Refractory Bladder Conditions:

Non-neurogenic dysfunction of the lower urinary tract in children

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Refractory Bladder Conditions
Objectives

• State the classifications of bladder dysfunction according to ICCS 2006 definitions.
• Discuss the decision making in the care of refractory bladder conditions in children.
• Discuss current therapies and interventions for treatment of refractory bladder conditions in children.

Disclosures – I will be discussing off label use of medications and devices. I do not have any industry relationships to disclose.
Overview of Discussion

Part 1
Review of normal bladder dynamics

Part 2
Classifications of bladder disorders

Part 3
Pharmacological treatment

Part 4
Refractory bladder conditions
Part 1 Review of normal bladder dynamics

**Bladder Filling and Storage**

- Accommodates normal volumes of urine for age
  
  *Formula*: \( \text{Age (years)} + 2 \times 30 \) (Koff, 1983)

- Maintain low intravesical pressure during filling with a closed and continent outlet at rest even with sudden intra-abdominal forces

**Part 1 Review of normal bladder dynamics**

## Storage Phase

### STORAGE

**Parasympathetic** (cholinergic) receptors are *inhibited*, prohibiting detrusor muscle contraction

*Cholinergic* receptors are throughout the “body” of the bladder, trigone and bladder neck

**Sympathetic** receptors (norepinephrine) are *stimulated*, resulting in:

- Relaxation of *beta* receptors controls detrusor muscle and increased stretch capacity of the bladder
- Contraction of the *alpha* receptors controls bladder neck & proximal urethra (internal sphincter – smooth muscle)
Part 1 Review of normal bladder dynamics

**Bladder Emptying**

Bladder contraction leading to emptying involves:

- Parasympathetic phase starts with acetylcholine stimulating the M2 and M3 receptors
- Coordinated urethral relaxation – 2 sphincters

*Internal sphincter* consists of the bladder neck and proximal urethral which are composed of smooth muscle. *External urethral sphincter* which is composed striated muscle.
Part 2 Classifications of bladder disorders

Bladder Problems in Children

• Peak incidence 5-7 years of age
• Girls more likely than boys
• Comorbidity may exist
  – Separation anxiety
  – Oppositional behavior
  – ADD/ADHD
  – Conduct disorder

### Classifications of Bladder Dysfunction

#### Storage phase disorders

- Overactive bladder
  - Urge syndrome
  - Urge incontinence

#### Bladder emptying disorders

- Dysfunctional voiding
  - Contraction of the external urethral sphincter during voiding
  - Uroflow shows staccato pattern
  - Post void residuals
  - Urodynamic EMG patterns
Dysfunctional Voiding Disorders

- Definition: Contraction of the external urethral sphincter during voiding
- Incidence: 4-30%
- EMG/Uroflow or UDS show staccato curve (ICCS, 2006)
Part 2 Classifications of bladder disorders

**Alpha Blockers**

Tamsulosin (Flomax) 0.4 mg once per day

- The rationale for use of alpha-blockers in voiding dysfunction is based on the presence of alpha-adrenergic receptors in the bladder outlet and proximal urethra
- Smooth muscle relaxation
- Off label medication

Animated Biofeedback

• Dysfunctional voiding
  – Goal of therapy
    • Identify the correct muscles responsible for continence
    • Pelvic floor relaxation during voiding

• Bladder overactivity
  – Goal of therapy
    Inhibit detrusor overactivity by contracting the pelvic floor muscles with sensation
Overactive Bladder and Urge Syndromes

- Hallmark symptom: Urgency with or without incontinence
- Involuntary detrusor contractions lead to voluntary contraction of the pelvic floor muscles leading to squatting maneuvers
- Etiology of OAB not yet defined
### Part 2 Classifications of bladder disorders

