Interstitial cystitis: definitions and confusable diseases
ESSIC Meeting 2005 Baden

Joop P. van de Merwe (left), Departments of Immunology and Internal Medicine
Erasmus MC, Rotterdam, The Netherlands
e-mail: j.vandemerwe@erasmusmc.nl

Jørgen Nordling (right), Department of Urology
Herlev Hospital, University of Copenhagen,
Denmark, e-mail: jnordling@dadlnet.dk

This report is the summary of the consensus obtained on definitions and confusable diseases for painful bladder syndrome / interstitial cystitis (PBS/IC) during the ESSIC (European Society for the Study of IC/PBS) Meeting in Baden, 16-18 June 2005 (www.ESSICoffice.org).
The report consists of 6 sections:

1. Definitions
2. Confusable diseases
3. Procedures /tests that are necessary to detect the confusable diseases
4. Proposed sequence of actions in patients with interstitial cystitis-like symptoms
5. Summary of the Report of the ESSIC Meeting Copenhagen 2003 with modifications
6. Comments

1. Definitions

1.1 Interstitial cystitis (IC)

The ICS definition 2002[1] of interstitial cystitis was adopted with modifications:

Interstitial cystitis is PBS (see 1.2) with typical cystoscopic **and/or** histological features in the absence of infection or other pathology; this definition differs from the ICS definition in the word **and/or** instead of **and**.

ICS definition 2002, modified ESSIC 2005

This results in the following preliminary definition of interstitial cystitis:

Interstitial cystitis is a disease of unknown origin consisting of the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms, such as increased daytime (>8x) and night-time (>1x) frequency[2], and with cystoscopic (glomerulations and/or Hunner's lesions) and/or histological features[3] (mononuclear inflammatory cells including mast cell infiltration and granulation tissue) in the absence of infection or other pathology.

[1] ICS definition 2002 refers to the following publication: Abrams P, Cardozo L, Fall M, et al. Neurourology and Urodynamics 2002;21:167-178 [PMUI: 11857671]

[2] preliminary cut-off points; optimal cut-off points will be determined during the classification tree analysis

[3] according to ESSIC definitions

1.2 Painful bladder syndrome (PBS)

Painful bladder syndrome is the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms, such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology. *ICS definition 2002*

1.3 Frequency

Daytime frequency is the number of voids recorded during waking hours and includes the last void before sleep and the first void after waking and rising in the morning.

ICS definition 2002

1.4 Nocturia

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

ICS definition 2002

1.5 Urgency

Urgency is the complaint of a sudden compelling desire to pass urine, which is difficult to defer. *ICS definition 2002*

Comment: during the discussion several people said that this definition is not adequate. It is the definition given in the ICS definition 2002 paper, but it will probably be changed in the near future.

1.6 Pain

An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. *IASP Pain Terminology*
http://www.iasp-pain.org/terms-p.html#Pain

1.7 Urethral pain

Urethral pain is felt in the urethra and the individual indicates the urethra as the site.

ICS definition 2002

1.8 Hunner's lesion

Comment
Hunner's ulcer is not in fact an ulcer; the term was replaced by Hunner's lesion with the following definition.

The Hunner's lesion typically presents as a circumscript, reddened mucosal area with small vessels radiating towards a central scar, with a fibrin deposit or coagulum attached to this area. This site ruptures with increasing bladder distension, with petechial oozing of blood from the lesion and the mucosal margins in a waterfall manner. A rather typical, slightly bullous edema develops post-distension with varying peripheral extension.

Magnus Fall, e-mail 1 August 2005

1.9 Bladder mastocytosis

Definition of bladder mastocytosis:
< 20 mast cells/mm^2 : no detrusor mastocytosis
20-28 mast cells/mm^2 : grey zone
> 28 mast cells/mm^2 : detrusor mastocytosis

ESSIC Copenhagen 2003
Nordling J et al. Eur Urol 2004;45:662-9

1.10 Glomerulations

Historically, glomerulations are pinpoint haemorrhages (petechiae) seen in the bladder mucosa following hydrodistension of the bladder. This term should be replaced by the classification grading (ESSIC Copenhagen 2003), summarized as follows:

