Overactive Bladder and Dysfuntional Voiding: Drug Therapy

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New Advances in LUT Dysfunction

The Standardization of Terminology of Lower Urinary Tract Function in Children and Adolescents: Report from the Standardisation Committee of the International Children's Continence Society


- **Overactive Bladder**: urgency +/- frequency, +/- incontinence
  May have detrusor overactivity [DO] on cystometry

- **Dysfunctional Voiding**: habitual contraction of the urethral sphincter during voiding
  Confirmed on uroflow with staccato (intermittent) pattern
  Not a storage phase malfunction

Overactive Detrusor and Dysfunctional Voiding (DV)
New advances in LUT dysfunction
ICCS Guidelines

Diagnostic evaluation of children with daytime incontinence
P. Hoebeke, W. Bower, A. Combs, T. De Jong, S. Yang
*J Urol* Vol 183, 699-703. Feb 2010

**New Advances in LUT Dysfunction**
**ICCS Guidelines**

- The Management of Dysfunctional Voiding in Children: A Report from the Standardization Committee of the International Children’s Continence Society
  J. Chase, P. Austin, P. Hoebeke, P. McKenna *J Urol* 183: 1296-1302, April 2010

- Define etiology
- Treat co-existing constipation
- Non-pharmacologic therapy
  - Behavioral modification
  - Pelvic floor therapy
- Pharmacologic therapy
  - Antimuscarinics
  - Alpha blockers
  - Botox
Etiology

• Neurologic
  – Myelomeningocele – 37% of newborns
  – Occult spinal dysraphism
  – Sacral agenesis
  – VACTERL syndrome
  – Spinal cord disease (injury, tumor)
  – CNS – cerebral palsy

• Anatomic
  – Posterior urethral valves (1% early; 5 -10% late 2\textsuperscript{o} nephrogenic DI)
  – Bladder outlet obstruction (sphincteric ureterocele, diverticulum, urethral stricture, 1\textsuperscript{o} bladder neck obstruction)
  – Vesico-ureteral reflux

• Functional
  – Voiding postponement
  – Dysfunctional voiding
  – Constipation

Presentation

• Normal Patterns of Elimination:
  – Voiding: 4 – 7 x / day
    – Steady, ‘bell-shaped’ curve
  – Bowel movements: daily / every other day
    – Type 3 or 4 on Bristol Stool Scale
Presentation

- Symptoms:
  - Urgency, urge incontinence
  - Incontinence – day & / or night,
  - Giggle incontinence (symptom or a disease)
  - Increased / decreased voiding frequency
  - Voiding postponement
  - Holding maneuvers (Vincent’s curtsy, squatting)

- Co-morbidities
  - Urinary infection
  - Constipation / fecal incontinence
  - High / low fluid intake
  - History of uropathy (puv, ureterocele)
  - ADD, ADHD
  - Psychological factors

Overactive Bladder

- Strong desire (or urgency) accompanied by a fear of leakage or pain
  - holding maneuvers (squatting, sit on heel, leg crossing, holding penis)
  - frequent voiding - day ($\geq 6$ x); night ($\geq 1$ x)

- Pseudo-urgency (behaviorally induced 2$^\circ$ voiding postponement)

- Accounts for the majority of cases of daytime incontinence

- 9 - 16% of adults have OAB

- Incidence in children remains unclear; may be related to age and gender

- Association that adults with OAB often have symptoms in childhood suggestive of the disease

Abrams et al, Urology 61: 37, 2003
Incidence of Incontinence

- Prevalence depends on several factors
- Assessment of symptoms
- Methods of data collection
- Criteria for definition
- Population to be analyzed
- In children, age and gender are factors
- Day incontinence varies between 30% at age 4 to 1.8% of 15 – 17 yr olds