#### Bladder & Bowel Interaction

#### Rome III Criteria

<table>
<thead>
<tr>
<th>Question</th>
<th>Option 1</th>
<th>Option 2</th>
<th>Option 3</th>
<th>Option 4</th>
<th>Option 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the last 2 months, how often did your child usually have poops? (RC)</td>
<td>2 times/week or less</td>
<td>2-3 times per week</td>
<td>3-6 times/week</td>
<td>Once per day</td>
<td>I don't know</td>
</tr>
<tr>
<td>Does your child have very large stools? (RC)</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the last 2 months, what was your child's poop usually like? (RC)</td>
<td>Very hard (RC)</td>
<td>Hard (RC)</td>
<td>Not too hard, not too soft</td>
<td>Very soft or mushy</td>
<td>It is sometimes hard, sometimes loose.</td>
</tr>
<tr>
<td>In the last 2 months, did it hurt when your child had a poop? (RC)</td>
<td>No</td>
<td>Yes</td>
<td>I don't know</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the past 2 months, how often was your child's underwear stained or soiled with poop? (RC)</td>
<td>Never</td>
<td>Once a week (RC)</td>
<td>Several times per week (RC)</td>
<td>Every day (RC)</td>
<td></td>
</tr>
<tr>
<td>If your child experiences any of the symptoms listed above, does it affect his/her family, social, or school life?</td>
<td>No</td>
<td>Sometimes</td>
<td>Yes, affects</td>
<td>Seriously affects</td>
<td></td>
</tr>
</tbody>
</table>

2 positive responses of Rome Criteria (RC) = Functional constipation

Positive RC: (Circle one) Yes / No
Dilation of posterior urethra
(Spinning top)
Pharmacologic Treatment of Bladder Overactivity

Parasympathetic Muscarinic Receptors
- M2 - cardiac, detrusor
- M3 - detrusor, gastrointestinal smooth muscle, salivary glands
  - M3 receptors (20%) responsible for smooth muscle contraction
  - M2 receptors (80%) responsible for inhibition of smooth muscle relaxation

Action of M blockers (anticholinergics)
- Decrease detrusor activity by blocking release of ACh from cholinergic nerves and block stimulation of M receptors
- Desired Effects
  - abolish involuntary detrusor contractions
  - increase volume at which they occur
  - increase compliance
Part 3 Pharmacological treatment

Pharmacologic Agents Bladder Overactivity

Anticholinergics (antimuscarinic agents)

- Oxybutynin (Ditropan IR/XL) BID/TID/QD
- Oxybutynin (Gelnique, 10%, 3%) Topical
- Oxybutynin (Oxytrol patch) Topical
- Tolterodine IR/ER (Detrol) BID/QD
- Tropsium (Sanctura) BID
- Solifenacin (Vesicare) QD
- Darifenacin (Enablex) QD
- Fesoterodine (Toviaz) QD
Part 4 Refractory bladder conditions

Refractory Bladder Conditions

Definition of Refractory Bladder Conditions:

• The term is poorly described in the literature
  – Not a searchable term, no MESH heading
  – PubMed – 0 results
  – Google - refractory bladder over activity in children
    – about 1,240,000 results (0.25 seconds)

Detrusor Overactivity is a urodynamic observation characterized by involuntary detrusor contraction that increase 15 cm H20 above baseline (ICCS, 2006)

Part 4 Refractory bladder conditions

Refractory Bladder Conditions

- Proposed working definition – Children over age 5 with normal neurological function with urgency, frequency with or without urinary incontinence who have not responded to medications, behavioral therapies and who continue to complain of distressing lower urinary tract symptoms (LUTS).
Part 4 Refractory bladder conditions

Treatment Algorithm

Initial Screening
H&P, Voiding questionnaire, bowel history

Voiding Diary

Renal ultrasound

Behavioral Techniques
Medications
EMG/Uroflow/Urodynamics

Continue as Appropriate

Consider Neuromodulation
Case Study 1

6 year old female (LG) who presented initially for recurrent UTI’s (some febrile), urge incontinence & NE

Other history: ADHD

RBUS NL – history of VUR, resolved

Placed on Ditropan at 0.2 mg/kg/day (no improvement per family)

