HAEMATURIA and CYSTITIS

- a practical approach

K J Ng
Consultant Urological Surgeon
24 Mar 2010
Haematuria

- Dipstick
  - False positive

- Microscopic (MSU)
  - For confirmation
  - > 5 RBCs / HPF

- Frank (macroscopic)
<table>
<thead>
<tr>
<th>Painful</th>
<th>Irritative</th>
</tr>
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</table>

Haematuria with symptoms (typical presentations)
Haematuria with symptoms

**Painful**
- Dysuria (burning)
- Suprapubic pain (severe ache, agony)
- Urethral pain (stabbing, pulling, pinching)

**Irritative**
## Haematuria with symptoms

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Haematuria with symptoms

**Painful**
- Dysuria (burning)
- Suprapubic pain
- Urethral pain

**Irritative**
- Urgency
- Urge incontinence
- Frequency / nocturia

? Bacterial cystitis
## Haematuria with symptoms

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Haematuria with symptoms

**Painful**
- Dysuria (burning)
  - Suprapubic pain
    + Urethral pain
      - ? Interstitial cystitis

**Irritative**
- Urgency
  - Urge incontinence
    - Frequency / nocturia
      - ? Bladder tumour
Haematuria *without* painful / irritative symptoms:

**Routine testing**
- RBCs only

? Bladder / renal tumour

( Age >40)
Haematuria without painful / irritative symptoms:

**Routine testing**

- RBCs only
  - ? Bladder / renal tumour

( Age >40)

- RBCs and WBCs
  - ? Mild cystitis
Haematuria without painful / irritative symptoms:

**Routine testing**

- RBCs and proteinuria

  ? Renal disease

  (Glomerulonephritis etc)
Haematuria without painful / irritative symptoms:

**Routine testing**
- RBCs and proteinuria
- ? Renal disease
- (Glomerulonephritis etc)

**Frank**
- Total (painless)
- Initial and Terminal
Haematuria without painful / irritative symptoms:

Routine testing
- RBCs and proteinuria
  - ? Renal disease

Frank
- Total (painless)
  - ? Renal / bladder tumours
- Initial and Terminal

(Glomerulonephritis etc)
Haematuria without painful / irritative symptoms:

**Routine testing**
- RBCs and proteinuria
  - ? Renal disease
  - (Glomerulonephritis etc)

**Frank**
- Total (painless)
  - ? Renal / bladder tumours
- Initial and Terminal
  - ? Prostatitis
  - (perineal discomfort)
CYSTITIS

- Bacterial
- Interstitial
CYSTITIS

- **Bacterial**
  - E. Coli
  - Dysuria
  - Sexual intercourse
  - Postmenopausal

- **Interstitial**

NB. Proteus / Klebsiella
(?)stone disease)
CYSTITIS

- **Bacterial**
  - E. Coli
  - Dysuria
  - Sexual intercourse
  - Postmenopausal

  NB. Proteus / Klebsiella
  (stone disease)

- **Interstitial**
  - No growth
  - WBCs or Normal
  - Suprapubic / urethral pain
    (pre- and postmicturition)
  - Dyspareunia
  - Any age
  - Often related to menstruation
  - IBS and pelvic musculature
E. Coli - discovered in 1885 by Theodor Escherich
Antibiotic damage to cell wall:
E.Coli adhering to urothelium:
Pathogenic pili:
Genotypic trait:

- Susceptible:
  - Lewis a+b-, Lewis a-b-
  - Receptor binding by pathogenic bacteria

- Identified by recurrent ‘UTI’ > 2x per year
Interlinked:

- **Bacterial cystitis**
  
  (Cracked urothelium)

- **Interstitial cystitis**
  (neurogenic inflammation)

**Antibiotic regimes**

- Hyaluronic acid
- Pentosan polysulphate
- Chondroitin sulphate

**Nerve stabilisation**
Interstitial Cystitis:
IC-Smart Diet
The truth about the foods you eat

Did you know that certain foods can cause additional distress when you’re suffering with interstitial cystitis (IC)? Typically, foods high in acid and potassium, as well as beverages containing caffeine and alcohol, should be avoided. Here are some helpful guidelines for an IC-smart diet:

Fruits
**Allowable:** Blueberries, melons (other than cantaloupe), and pears
**Avoid:** Other fruits and juices

Meats/Fish
**Allowable:** Poultry, fish, and some meats (not including those listed below)
**Avoid:** Aged, canned, cured, processed, or smoked meats/fish; anchovies; caviar; chicken livers; canned beef; or meats that contain nitrates or nitrates

Vegetables
**Allowable:** Potatoes, homegrown tomatoes, and some vegetables (not including those listed below)
**Avoid:** Fava beans, lima beans, onions, rhubarb, tofu, and store-bought tomatoes

Nuts
**Allowable:** Almonds, cashews, and pine nuts
**Avoid:** Most other nuts

Milk/Dairy
**Allowable:** White chocolate, cottage cheese, American cheese, and milk
**Avoid:** Aged cheeses, sour cream, eggs, yogurt, and chocolate

Beverages
**Allowable:** Bottled or spring water; decaffeinated, acid-free coffee or tea; some herbal teas
**Avoid:** Alcoholic beverages, including beer and wine; carbonated drinks; coffee; tea; and cranberry juice

Carbohydrates/Grains
**Allowable:** Pasta, rice, and some breads (not including those listed below)
**Avoid:** Rye and sourdough breads

Seasonings
**Allowable:** Garlic and some other seasonings (not including those listed below)
**Avoid:** Mayonnaise, niso, spicy foods (especially Chinese, Mexican, Indian, and Thai foods)

Don’t forget about preservatives
**Avoid:** Bimale alcohol, citric acid, monosodium glutamate, aspartame, saccharin, and foods containing preservatives, artificial ingredients/colors
When considering chronic pelvic pain associated with IC...

ELMIRON is the only FDA-approved oral medication

Fundamental for lasting relief from the pain or discomfort of Interstitial Cystitis (IC)

- ELMIRON is fundamental therapy for IC
- Whatever else you may use for short-term relief of IC pain, ELMIRON should be your choice for long-term therapy.
- More may be needed as bladder protection increases. Studies suggest that glycerine or other DMSO (GAG) may enhance a physical barrier between the bladder wall and the urine, so inhibiting urinary solute and cellular adherence.
- ELMIRON appears to reinforce the protective layer. Although its mechanism of action is not fully understood, ELMIRON replaces the GAG layer that protects the bladder lining.
- ELMIRON acts on underlying pathology. ELMIRON may act as an buffer to control cell permeability, preventing irritants from reaching epithelial cells.
- ELMIRON reduces painful symptoms long term. Significant improvement in 3 months in a majority of patients. With sustained relief for up to 3 years in patients who remain on therapy.

Visit us at www.elmiron100.com

ELMIRON is a registered trademark of NIA Research, Inc.
Ortho McNeil Pharmaceuticals, Inc.

Please see the full summary of prescribing information on the enclosed page.

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Ortho McNeil
A subsidiary of Ortho-McNeil Pharmaceutical, Inc.
Botox:
Botox:
Botox:
Botox – cystoscopic injections:
Summary: Haematuria – Urgent referral

- Painless frank haematuria

- Microscopic haematuria
  - Age > 40
  - RBCs only
  - Exclude proteinuria
  - Dipstick analysis unreliable
Bacterial Cystitis – treatment in primary care

- **Antibiotic regimes**
  - 3 days: Nitrofurantoin (Macrodantin) 100mg BD
  - 3-6 months: Nitrofurantoin (Macrodantin) 100mg nocte
  - 3 doses: sexual intercourse

- **Do’s and Don’ts (cranberry)**

- **Vaginal oestrogenisation (lactobacilli)**
  - Vagifem ? indefinitely

- **NB. Consider referral if no better or > x2 a year**
Interstitial Cystitis: primary care treatment

- Very little effective regime
- Smart diet
- Exclude bacterial UTI

Recurrent 'cystitis'
> x2 a year

Or persistent pelvic pain
- referral for treatment
Thank you
Other interesting aspects in Urology:

- Botox bladder injections
- TOT
- HIFU
TOT (transobturator tape)
HIFU (High Intensity Focused Ultrasound):
HIFU – for prostate cancer
HIFU:

- A new modality of treatment for prostatic carcinoma
- Can be repeated for reactivated disease
- Equally impressive survival compared with radical surgery and radiotherapy
Questions:

K J Ng
Consultant Urological Surgeon

Email: urology@DrNg.co.uk
Anatomy of the bladder

Female bladder

- Ureter
- Peritoneal coat
- Detrusor smooth muscle
- Inner mucous membrane
- Trigone

Male bladder

- Prostate gland
- Urethral sphincter
- Pelvic floor striated muscle (levator ani muscle)
Functions of the bladder

- Storage (mainly)
- Emptying of urine (micturition)
The somatic, sympathetic and parasympathetic nervous systems are involved in normal bladder function.