_Wellstrom et al, Brit J Urol 76: 231, 1995
Yeung et al, J Urol 171: 2595, 2004_

Incidence of OAB in Childhood

- 19,240 Korean children ages 5 – 13 responded to a questionnaire about elimination habits
  - Overall incidence of OAB = 16.6%
  - No differences in gender
  - Incidence 23% → 12.2%
  - The ratio of children with OAB who were dry : wet changed with increasing age from 47.5 → 77.3
  - Thus, with ↑ age children control OAB better but don’t lose the OAB

_Chung et al, Urology 73: 69, 2009_
Prevalence of Overactive Bladder in Korean School Aged Children

Chung et al, Urology 73: 69, 2009

Prevalence of Overactive Bladder in Korean School Aged Children

Chung et al, Urology 73: 69, 2009
Overactive Bladder

Uroflow curve

Voided volume: Decreased
Residual urine: None
Dysfunctional Voiding

Warning! May be neuropathic bladder!

Uroflowmetry plus EMG

PF - Overactivity (EMG)
Dysfunctional voiding

Uroflow curve

Residual urine: yes

Voided volumes: variable

Pharmacotherapy: Anticholinergics

- Mollifies OAB symptoms
- Targets detrusor overactivity
  - NGB
  - LUTS
- Level 1 evidence of ACh efficacy
  Andersson et al, Curr Opin Urol, 19:380, 2009
- Must monitor constipation and post-void residuals
LUT Dysfunction
Therapeutic Options (pharmacological)

Anticholinergics
α-blockers
Botulinum-A toxin injection

Pharmacotherapy should preferably not be a first-line treatment!

Pharmacotherapy: Antimuscarinics
Muscarinic receptors: 5 subtypes

\[ M_1 \] – brain, eye, salivary glands, sympathetic ganglia
\[ M_2 \] – bladder, brain, eye, heart
\[ M_3 \] – bladder, brain, eye, GI tract, salivary glands
\[ M_4 \] – brain, eye
\[ M_5 \] – brain, eye

**Problem:**
- No organ specific M receptor drugs
- Systemic implications

Bladder muscarinic receptors

- **\[ M_2 \] (66%)**
  - Stimulation reverses sympathetically mediated smooth muscle relaxation
  - May facilitate \[ M_3 \] receptors in neuropathic conditions

- **\[ M_3 \] (33%)**
  - When stimulated evokes a smooth muscle contraction at capacity
Muscarinic Receptor Interaction: Lower Urinary Tract

Signal pathways for muscarinic receptors
Stimulatory: M₁, M₃, M₅
Inhibitory: M₂, M₄

ACh = Acetylcholine, PLC = phospholipase C; IP₃ = inositol trisphosphate, AC = adenyl cyclase; SR = sarcoplasmic reticulum, Gq, Gi = G-proteins

Effect of Anticholinergic Agents on Detrusor Function

<table>
<thead>
<tr>
<th>Detrusor overactivity</th>
<th>Detrusor compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment</td>
<td></td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td>Post-treatment</td>
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<td></td>
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</tr>
</tbody>
</table>
Antimuscarinics

- Oxybutynin (Ditropan, Oxytrol, Gelnique)
- Darifenacin (Enablex)
- Solifenacin (Vesicare)
- Tolterodine (Detrol)
- Trospium (Sanctura)
- Propiverine (Detrunorm)
- Fesoterodine (Toviaz)

Oxybutynin

- Prototype anticholinergic
- Extensive study in pediatrics (NGB)
- FDA labeling – indication & usage
Antimuscarinic Agents

- Propantheline
  - Quaternary amine non-selective low M receptor affinity

- Oxybutynin (Ditropan [IR / XL], Oxytrol)
  - Tertiary amine ↑ affinity 1⁰ for M₃ + some M₂
  - Active metabolite (N desethyloxybutynin) M₁ affinity
    side effects - dry mouth, blurry vision, drowsiness, headache and behavioral Δ’s
  - Direct effect on smooth muscle
  - Short $T_{1/2}$ (2 hours)