EMG/uroflow done
Part 4 Refractory bladder conditions

Patient: LC (6 yr female)

1st EMG/Uroflow
PVR 100 ml after 2 voids
Meds: Ditropan 3 mg bid
Case 1
LG

Part 4 Refractory bladder conditions

BC 100 ml (240ml)
No meds
Detrusor overactivity

Placed on 1 mg Detrol bid after study
Follow up - 3 months later

No improvement on Detrol 1 mg, Detrol LA 4 mg or Ditropan XL 5 mg

Increased to Ditropan XL 10 mg

MRI of L/S (D/T refractory to medications) - negative
Follow up - 2 months later

- Seen for persistent urge incontinence, new onset of afebrile UTI’s - mom stopped Ditropan and Miralax d/t no effect

Plan:
- Restart Ditropan XL 10 mg per day
- Senna 1/2 square at bedtime, continue on Miralax
- Urodynamics (evaluate effect of Ditropan XL 10 mg)
- Discussed Posterior Tibial Nerve Stimulation (PTNS) or Sacral Nerve Stimulation (SNS) options if she does not respond to medication
Part 4 Refractory bladder conditions

Case 1

LG

UDS on Ditropan XL
10 mg/day

At 200 ml, 50 cm pDet
Case 1
LG

Part 4 Refractory bladder conditions
Part 4 Refractory bladder conditions
Next Steps

• Follow up visit with urologist in Complex Care Clinic

• Sacral neuromodulator planned
  – Temporary lead placement
  – If responds, permanent device implanted
Part 4 Refractory bladder conditions

Treatment Strategies

- Biofeedback – used primarily in DV, OAB
- Transcutaneous electrical nerve stimulation (TENS)
- Posterior tibial nerve stimulation (PTNS)
- Injectable therapy (Botox A)
- Sacral neuromodulation (InterStim)
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Transcutaneous electrical nerve stimulation (TENS)

Low levels of electrical current to inhibit detrusor overactivity and modulate the inhibition and excitatory components of bladder control

- 41 children, mean age 10 years with documented OA
- TENS used at home (2 Hz) every 2 hours – S3 level, on anticholingerics
- 28 response rate (68%) after 1 month- symptomatic improvement
- Strengths: Non invasive
- Limitations: Time consuming, pt motivation essential

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Posterior tibial nerve stimulation

- Based on acupuncture points over the posterior tibial nerves to inhibit bladder activity
- Posterior tibial nerve is a mixed sensory motor nerve originating from L4-S3
- Electrical stimulation of S3 activates the pelvic floor & modulates sphincter, bladder, & pelvic floor

- PTNS
- Prospective study n=32 (17 boys, 15 girls)
- Mean age 11 years
- Failure of meds/therapy over 2 years
- 84% responders
- Mean sessions/pt – 10
- Strengths: p > 0.001 for frequency, uroflow and BC

Case Study 2

- KD – initially seen at age 6 yrs. for urge incontinence, UTI’s and constipation/encopresis (2008) Ditropan XL 5 mg, then 10 mg, bowel management
Case 2
KD

2010 – Ditropan XL 10 mg/day
Case 2
KD

2012
pDet 230 cm/h20 – 63 ml on Ditropan XL 15 mg/day
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(PTNS)

Case 2
KD

PTNS procedure

34 gauge needle electrode

- three fingerbreadths cephalad medial malleolus
- one fingerbreadth posterior to the tibia
- 30 minute treatment setting of 3 (setting based on foot response)

KD had 6 biofeedback sessions followed by 10 PTNS sessions over a 3 month period.