Grade 0 : normal mucosa
Grade I : petechiae in at least two quadrants
Grade II : large submucosal bleeding (ecchymosis)
Grade III : diffuse global mucosal bleeding
Grade IV : mucosal disruption, with or without bleeding/oedema

ESSIC Copenhagen 2003
Nordling J et al. Eur Urol 2004;45:662-9

1.11 Overactive bladder syndrome

Urgency, with or without urge incontinence, usually with frequency and nocturia, can be described as the overactive bladder syndrome, urge syndrome or urgency-frequency syndrome. *ICS definition 2002*

2. Confusable diseases

Diagnostic criteria are needed for diseases with unknown origin and overlapping features with other diseases, the so-called confusable diseases.
Possible confusable diseases (CD) for PBS/IC were discussed during the meeting. The participating ESSIC members were asked to indicate or discuss:

- whether the disease was considered to be a true confusable disease;
- whether the disease could be ignored in situations where there is no clinical suspicion for the disease ("ignored unless");
- the way in which the disease can be distinguished from PBS/IC;
- to classify the disease as "rare" or "not rare";

The following diseases or disease groups are considered to be confusable diseases:

2.1 Bladder malignancies

Bladder carcinoma (not rare) and carcinoma *in situ* (rare) are true confusable diseases and diagnosed by cystoscopy and biopsy. Metastatic bladder disease, primary lymphoma and plasmacytoma can be "ignored unless".

2.2 Bladder infections

More information and clear guidelines are probably needed to ensure the correct exclusion of all known microbiological causes (other than by the common uropathogens) of inflammation of the bladder and lower urinary tract.

– ***Bacterial infections***

Infections with:

- common intestinal bacteria (not rare)
- *Mycobacterium tuberculosis* (rare in most western countries)
- *Chlamydia trachomatis* (not rare)
- *Ureaplasma urealyticum* (not rare)
- *Mycoplasma genitalium* (rare)
- *Corynebacterium urealyticum* (prevalence unknown)

were considered to be true confusable diseases.

Infections with common intestinal bacteria can be diagnosed with urinalysis and routine bacterial culture. In situations of "sterile" pyuria, additional cultures should be performed to detect bladder tuberculosis. These cultures must also be done in regions with a high prevalence of tuberculosis.

Infections with *Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma genitalium* and *Corynebacterium urealyticum* must be excluded with special culture methods.

Mycoplasma hominis was not discussed but should be added to the list of special urine cultures as the literature indicates that it is a common cause of cystitis symptoms.

– ***Parasitic infections***

Bladder bilharziasis is considered to be a true confusable disease that can be "ignored unless". If relevant, the disease can be diagnosed by the finding of parasite eggs in the urine.

– ***Fungal infections***

Bladder infection with Candida species is considered to be a true confusable disease that must be excluded by special culture.

– ***Viral infections***

Urogenital infections with:
- *Herpes zoster*
- *Herpes simplex*
- *Human Papilloma Virus*

are considered to be true confusable diseases but can be ignored unless physical examination indicates otherwise.

2.3 Bladder inflammation induced by physical or chemical agents

Bladder inflammation as a result of radiation, chemotherapy and/or therapy with cyclophosphamide (Endoxan®) and tiaprophenic acid (Surgam®) are considered to be true confusable diseases but can be "ignored unless" the disease history indicates otherwise.

2.4 Bladder inflammation: various mechanisms

Eosinophilic and plasma cell cystitis and isolated bladder vasculitis are considered to be true confusable diseases that can be "ignored unless". Furthermore, a biopsy will reveal these diseases.

Endometriosis in or near the bladder is considered to be a true confusable disease that can be excluded as he cause of the IC-like symptoms by disease history and gynaecological examination.

A myofibroblastic tumor is a true confusable disease that can be "ignored unless".

Cystitis glandularis is not considered to be a true confusable disease.

Bladder sarcoidosis can be "ignored unless".

2.5 Abnormal bladder function

Bladder outlet obstruction
Bladder neck obstruction and neurogenic outlet obstruction are considered to be true confusable diseases. Disease history, flow rate and ultrasound are the diagnostic methods.