Oxybutynin: Immediate Release in Children with OAB Symptoms

- 81 children treated with 0.39 mg/kg/day for 1.2 yrs
- UDS parameters of flow rate + PVR (scan) and voiding diary monitoring symptom changes
- 31 (38.3%) became dry but 25 (31%) had little Δ
- No differences in bladder cap., flow pattern or pvr was noted in those becoming dry vs those with no improvement
- Side effects were seen in 34 (42%)
  - Constipation, dry mouth, flushing, heat intolerance

Oxybutynin: Extended Release in Children with OAB Symptoms

- 27 children treated with 0.38 mg/kg/day for 19.9 months after failure with regular oxybutynin for daytime incontinence
- UDS parameters of flow rate + PVR (scan) and voiding diary monitoring symptom changes
- Predicted bladder capacity (age/2 + 6 x 30)
- Symptom change in wetness
  - excellent: 1 / month
  - good: 1-3 / month
  - fair: 1 / week
  - poor: 1 /day


Oxybutynin: Extended Release in Children with OAB Symptoms

- Flow rate results (%PBC)
  - Volume: 27% → 52%
  - Total capacity: 40% → 64%
- Symptom improvement: initially all 27 wet daily
  - excellent: 44%
  - good: 11%
  - fair / poor: 44%
- Side effects
  - 6 of 12 (50%) with SE resolved
  - 7 of 15 (46%) without SE developed them

Oxybutynin and Treatment of LUT Symptoms in Children

- Review of available literature only produced 1 placebo controlled study vs oxybutynin
- No change in frequency of day wetting episodes vs placebo but an ↑ SE vs placebo was seen
- Side effects included dry mouth, headache, GI complaints


Drug delivery strategies:
Minimization of side effects

- Intravesical & transdermal deliveries
  - Avoids 1st pass hepatic metabolite N-desethyloxybutynin
- Limitations
  - Local skin irritation
  - Necessity for continual skin adherence
  - Pharmacokinetics for dosing and efficacy have not been established in children
  - Durability
    - Wan & Rickman, J Urol. 2007
- Intravesical instillation – time consuming, parents often non-compliant
Antimuscarinic Agents

- Tolterodine (Detrol [IR / LA])
  - Tertiary amine mostly selective for $M_3 + M_2$ receptors
  - Seems to have efficacy similar to oxybutynin
  - Does not cross blood / brain barrier $\rightarrow$ ↓ side effects, so increased dose does not lead to ↑ CNS SE
  - Moderate $T_{1/2}$ (4 hours)

Tolterodine and LUTS in Neurologically Normal Children

- 44 children with LUTS, normal pvr + no febrile UTI
- Dosing 1 mg BID x 3 months
- DVSS used to evaluate efficacy
- DVSS: 14.0 $\rightarrow$ 6.68 (p. = 0.001)
- Girls: greater drop in DVSS than boys
- DVSS subgroup measuring OAB symptoms only
  - DVSS: 7.63 $\rightarrow$ 2.59 (p. = 0.001)

- Side effects:
  - 14 (31%) dry mouth
  - 2 (4%) headache

- Good 1st line therapy prior to invasive studies

Tolterodine and LUTS in Neurologically Normal Children

- 31 children with LUTS, normal pvr + no febrile UTI
- Dosing: 0.5, 1, 2 mg  BID x 14 days
- Voiding diaries to evaluate efficacy
- Urinary frequency ↓ irrespective of dose
- Incontinent episodes / wk ↓ most in 1 mg group
- PVR changed slightly with ↑ dose (p. = >0.05)
- Side effects 60%, mostly in 2 mg group
  - headache, ↑ HR, visual Δs
- 1 mg BID is safe, effective for OAB with few SE


Antimuscarinic Agents

- Glycopyrrolate (Robinul)
  - Quaternary amine primarily selective for M₃ with low affinity for M₂ receptors
  - Moderate $T_{1/2}$ (8 hours)
  - Has more cardiac SE than other antimuscarinics
  - No studies in children involving bladder function
Antimuscarinic Agents

• Trospium (Sanctura)
  - Quaternary amine mostly selective for M₃ + M₂ receptors
  - More effective than oxybutynin / tolterodine
  - Crosses blood brain barrier but low M₁ affinity thus producing ↓ SE
  - Long T₁/2 (20 hours)