Brain

Sympathetic hypogastric nerve

T10–L2

Parasympathetic pelvic nerve

S2–S4

Somatic pudendal nerve

Bladder detrusor smooth muscle

Internal sphincter smooth muscle

Intramural striated muscle

Extramural striated muscle

Urethral smooth muscle

Adapted from Abrams P and Wein A. The overactive bladder – a widespread but treatable condition; 1998.
Physiology of the bladder

- Normal bladder contraction is caused by
  - release of acetylcholine (ACh) from cholinergic (parasympathetic) nerves
  - stimulation of muscarinic receptors on the detrusor smooth muscle by ACh
  - $M_3$ receptors are the primary mediators of detrusor muscle contraction

What is urinary incontinence?

- A condition in which involuntary loss of urine is objectively demonstrable and causes social or hygienic problems.

- 3 most common types:
  - Stress incontinence: involuntary leakage on effort or exertion, or on sneezing or coughing
  - Urge incontinence: involuntary leakage accompanied by or immediately preceded by urgency
  - Mixed (a combination of stress and urge incontinence): involuntary leakage associated with urgency and with exertion, effort, sneezing or coughing

Stress incontinence

• Involuntary leakage on effort, or on sneezing or coughing

Sudden increase in intra-abdominal pressure (e.g. caused by sudden movements such as coughing/sneezing)

Continent subject

Patient with genuine stress incontinence

Insufficient closing pressure (poor transmission of pressure to the urethra due to inadequate support)

Urge incontinence

- Involuntary urine leakage associated with the urge to urinate
- One symptom of an overactive bladder

1. Uninhibited contractions of the detrusor muscle during filling phase increase pressure in the bladder.
2. Bladder pressure exceeds the urethral pressure.
3. Leakage (bladder empties).
4. Urethra relaxes and large volumes of urine are leaked.
Prevalence of different types of urinary incontinence

- Stress incontinence
- Mixed incontinence
- Urge incontinence
- Other

What is OAB?

- Multiple symptom syndrome
  - *Urinary urgency*, with or without *urge incontinence*, usually with *increased frequency* of micturition and *nocturia*, which is not explained by metabolic or local pathologic factors

- Chronic condition

Symptoms of OAB as defined by the International Continence Society (ICS)

- **Urgency** is the complaint of a sudden compelling desire to pass urine, which is difficult to defer.

- **Urge incontinence** is the complaint of involuntary urine leakage associated with the urge to urinate.

- **Increased Daytime Frequency** is the complaint by the patient that he/she voids too often by day.

- **Nocturia** is the complaint that the individual has to wake at night one or more times to void.

Prevalence of OAB in EU

Prevalence (%)†

Men

Women

n=16,766

France
Germany
Italy
Spain
Sweden
UK

17% EU Average

† Age ≥40 years

Milsom I, et al. BJU Int 2001;87:760–6
OAB significantly affects quality of life

Comparison of quality of life scores in patients with OAB, diabetes and normal subjects

Diagnosis of OAB

- **History**
  - Symptoms
  - PMH e.g. DM, BPH, risk factors for stress incontinence
  - DH e.g. diuretics

- **Examination**

- **Simple tests**
  - Urinalysis, MSU
  - Bladder diary
    - frequency/volume; drinks; urge episodes; leakage & activity at the time
  - Pad test (not routinely recommended)
  - Ultrasound (not routinely recommended)
Diagnosis of OAB