Detrusor muscle function
Incomplete bladder emptying (retention) is considered to be a true confusable disease that can be diagnosed on the basis of post-void residual urine volume measured by ultrasound scanning.

Overactive bladder is not considered to be a true confusable disease as it is not associated with pain.

Bladder stones
Bladder stones and lower ureteric stones are considered to be true confusable diseases that can be diagnosed on the basis of imaging techniques and history, respectively.

Comment. In patients with PBS/IC-like symptoms, there is no need to exclude bladder stones by imaging techniques as stones will be found at cystoscopy. Lower ureteral stones will be found because the patients either have typical history and one-sided symptoms or haematuria implying some kind of upper tract imaging (CT or i.v. pyelography).

Various
Urethral diverticulum is a true confusable disease that can be excluded by disease history and digital vaginal examination.

2.6 Sex dependent diseases

Female diseases
Endometriosis, vaginal candidiasis and *Herpes simplex* infection have been discussed above. Infection with *Human Papilloma Virus* (HPV) is considered to be a true confusable disease that

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can be excluded on the basis of physical examination (see above).

Cervical, uterine and ovarian cancer can be excluded as the cause of PBS/IC-like symptoms on the basis of physical examination.

Male diseases
Benign prostatic obstruction (BPO), chronic bacterial prostatitis, chronic non-bacterial prostatitis and prostate cancer were considered to be true confusable diseases that should not be ignored.

BPO can be excluded on the basis of flow rate measurement and pressure-flow studies. Chronic prostatitis can be excluded on the basis of disease history, physical examination and culture.

Prostate cancer can be excluded as the cause of PBS/IC-like symptoms on the basis of digital rectal examination and measurement of PSA

Comment: PSA should be measured in every male patient over 40 yrs.

2.7 Abnormal bowel function
Irritable bowel syndrome, constipation and Crohn's disease were not considered to be true confusable diseases.

2.8 Summary
Table 2.1 shows a list of relevant confusable diseases and how they can be excluded or diagnosed.

3. Procedures/tests necessary to detect the confusable diseases

From the list of diseases that are true confusable diseases and cannot be ignored, it can be concluded that the following procedures / tests are necessary to detect these confusable disease:

1. medical history
2. physical examination
3. selected laboratory tests
4. urodynamics and ultrasound scanning if indicated
5. cystoscopy and biopsy if indicated

3.1 Medical history
A general thorough medical history should be taken with emphasis paid to:
- previous pelvic operations
- previous urinary tract infections
- bladder history/urological diseases
- location of pelvic pain (referred pain) and relation to bladder filling/emptying
- characteristics of pain: onset, correlation with other events, description of pain
- previous pelvic radiation treatment
- autoimmune diseases

ESSIC, Copenhagen 2003

In addition, emphasis should also be paid to previous medication such as chemo-therapeutics, immunosuppressants such as cyclophosphamide and anti-inflammatory drugs such as tiaprophenic acid.

3.2 Physical examination
A common physical examination should be performed including palpation of the lower abdomen for bladder fullness and tenderness:
- standing: kyphosis, scars, hernia
- supine: abduction/adduction of the hips, hyperaesthetic areas

– ***Females***
In females, physical examination should include a vaginal examination with pain mapping of the vulvar region and vaginal palpation for tenderness of the bladder, urethra, levator and adductor muscles of the pelvic floor. Tenderness might be graded as mild, moderate or severe.

Pain mapping inspection:
- vulva
  - exclusion of vulvar/vestibular diseases (vulvitis, dermatosis etc.)
  - evaluation of introital area (endometriosis)
  - tenderness of vestibular glands or vulvar skin (Touch Test: use wet cotton stick or fingertip)
- vagina
  - tenderness during insertion and opening of speculum
  - cervical pathology
  - vaginal fornices (endometriosis)
- bimanual physical examination
  - tenderness of urethra, trigone and bladder
  - superficial/deep vaginal tenderness
  - tenderness of pelvic floor muscles (levator, adductor)
  - tenderness in adnexal areas

– ***Males***
In males digital rectal examination should be performed with pain mapping of the scrotal-anal region and palpation of tenderness of the bladder, prostate, levator and adductor muscles of the pelvic floor and the scrotal content.