Trospium HCl for Overactive Bladder

• 50 children with OAB treated with varying doses of Trospium HCl x 21 days with pre- & post UDS compared with 8 given placebo
• Randomized dosing (10, 15, 20 and 25 mg/day) but highest dose given only if wt >40 kg
• UDS parameters: # of detrusor contractions, volume at 1st contraction, Prₘₐₓ of overactive contraction
• Response graded
  - excellent: >30% ↑ in 1 UDS finding + no incontinence
  - good: >30% ↑ in 1 UDS finding + >50% ↓ incontinence
  - fair: no Δ UDS findings + >50% ↓ incontinence
  - poor: no Δ UDS findings + <50% ↓ incontinence

Tropium HCl for Overactive Bladder

• Results drug vs placebo
  – Excellent: 16 (32%) vs 1 (12.5%) \( \{ 74\% (p = 0.006) \)
  – Good: 21 (42%) vs 2 (25%)

• Urodynamic changes
  – DO reduction: 4.6 \( \rightarrow \) 2.1 (35% no D.O.; 54% some ↓)
  – Volume at 1st contraction: 71 \( \rightarrow \) 122 ml
  – \( Pr_{\text{max}} \) reduction: 47.6 \( \rightarrow \) 19 cm H\(_2\)O
  – 4 (8%) had ↑ pvr

• Side effects 4 (8%)


Antimuscarinic Agents

• Solifenacin (Vesicare)
  – Tertiary amine with primarily \( M_3 \) affinity
  – Rapid onset effect
  – Very long \( T_{1/2} \) (50 hours)
  – Minimal SE of dry mouth, constipation, blurry vision
  – Effective in OAB

• Darifenacin (Enablex)
  – Tertiary amine primarily \( M_3 \) antagonist with ↑ affinity
  – Good detrusor effect but may cause constipation
  – Does not cross blood brain barrier so minimal SE
  – Prolonged \( T_{1/2} \) (24 hours)
  – No studies in children
Solifenacin for Overactive Bladder

- 72 children with OAB [CMG determined] who failed bladder retraining + anticholinergic Rx in past
- 27 – NBD; 45 – OAB; mean age 9 yrs (4.7 – 13.3)
- Dose (0.19 mg/kg [max 5mg/D] \(\rightarrow\) 0.31 mg/kg [max 10 mg/D])
- PVR
- Voiding parameters: Voided volume, incontinence episodes
- UDS parameters: cap (ml), DO (height cm \(\text{H}_2\text{O}\)),
- Subjective experience (QoL): PPBC
  [Patient/Parent/Bladder/Condition] – 6 point questionnaire
- ICCS criteria for improvement
- Monitored for SE


Solifenacin for Overactive Bladder

- UDS changes: Capacity - 146 \(\rightarrow\) 311 ml
  DO height – 70 \(\rightarrow\) 20 cm \(\text{H}_2\text{O}\)
- Voided (CIC) volume \(\text{mean}\): 107 \(\rightarrow\) 251 ml
- Incontinence episodes/day: 3.0 \(\rightarrow\) 0.3
- PPBC score: 4.9 \(\rightarrow\) 1.8
  - Overall response:
    100% dryness – 33.3%
    >90% improvement – 58.3%
    50 – 89% improvement – 8.3%
- Side effects:
  mild – 21%
  moderate – 7%

Antimuscarinic Agents

- Propiverine (Detrunorm)
  - N-oxide is the main therapeutic metabolite
  - Easily binds to plasma proteins with steady state levels < 4 - 5 days
  - Ca\(^{2+}\) channel blocker - prevents influx of Ca\(^{2+}\) intra-cellularly that activates a rho kinase → contraction
  - Binds to calmodulin which inhibits actomyosin ATPase
  - High affinity for M\(_3\) receptor
  - Some binding to M\(_1\) without crossing blood brain barrier
  - Few CNS and cardiac side effects d/t ↓ affinity
  - Causes dry mouth (parotid gland affinity - M\(_1\))
  - Moderate T\(_{1/2}\) (8 hours)