Doing well at this time
Part 4 **Refractory bladder conditions**

**Injectable therapy (Botox A)**

Part 4 Refractory bladder conditions

Sacral Neuromodulation (SNS)

Identification of complex pathways in the voiding cycle
• Dates back to 1958 when electrical stimulation and biofeedback used for neurogenic bladder
• SNS first approved in adults in 1997

• Pediatric use first reported in 2006 at Mayo Clinic
• Percutaneous access to S3 to implant a temporary programmable external device (Stage 1)

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SNS: Test Stimulation Procedure Stage 1

- OP or 23 hr stay
- General anesthesia
- [FDA approved test stimulation procedure using the percutaneous test stimulation lead (3-5 days in adults) and (2-3 weeks in peds)]
- Stage 1: FDA approved up to three weeks (or following an inconclusive percutaneous test stimulation)
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Stage 2: The Implant

- Stage 2 if there is > 50% improvement during trial
- Conventional approach
  - Fluoro used for placement of tined lead
- Mayo developed a second stage without fluoro
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Mechanism of Action

- Sacral neuromodulation is delivered via the InterStim system

- Implantable system sends electrical impulses through a lead to the sacral nerves to modulate the neural activity that influences the behavior of the pelvic floor, lower urinary tract, urinary and anal sphincters, and colon.

Mechanism of Action, Continued

• Mechanism of action for SNS is not fully understood at this time - many theories exist
• Generally agreed that stimulation of the sacral nerves modulates the neural reflexes that influence the bladder, sphincter and pelvic floor that control/influence voiding
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Tined lead for Interstim
SNS Success/Issues

• Report in 2008 after 20 patients underwent SNS (18 went to second stage)
  – 75% improvement in **incontinence** (2 pt no improvement)
  – 38% improvement in **nocturnal enuresis**, 31% unchanged
  – 69% improvement in urgency

SNS Success/Issues

- Infection risk is low
- SQ fluid collection has been reported
- Lead migration
- Pain at insertion site
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Case Study 3

• 10 year old female (MC) who presented initially with chronic constipation to the GI service.

• Previously had a cecostomy tube without improvement

• Daily urinary incontinence – referred for UDS
Case 3
MC

UDS pre-op, no meds
3 months after SNS
Part 4 Refractory bladder conditions

Case Study 4

- MC – 6 year old female
- PMH – Tethered cord release (2009)
  - Cecostomy tube placed 2008
- Present OSH in 2010 with acute retention
- UDS at OSH (2010) showed bladder contractions at 190 ml and DSD with 60 ml post void residual
- CIC started 2010
Case 4
MC

Part 4 Refractory bladder conditions

- CIC was in place for 1 year
- SNS device placed in October, 2012
- MC started voiding weeks after the SNS was in place
Case 4

MC

UDS after SNS placement, no CIC, meds, no PVR
What is on the horizon for refractory bladder conditions in children?
Part 4 Refractory bladder conditions

Beta 3 adrenergic agonist

- Adrenergic agonist stimulate a response from the adrenergic receptors
- Five categories of adrenergic receptors are: $\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$, and $\beta_3$

$\beta_1$, $\beta_2$, and $\beta_3$ receptors are found in bladder, highest number is $\beta_3$
## Pharmacological Comparison

<table>
<thead>
<tr>
<th>Current medications target the parasympathetic (cholinergic) receptors</th>
<th>Beta 3 agonists target the sympathetic receptors which when <em>stimulated</em>, results in:</th>
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<tbody>
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<td>Relaxation of beta receptors controlled detrusor muscle and increased stretch capacity of the bladder dome.</td>
<td>Contraction of the alpha receptors controlled bladder neck (proximal urethra)</td>
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Part 4 Refractory bladder condition

New Pharmacological Class

For Immediate Release
FDA Approves Overactive Bladder Treatment
Myrbetriq™ (mirabegron) from Astellas

Refractory Bladder Conditions: Non-neurogenic dysfunction of the lower urinary tract in children

Summary

• Classifications of bladder dysfunction according to ICCS 2006 definitions.
• Decision making in the care of refractory bladder conditions in children.
• Current therapies and interventions for treatment of refractory bladder conditions in children.
Conclusion

O-H-I-O

Source- Hood of my car, 1/20/2013
Thank you!