ESSIC, Copenhagen 2003

3.3 Laboratory tests
- urine dipstick (ABS, pH, leukocytes, nitrate)
- urine culture (standard and special; see below)
- if sterile pyuria: culture for *Mycobacterium tuberculosis*
- urine cytology in risk groups
- investigations for vaginal Ureaplasma and Chlamydia in females and prostatitis in men are optional
- serum PSA level in every male over 40 years of age

ESSIC, Copenhagen 2003; Baden 2005

Special cultures are done to detect infection with micro-organisms as the cause of PBS/IC-like symptoms that are not detected with routine urine cultures:
- *Chlamydia trachomatis*
- *Ureaplasma urealyticum*
- *Mycoplasma genitalium* and *Mycoplasma hominis*
- *Corynebacterium urealyticum*
- Candida species

3.4 Urodynamics and ultrasound scanning
A post-void residual urine volume measured by ultrasound scanning to detect incomplete bladder emptying (retention) as the cause of PBS/IC-like symptoms.

Flow rate measurement and pressure-flow study if indicated to detect bladder neck obstruction and neurogenic outlet obstruction as the cause of PBS/IC-like symptoms.

In males, a flow metry should be done in all, and if maximum flow rate < 20 ml/sec a pressure-flow study and measure of residual urine volume should be done.

3.5 Cystoscopy and biopsy if indicated
Cystoscopy under anaesthesia, either spinal or general, is mandatory in cases with suspected IC. *ESSIC, Copenhagen 2003*

Cystoscopy with biopsy if indicated are necessary to detect bladder carcinoma, carcinoma *in situ* and bladder stones as the cause of IC-like symptoms. For technical details see paragraph 5.7 of the Summary of the ESSIC Meeting with modifications, Copenhagen 2003 (section 5).

– ***Inspection***
Describe lesions in anterior wall, posterior wall, lateral quadrants and fundus. At the fundus one should be alert for possible artefacts if there is blind introduction of the scope. Bladder mapping by drawing is mandatory. Photographs are recommended but optional.

– ***Classification***
Grade 0 : normal mucosa
Grade I : petechiae in at least two quadrants
Grade II : large submucosal bleeding (ecchymosis)
Grade III : diffuse global mucosal bleeding
Grade IV : mucosal disruption, with or without bleeding/oedema

The highest grade is to be reported and the observations should be detailed. It is recommended to take the biopsies including muscle under good visibility and not at full bladder capacity. A minimum of three biopsies are taken plus a biopsy from an area with maximum post-distension reaction.

ESSIC, Copenhagen 2003

– ***Biopsies***
For technical details of biopsies and the pathology report see paragraph 7 of the Summary of the ESSIC Meeting, Copenhagen 2003.

3.6 Additional comments on diagnostic procedures

– ***Potassium Sensitivity Test***
It was concluded on the basis of presentations by Gero Hohlbrugger and Claus Riedl and the discussions that followed that the Potassium Sensitivity Test lacks properties to allow its use as an aid for the diagnosis of PBS/IC. It was also concluded that no efforts should be undertaken to evaluate its possible value for the diagnosis of PBS/IC in connection with the future data collection for the development of diagnostic criteria.

Gero Hohlbrugger gave an additional comment (see paragraph 6.1).

– ***Antiproliferative Factor and other markers***
It was concluded that no efforts should be undertaken to evaluate the possible value of the Antiproliferative Factor (APF) and other possible disease markers for the diagnosis of IC in connection with the future data collection for the development of diagnostic criteria.

4. Proposed sequence of actions in patients with IC-like symptoms

4.1 Medical history eliminates PBS/IC-like symptoms due to radiation, therapy with cyclophosphamide or tiaprophenic acid and lower ureteric stone (see Table 2.1)

4.2 Physical examination further eliminates infections with *Herpes simplex* and *Human Papilloma Virus*, urethral diverticulum, endometriosis, vaginal candidiasis, cervical cancer, uterine cancer, ovarian cancer, chronic bacterial prostatitis and chronic nonbacterial prostatitis (confirmed by culture), prostate cancer (initial confirmation with PSA),