Propiverine HCl Efficacy in Children

- 2 studies (1 placebo controlled) of 74, & 280 children
- Dose = 0.4 mg / kg BID
- Results
  - Improved symptoms of wetting in 55%
  - FBC: 153 → 185 ml

- 3 prior older studies of 154 children
  - 80% improvement in enuresis +/- day symptoms

Propiverine HCl Efficacy in Children

- Multi-center study comparing propiverine to oxybutynin in 621 children w OAB symptoms (no invasive testing)
- Cohort: 437 – propiverine; 184 oxybutynin
- Dose / day: Propiverine 15 mg; oxybutynin 10mg
- Measurements
  voiding/day: Propiverine [9.2 → 6.6]; oxybutynin [9.1 → 6.5]
  Incontinence/week: Propiverine [6.2 → 1.8]
  oxybutynin [6.4 → 1.3]
  Continence: Propiverine (61.6%) oxybutynin (58.7%)
- Side effects: Propiverine (2.8%) oxybutynin (9.2%) \( p = <0.001 \)


Propiverine HCl Side Effects

_No significant ↓ in efficacy or tolerability of propiverine vs tolterodine_


_366 adults with OAB: fewer severe SE with propiverine compared to oxybutynin 12% vs 25% \( p = 0.0093 \)_

Comparison of Antimuscarinics in Relation to M Receptor Affinity

Table 2  Affinity (pK) of antimuscarinic compounds for the human recombinant receptor subtypes M1–M5 (14) [Mean (SEM)]

<table>
<thead>
<tr>
<th>Compound</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
<th>M5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin</td>
<td>8.2 (0.06)</td>
<td>7.4 (0.1)</td>
<td>9.1 (0.1)</td>
<td>7.3 (0.1)</td>
<td>8.0 (0.1)</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>8.8 (0.01)</td>
<td>8.0 (0.1)</td>
<td>8.5 (0.1)</td>
<td>7.7 (0.1)</td>
<td>7.7 (0.03)</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>8.7 (0.04)</td>
<td>7.8 (0.1)</td>
<td>8.9 (0.1)</td>
<td>8.0 (0.04)</td>
<td>7.4 (0.03)</td>
</tr>
<tr>
<td>Propiverine</td>
<td>6.6 (0.1)</td>
<td>5.4 (0.1)</td>
<td>6.4 (0.1)</td>
<td>6.0 (0.1)</td>
<td>6.5 (0.1)</td>
</tr>
<tr>
<td>Trospium</td>
<td>9.1 (0.1)</td>
<td>9.2 (0.1)</td>
<td>9.3 (0.1)</td>
<td>9.0 (0.1)</td>
<td>8.6 (0.1)</td>
</tr>
</tbody>
</table>

Darifenacin seems to have ↑ affinity for bladder receptors with least attraction for brain and salivary gland receptors but controlled studies are needed

Table 3  Comparison of the M3 : M1 selectivity of the antimuscarinic compounds (14)

<table>
<thead>
<tr>
<th>Compound</th>
<th>kB3</th>
<th>kM1</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin</td>
<td>9.3</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>0.51</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>1.5*</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Propiverine</td>
<td>0.51</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Trospium</td>
<td>1.3</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

*Significant but unlikely to be biologically relevant; **Significant selectivity for M3 but unlikely to be biologically relevant.