- Urodynamics assess ability of bladder/urethra to store & expel urine:
  - Pressure flow studies
  - Videourodynamic
  - Ambulatory urodynamics
  - Urethral function tests
  - Filling cystometry
    - Assess ability of bladder to act as reservoir for storage of urine by measuring pressure changes
    - Bladder is filled with sterile water/normal saline through a urethral catheter (~ 30-100 ml/min)
    - Pressure inside the bladder (Pves) is monitored by a fluid-filled pressure line, usually placed transurethrally, connected to pressure transducer
    - Abdominal pressure (Pabd) is simultaneously measured by a sensor placed in the rectum
    - Pressure generated by the detrusor muscle, Pdet = Pves - Pabd
The aetiology of OAB may be neurogenic, myogenic or both

- **Neurogenic**
  - reduced inhibition from brain
  - damaged axonal paths in spinal cord
  - increased afferent input

- **Myogenic theory**

  Partial denervation
  \[\uparrow\text{Excitability}\]
  \[\uparrow\text{Electrical coupling between myocytes}\]
  Propagation of coordinated contractions
Muscarinic receptors are involved in a variety of functions in addition to bladder contraction

<table>
<thead>
<tr>
<th>Location</th>
<th>Functions</th>
</tr>
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<tbody>
<tr>
<td>M₁</td>
<td>Cerebral cortex, hippocampus, salivary glands, eye</td>
</tr>
<tr>
<td>M₂</td>
<td>Cardiac muscle, eye, hippocampus, hindbrain, smooth muscle</td>
</tr>
<tr>
<td>M₃</td>
<td>Smooth muscle, salivary glands, eye, brain, heart</td>
</tr>
<tr>
<td>M₄</td>
<td>Basal forebrain, striatum, salivary glands, eye</td>
</tr>
<tr>
<td>M₅</td>
<td>Substantia nigra, eye, heart</td>
</tr>
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Abrams et al 2006; Caulfield & Birdsall 1998
M₃ receptors mediate detrusor contraction

- M₃ receptors are the primary mediators of detrusor muscle contraction¹
- Mice lacking M₃ receptors have severely impaired detrusor contractility in response to muscarinic receptor stimulation²

Detrusor contractility (% of 50 mM KCl)

Log [carbachol] (M)  Log [carbachol] (M)

-8   -7   -6   -5   -4   -3   -2

400   300   200   100   0

Male

Wild-type

Knockout

Female

Wild-type

Knockout

In the brain, postsynaptic cortical M1 receptors are critically involved in cognitive function (especially memory). M3 selectivity or lack of drug CNS penetration should minimize cognitive effects.
Immediately release non-proprietary oxybutinin should be offered to women with OAB or mixed UI as first-line drug treatment if bladder training has been ineffective. If immediate release oxybutynin is not well tolerated, darifenacin, solifenacin, tolterodine, trospium, or an extended release or transdermal formulation of oxybutinin should be considered as alternatives. Women should be counselled about the adverse effects of antimuscarinic drugs.
Emselex – a new option in OAB

- Proven efficacy in reducing urge incontinence, urgency and frequency\(^1\)
- Long-term benefits in patients with OAB\(^2\)
- Adverse events (e.g. dry mouth, constipation) were generally mild to moderate in intensity\(^1,3\)
- Low incidence of treatment-related cardiovascular adverse events\(^1,3\)
- Unlike oxybutynin ER 15-20mg od, Emselex 7.5-15mg od had no significant effect on delayed recall in healthy elderly volunteers\(^4\)
Darifenacin is selective for M3 receptors
Relative affinity *in vitro*

Relative affinity ($K_i$) for muscarinic receptor subtypes ($M_3 = 1.0$)
How to prescribe Emselex

