een opname in de plasschool voorgesteld.
Bij persistenderende urinaire incontinentie, met urodynamisch bewezen overactiviteit van de blaas en beperkte blaascapaciteit, ondanks een adequate therapie en therapietrouw, heeft een intravesicale injectie met Botuline-A toxine zijn plaats.

De dag plaswekker wordt voorbehouden voor de zogenaamde “hard core” broekplassers.

Bij kinderen met een mentale en/of motorische handicap is optimalisatie van het drinkgedrag en de vochtinname de eerste stap in de behandeling. Een vochtinname van 1500ml/m² lichaamsoppervlak, gespreid in de dag, dient te worden nagestreefd. Ook aandacht voor de toilethouding is bijzonder belangrijk.

Indien een behandeling met anti-muscarine medicatie noodzakelijk is, verdienen tolterodine en solifenacine de voorkeur omwille van hun gunstiger bijwerking spectrum.

De dag plaswekker werd enkele keren gebruikt zonder gunstig resultaat.

Tot op heden hebben we geen ervaring met Neuromodulatie en Botuline-A toxine bij deze patiënten.

De zoektocht naar nieuwe, veiligere, meer adequate middelen om de urinaire incontinentie, en dan zeker de resistentie vormen ervan, te behandelen dient onverminderd verder gezet te worden. Belangrijk daarbij is het feit dat kinderen geen minivolwassenen zijn en dat studieresultaten bij volwassen vaak niet geëxtrapoleerd kunnen worden naar de pediatrische populatie. Uitgebreid onderzoek naar de farmakokinetiek en grote gerandomiseerde, gecontroleerde, dubbel blinde prospectieve studies naar de farmokodynamiek van nieuwe geneesmiddelen zijn dan ook uiterst noodzakelijk.


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Fields of special interest:  
- Paediatric Urological Laparoscopy  
- Voidingdysfunction in children with a mental and/or motor disability  
- Uro-lithiasis in children
Membership:
- ESPU
- EAU
- ICCS

Awards:
- Laureate of the “Professor Elautprijs” 1999 Belgium
- Best Poster Presentation in the session « Pediatric voiding disorders – trauma and tumours » van XV th Congress of the European Association of Urology, Brussels 2000, with the poster « Detrusor pressure is more harmful for renal function then bacteriuria in patients with voiding dysfunction and vesico - ureteral reflux »

Courses:
- Training Endoscopic Surgery : Ethicon Endo - Surgery : 14 April 1992
- ESPU Study Day : Perinatal Uro-Nephrology Symposium, Robinson College Cambridge, September 29, 1995
- 1st Annual European Course in Urology, Rome, November 4-9, 1996
- 1997 Second Course on Paediatric Urodynamics, September 12-13, 1997, Utrecht
- 1999 ESPU Course Aarhus Denmark, September 16-18, 1999
- 2e ICCS - Course : Diagnostic and therapeutic approach to non-neuropathic bladder sphincter dysfunction in children, Ghent, September 24-25, 2000
- 2001 Laparoscopic Paediatric Urology ESPU Practical Post-Congress Course ; April 29-30, 2001
- 2004 Laparoscopic Paediatric Urology ESPU Course; April 2004, Regensburg: Germany

Co-ordination and organization of Voiding Camp Deinze, Belgium

Publications and abstracts:

A. Publications


11. Persistent enuresis caused by nocturnal polyuria is a maturation defect of the nycthemeral rhythm of diuresis: J. Vande Walle, P. Hoebeke, E. Van Laecke, D. Castillo, D. Milićič, Che Maraina Che Hussein, A. Raes; BJU Int. 1998 May; 81 Suppl. 3: 40-5


B. Books

C. Publications

D. Abstracts
Author and co-author of several abstracts presented in international paediatric urology meetings.
Dankwoord
Een thesis schrijven is als een berg beklimmen. Je begint eraan met het idee dat je weet wat je te wachten staat, maar gaande weg wordt je geconfronteerd met de realiteit. Bergpaden blijken steile rotswanden te zijn en sneeuwvelden blijken gletsjers met aardig wat spleten.

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nog vaker kattenkwaad uithalen. Drie werf hoera!!!
Approach to refractory urinary incontinence in children, with special emphasis on children with intellectual and/or physical disability.