α-Adrenergic Receptor Activity

• Lower urinary tract
  – Bladder neck
  – Urethra

• ↑ smooth muscle contractility
• ↑ outlet resistance

• Mediates DO via M2 receptors

LUTS: Emptying issues

- Pediatric α-blocker studies
  - Austin et al. J Urol, 162: 1064, 1999
  - Van Batavia et al., J Urol, 183: 724, 2010

α-Adrenergic Blocking Agents - Usefulness

- Conclusions:
  - Underactive bladder with incomplete emptying
  - Alternative prior to CIC
  - Alternative to biofeedback retraining
  - May facilitate behavioral modification

- Neuropathic bladder with poor compliance
  - ↓ LPP
  - ↑ compliance
  - ↓ hydronephrosis
  - May ↓ grade of reflux
  - Protects upper urinary tract

- Limitations
  - Need randomized, placebo controlled double-blind studies in uniform populations using standardized testing to evaluate the true effectiveness of this class of drugs
Combination Therapy of \( \alpha \) Blocking Agents & Antimuscarinics for LUT Symptoms

- No studies in children

- 100 adults prospectively randomized propiverine alone vs propiverine + urapidil, assessed by symptom change + QOL questionnaire

- Urinary symptoms improved significantly in both groups but no difference between groups


Emerging Pharmacotherapies - Neuropathic Bladder

- \( \text{Ca}^{++} \) & \( \text{K}^{+} \) channel openers
- Modulation of afferent pathways
  - Vanilloids: resiniferatoxin and capsaicin
  - Neurokinin receptor-1 antagonists
- Beta 3 adrenoceptor agonists
- Vitamin D\(_3\) receptor analogues
- Centrally acting drugs
Conclusions

• Variety of treatment options
• Important to identify bladder behavior
  – Ability to control and empty it!
• Important to identify bowel behavior
• Majority respond to behavioral modifications
• Ancillary measures are reserved for “refractory” patients
• Targeted approach optimizes treatment
• The horizon looks promising
New Advances in LUT Dysfunction

The Standardization of Terminology of Lower Urinary Tract Dysfunction in Children and Adolescent: Report from the Standardisation Committee of the International Children’s Continence Society

Tyagnn Nithyananthan, Alexander van Ganse, Piotr Bukowski, Robin Hibbells,
Shirat Laurion, Wendy Limone, Mary McNamee, Benjamin Genders, Billi Blaj, Adam Y. Wolfe,
Chongyong Wang and John van Biesen

Abstract

Background

Lower urinary tract dysfunction (LUTD) is a common problem in childhood, affecting up to 5% of children. It is characterized by symptoms such as urinary incontinence, overactive bladder, and dysuria. The International Children’s Continence Society (ICCS) has published guidelines for the diagnosis and management of LUTD, but there is still a lack of standardization in terminology. The Standardisation Committee of the ICCS has been established to address this issue.

Objective

The objective of this report is to standardize the terminology used to describe LUTD in children and adolescents to improve communication and facilitate research.

Methods

A multidisciplinary group of experts convened to develop a consensus on the terminology used to describe LUTD. The group reviewed existing terminologies and conducted a review of the literature to identify the most appropriate terms.

Results

A standardized terminology was developed, incorporating terms for specific conditions such as voiding dysfunction and dysfunctional voiding. The terminology was refined through a consensus process and was approved by the ICCS.

Conclusion

The standardized terminology developed by the ICCS is intended to improve communication and facilitate research in the field of LUTD. The terminology will be disseminated through publications and educational materials.

Acknowledgments

The authors gratefully acknowledge the contributions of all members of the Standardisation Committee of the ICCS.

References

New Advances in LUT Dysfunction
ICCS Guidelines

LUT dysfunction management
Botox
External spincter

- Steinhardt, J Urol, 158: 190, 1997
- Mokhless et al, J Urol, 176: 1767, 2006

• Allows “window” for behavioral modification

Management of lower urinary tract dysfunction:
A stepwise approach

Matthew Thom\textsuperscript{a,1}, Mary Campigotto\textsuperscript{a,2}, Vijaya Vemulakonda\textsuperscript{b,2}, Douglas Coplen\textsuperscript{a,2}, Paul F. Austin\textsuperscript{a,1,2}

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\textsuperscript{b}Division of Urologic Surgery, Washington University in St Louis, St. Louis Children’s Hospital, One Children’s Place, Suite A, Second Floor, St. Louis, MO 63110, USA