The following diseases are not yet excluded:
- carcinoma
- carcinoma *in situ*
- infection with common intestinal bacteria
- infection with *Mycobacterium tuberculosis*
- infection with *Chlamydia trachomatis*
- infection with *Ureaplasma urealyticum*
- infection with *Mycoplasma hominis*
- infection with *Mycoplasma genitalis*
- infection with *Corynebacterium urealyticum*
- infection with Candida species
- incomplete bladder emptying (retention)
- bladder neck obstruction
- neurogenic outlet obstruction
- bladder stone
- benign prostatic obstruction

4.3 Dipstick urinalysis, routine and special cultures eliminate the various infectious causes.

The following diseases are not yet excluded:
- carcinoma
- carcinoma *in situ*
- bladder neck obstruction
- neurogenic outlet obstruction
- incomplete bladder emptying (retention)
- bladder stone
- benign prostatic obstruction

4.4 Flow metry and post-void residual urine volume measured by ultrasound scanning detects benign prostatic obstruction, neurogenic outlet obstruction, bladder neck obstruction and incomplete bladder emptying (retention).

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Table 2.1 List of relevant confusable diseases and how they can be excluded or diagnosed

confusable disease	*excluded or diagnosed by*
carcinoma	cystoscopy and biopsy
carcinoma *in situ*	cystoscopy and biopsy
infection with common intestinal bacteria	routine bacterial culture
infection with *Mycobacterium tuberculosis*	dipstick; if "sterile" pyuria culture for *M. tuberculosis*
infection with *Chlamydia trachomatis*	special culture
infection with *Ureaplasma urealyticum*	special culture
infection with *Mycoplasma hominis*	special culture
infection with *Mycoplasma genitalis*	special culture
infection with *Corynebacterium urealyticum*	special culture
infection with Candida species	special culture
infection with *Herpes simplex*	physical examination
infection with *Human Papilloma Virus*	physical examination
radiation	medical history
chemotherapy	medical history
immunotherapy with cyclophosphamide	medical history
anti-inflammatory therapy with tiaprophenic acid	medical history
bladder neck obstruction	flow metry and ultrasound
neurogenic outlet obstruction	medical history, flow metry and ultrasound
bladder stone	imaging or cytoscopy
lower ureteric stone	medical history and/or haematuria (→ upper urinary tract imaging such as CT or IVP)
urethral diverticulum	medical history and physical examination
endometriosis	medical history and physical examination
vaginal candidiasis	medical history and physical examination
cervical, uterine and ovarian cancer	physical examination
incomplete bladder emptying (retention)	post-void residual urine volume measured by ultrasound scanning
prostate cancer	physical examination and PSA
benign prostatic obstruction	flow metry and pressure-flow studies
chronic bacterial prostatitis	medical history, physical examination, culture
chronic non-bacterial prostatitis	medical history, physical examination, culture

Continued from page 7

The following diseases are not yet excluded:
- carcinoma
- carcinoma *in situ*
- bladder stone

4.5 Cystoscopy detects carcinoma, carcinoma *in situ* (confirmation with biopsy) and bladder stones.

Biopsy further excludes rare causes of PBS/IC-like symptoms due to e.g. vasculitis, lymphoma and eosinophilic cystitis.

4.6 Confirmation of the diagnosis of IC
The diagnosis of IC is confirmed by cystoscopy with hydrodistension if glomerulations and/or Hunner's lesions are seen and/or biopsies show mononuclear inflammatory cells including mast cell infiltration and granulation tissue.