Single price

- £26.13 for 28 days’ supply of 7.5mg or 15mg tablets
<table>
<thead>
<tr>
<th>Product</th>
<th>Daily dose</th>
<th>Daily cost</th>
<th>Monthly cost (30 days)</th>
</tr>
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<tbody>
<tr>
<td>Detrusitol XL (tolterodine m/r)</td>
<td>4mg od</td>
<td>£1.04</td>
<td>£31.10</td>
</tr>
<tr>
<td>Detrusitol (tolterodine)</td>
<td>1-2mg bd</td>
<td>£1.04 - £1.09</td>
<td>£31.10 – £32.74</td>
</tr>
<tr>
<td>Emselex (darifenacin)</td>
<td>7.5-15mg od</td>
<td>£0.93</td>
<td>£28.00</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>2.5mg bd – 5mg qds</td>
<td>£0.24 (2.5mg bd) – £0.17 (5mg qds)</td>
<td>£7.17 (2.5mg bd) - £5.16 (5mg qds)</td>
</tr>
<tr>
<td>Cystrin (oxybutynin)</td>
<td>3mg bd – 5mg qds</td>
<td>£0.33 – £1.09</td>
<td>£9.80 - £32.69</td>
</tr>
<tr>
<td>Ditropan tablets (oxybutynin)</td>
<td>2.5mg bd – 5mg qds</td>
<td>£0.16 - £0.64</td>
<td>£4.90 - £19.06</td>
</tr>
<tr>
<td>Lyrinel XL (oxybutynin m/r)</td>
<td>5-20mg od</td>
<td>£0.41 - £1.65</td>
<td>£12.34 - £49.36</td>
</tr>
<tr>
<td>Kentera (oxybutynin patch)</td>
<td>1 patch twice a week</td>
<td>£0.97</td>
<td>£29.14</td>
</tr>
<tr>
<td>Regurin (trospium)</td>
<td>20mg bd</td>
<td>£0.87</td>
<td>£26.00</td>
</tr>
<tr>
<td>Vesicare (solifenacin)</td>
<td>5-10mg od</td>
<td>£0.92 - £1.20</td>
<td>£27.62 - £35.91</td>
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New therapeutic options:

- Sacral Nerve stimulation
  - bladder ‘pacemaker’ implant, very expensive

- Posterior Tibial Nerve Stimulator
  - outpatient sessions, nurse-led

- Botox bladder injections
Sacral nerve stimulation:
Posterior tibial nerve stimulation:
BOTOX® Development: The First Commercial Botulinum Neurotoxin Product

- **Type A 900 kD complex purification optimisation**
- **1968 medical use evaluation**
- **A. Scott**
- **Botulism by Clostridium botulinum 1700s–1800s**
- **1989 FDA approval**
- **First clinical development**
- **Strabismus, Blepharospasm**
- **Clinical development: cervical dystonia & other uses**
Botulinum Toxin - Structure and Implications

- Seven serotypes
  - A, B, C1, D, E, F, G

- Large Heterodimeric molecule
  - 150 KD protein,
  - 900 KD protein complex
  - Heavy chain --> “docking”
  - Light chain --> “cutting”

- Only intact molecule works
- Does not penetrate the skin
- No topical application
Botulinum Toxin Mechanism
Current Hypothesis

dePaiva et al., 1999
How is it performed:
How is it performed?
Cystoscopic injections:
Cystoscopic injections:
DANGERS OF BOTOX®

SURE, BOTOX® WORKS. BUT IS IT WORTH IT?

BOTOX® SIDE EFFECTS

<table>
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<tr>
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<tr>
<td>headaches</td>
</tr>
<tr>
<td>chest pain</td>
</tr>
<tr>
<td>swelling</td>
</tr>
<tr>
<td>flu symptoms</td>
</tr>
<tr>
<td>respiratory infection</td>
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<tr>
<td>bruising</td>
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<tr>
<td>facial pain</td>
</tr>
<tr>
<td>allergic reactions</td>
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<tr>
<td>nausea</td>
</tr>
<tr>
<td>muscle weakness</td>
</tr>
<tr>
<td>difficulty breathing</td>
</tr>
<tr>
<td>dizziness</td>
</tr>
</tbody>
</table>

44% OF BOTOX® PATIENTS EXPERIENCE SIDE EFFECTS**

BOTOX® EXPENSES

$300-$1000 per treatment, repeated every 3-4 months

BOTOX® ALTERNATIVE

Click Here for the #1 Botox® Alternative

*Botox® is a registered trademark of Allergan, Inc
**According to Botox's® Prescribing Information provided to physicians and patients
Current Practice in Urology: Botox

- Good safety profile
- Effective
- May need repeat procedure every 9-12 months
- Cost benefit
- Recommended by NICE, Oct 2006
Current Practice

- Oral medication, failure to control symptoms
- ? Posterior Tibial Nerve Stimulation
- Botox bladder injections ??
- Clam cystoplasty

NB. New drugs: Darifenacin/Solifenacin