• J Pediatr Urol. 7 (3): 2011
Incomplete emptying
Stepwise approach

1) Behavioral Modification
2) Pharmacotherapy
3) Pelvic floor rehab
4) Botox


LUTS – Stratification and Outcome

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>% Of total breakdown</th>
</tr>
</thead>
<tbody>
<tr>
<td>UI with CE</td>
<td>50</td>
<td>18%</td>
</tr>
<tr>
<td>UI with IE</td>
<td>144</td>
<td>52%</td>
</tr>
<tr>
<td>IE without UI</td>
<td>81</td>
<td>30%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Improved (inc. Dry)</th>
<th>Dry</th>
<th>Failed</th>
</tr>
</thead>
<tbody>
<tr>
<td>UI with CE</td>
<td>34 (68%)*</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>UI with IE</td>
<td>70 (49%)</td>
<td>39</td>
<td>74</td>
</tr>
<tr>
<td>IE without UI</td>
<td>48 (59%)</td>
<td>24</td>
<td>33</td>
</tr>
</tbody>
</table>

*P < 0.05 CE vs IE.

- Thom et al, J Pediatr Urol. 7 (3): 2011
### Table 3: Outcomes for BM failures following treatment with alpha blocker medication.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Alpha blockers</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Improved</td>
<td>Dry</td>
<td></td>
</tr>
<tr>
<td>UI with CE</td>
<td>16</td>
<td>6 (38%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>UI with IE</td>
<td>74</td>
<td>53 (72%)*</td>
<td>32 (43%)</td>
<td></td>
</tr>
<tr>
<td>IE without UI</td>
<td>33</td>
<td>30 (91%)*</td>
<td>17 (52%)</td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.001 CE vs IE.

### Table 4: Outcomes for BM failures following treatment with anticholinergic medication stratified by emptying.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Anticholinergics</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Improved</td>
<td>Dry</td>
<td></td>
</tr>
<tr>
<td>CE</td>
<td>16</td>
<td>6 (38%)*</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>IE</td>
<td>24</td>
<td>3 (13%)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.001 CE vs IE.

### Table 5: Outcome for medication failures following BTX injection.

<table>
<thead>
<tr>
<th>Group</th>
<th>Improved</th>
<th>Dry</th>
<th>Failed</th>
</tr>
</thead>
<tbody>
<tr>
<td>UI with CE</td>
<td>1 (100%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>UI with IE</td>
<td>4 (100%)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>IE without UI</td>
<td>1 (100%)</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Refractory OAB

Botox injection
Detrusor muscle

• The Effect of Botulinum-A Toxin in Incontinent Children With Therapy Resistant Overactive Detrusor

• 1st pediatric report of non-NGB refractory OAB
• Non-randomized, selected, clinical cohort (21 pts)
• 15 children > 6 mos follow-up
• 67% had full response
• 1 child (5%) had transient urinary retention

• Hoebeke et al, J Urol, 176: 328-331, 2006
Non-Pharmacologic therapy

- Neuromodulation
  - TENS
- Sacral neuromodulation
  - InterStim

Sacral neuromodulation

- FDA approved in the United States
- Indications
  - Treatment of urinary retention
  - Treatment for symptoms of OAB
    - Failed ACh tx
    - Unable to tolerate more conservative txs
Sacral neuromodulation

- Multicenter, open label, randomized, crossover study
- Overall positive response rate was more than 75% for urinary (81%) and bowel (78%) function
- Crossover analysis
  - Sacral neuromodulation is more effective than conservative treatment for both types of incontinence (p = 0.001)

*Haddad et al, J Urol, 184:696, 2010

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TENS

Transcutaneous Electrical Nerve Stimulation in Children With Overactive Bladder: A Randomized Clinical Trial

Patrícia Lordêlo, Aiciná Teles, Maria Luiza Veiga, Luis Cláudio Correia and Ubirajara Barroso, Jr.*

From the Department of Urology and Physical Therapy, Section of Pediatric Urology, Bahiana School of Medicine, Salvador, Bahia, Brazil

*J Urol. 184: 683-689, 2010
Conclusions

- Variety of treatment options
- Important to identify bladder behavior
  - Ability to empty!
- Important to identify bowel behavior
- Majority respond to behavioral modifications
- Ancillary measures are reserved for “refractory” patients
- Targeted approach optimizes treatment
α adrenergic receptors

Lower urinary tract
- Bladder neck
- Urethra

Smooth muscle contraction
↑ Outlet resistance

Percutaneous Tibial Nerve Stimulation (PTNS)

34 G needle inserted on the tibial nerve ~ 2 cm cephalad to medial malleolus
Surface electrode on medial side of foot
Portable stimulator provides pulsations between needle & electrode
(frequency 20 Hz, 200 microseconds, up to 10 mA)
Correct placement → flexion (or fanning) of great toe
Stimulation performed weekly for 30 min x 12 sessions
Percutaneous Tibial Nerve Stimulation (PTNS)

- Bower, Hoebeke 1st reported responses in children with OAB (2001)
- DeGennaro: 23 (10 OAB; 7 retention; 6 NBD)
  - Results (OAB):
    - 80% ↓ OAB
    - 44% resolution of incontinence
    - 62.5% with ↓ CBC → normalized
  - Results (retention):
    - 72% improvement in symptoms
    - PVR 109 ml (pre-Tx) → ↓ 66% w 0 ml in 50%
    - \( P_{\text{max}} \) 33.8 → 50.2 cm H₂O \( (p = 0.09) \)
    - \( Q_{\text{max}} \) 6.2 → 12.3 ml/sec \( (p = 0.05) \)
  - Results (NBD):
    - CBC 239 → 289 ml
    - PVR 173 → 154 ml


Lumbo-sacral Nerve Re-routing for Spina Bifida

- Artificial voiding reflex using
  - Micro-anastomosis of healthy lumbar motor root to abnormal sacral motor root
  - At follow-up stimulation of sacral dermatome of re-routed nerve → bladder contraction & voiding
- Xiao – 20 pts followed 1 year → 85% able to void w/o CIC
  - both OAB and UB pts responded
  - bladder capacity doubled
  - bladder compliance improved
  - residual urine ↓ 100 → 57 ml
  - bladder sphincter synergy during voiding

Lumbo-sacral Nerve Re-routing for Spina Bifida

- 9 pts - neurologic levels from L3 to S3
- Follow-up 1 year
  - CBC: ↑ 5; no change or ↓ 4
  - OAB: ↓ 5 of 7; none developed
  - bladder sensation of bladder filing: 1 developed
  - voiding: 5 of 7 developed (V Vol_{avg} 133 ml; pvr_{mean} 119 ml; Q_{max} 10 )
  - bladder compliance: ↑ 16.1 → 21.8
  - 2 pts voided to completion on stimulation + off all anticholinergic meds
  - 1 F permanent foot drop

Future Prospects for Improving Neuropathic Lower Urinary Tract Function

Caution!

Today’s panacea may be tomorrow’s curse
Detrusor Overactivity

Small OAB

Incomplete Emptying
DETRUSOR OVER/UNDERACTIVITY ASSESSMENT

- Pelvic U/S
- Flow +/- EMG
- Diary

- Small bladder with complete emptying
- Large bladder with incomplete emptying

LUT DYSFUNCTION MANAGEMENT

- Treatment must be targeted to specific LUT dysfunction(s)
- LUT dysfunction is often multifactorial
- Treatment may be
  
  unimodal and sequentially progressive
  OR

  multimodal and simultaneous

  NO "ONE-SIZE-FITS-ALL" APPROACH!
Refractory cases
LUTS

- Incomplete Emptying
  - Large bladders
- Sphincter dyssynergia
  - External DSD
  - Internal DSD
  - Small OAB

Refractory cases
Incomplete emptying

- Internal sphincter dyssynergia
  - α-blockers
- External sphincter dyssynergia
  - Pelvic floor rehab
  - Botox
Refractory cases
External DSD

- Pelvic Rehab
- Botox