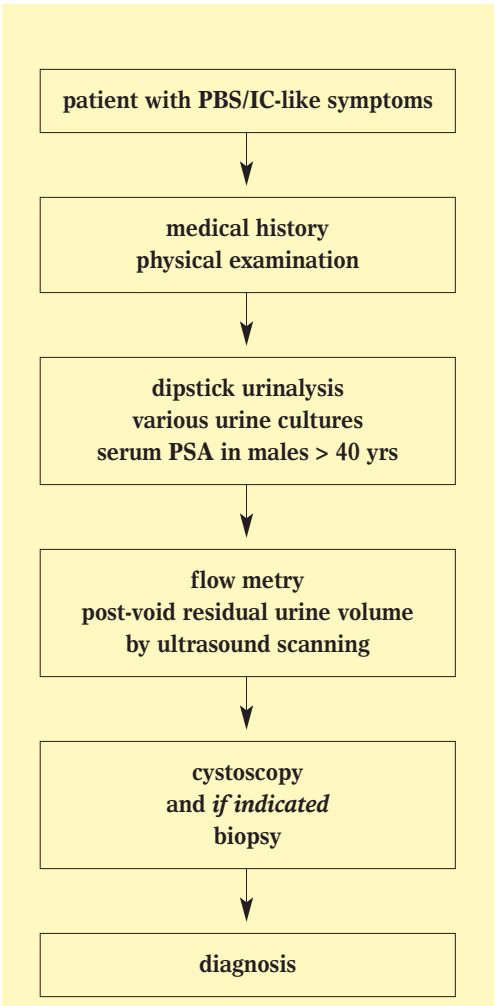

Figure 4.1 *Schematic representation of the sequence of actions to detect confusable diseases, painful bladder syndrome and interstitial cystitis in patients with PBS/IC-like symptoms*

5. Summary ESSIC Meeting Copenhagen 2003 with modifications

The following recommendations were accepted by al participants.*

Interstitial cystitis (IC) is characterized by urinary frequency, urgency and pelvic pain often localized to the bladder or urethra. The disease is poorly defined and epidemiological and clinical investigations often difficult to compare due to differences in definition.

5.1 Medical history
A general thorough medical history should be taken with emphasis paid to:
- previous pelvic operations
- previous urinary tract infections
- bladder history/urological diseases
- location of pelvic pain (referred pain) and relation to bladder filling/emptying
- characteristics of pain: onset, correlation with other events, description of pain
- previous pelvic radiation treatment
- autoimmune diseases

* The consensus and recommendations report has been published: Nordling J et al. Primary evaluation of patients suspected of having interstitial cystitis (IC). Eur Urol 2004;45:662-9.

5.2 Physical examination
A common physical examination should be performed including palpation of the lower abdomen for bladder fullness and tenderness:
- standing: kyphosis, scars, hernia
- supine: abduction/adduction of the hips, hyperaesthetic areas

– ***Females***
In females physical examination should include a vaginal examination with pain mapping of the vulvar region and vaginal palpation for tenderness of the bladder, urethra, levator and adductor muscles of the pelvic floor. Tenderness might be graded as mild, moderate or severe.

Pain mapping inspection:
- vulva
  - exclusion of vulvar/vestibular diseases (vulvitis, dermatosis etc.)
  - evaluation of introital area (endometriosis)
  - tenderness of vestibular glands or vulvar skin (Touch Test: use wet cotton stick or fingertip)
- vagina
  - tenderness during insertion and opening of speculum
  - cervical pathology
  - vaginal fornices (endometriosis)
- bimanual physical examination
  - tenderness of urethra, trigone and bladder
  - superficial/deep vaginal tenderness
  - tenderness of pelvic floor muscles (levator, adductor)
  - tenderness in adnexal areas

– ***Males***
In males, digital rectal examination (DRE) should be performed with pain mapping of the scrotal-anal region and palpation of tenderness of the bladder, prostate, levator and adductor muscles of the pelvic floor and the scrotal content.

5.3 Laboratory tests
- urine dipstick (ABS, pH, leukocytes, nitrate)
- urine culture in all
- if sterile pyuria culture for *Mycobacterium tuberculosis*
- urine cytology in risk groups
- investigations for vaginal Ureaplasma and Chlamydia in females and prostatitis in men are optional

5.4 Symptom evaluation
- voiding diary with volume intake and output for 3 days at initial evaluation; patient sensation at voiding might be recorded
- at follow-up, only number of voidings during day and night time is necessary; morning volume might be recorded as a help to monitor highest functional capacity
- the O'Leary-Sant Symptom Score supplemented with a sex score (suitable sex score to be constructed) should be used as basic symptom score supplemented with the Quality of Life Score from the International Prostate Symptom Score
- pain should be recorded using a Visual Analogue Scale (VAS) for pain during the last 24 hours (to match the voiding diary); separate scores for the average, mildest and worst pain should be obtained:
  - average pain during the last 24 hours: no pain intolerable pain
  - worst pain during the last 24 hours: no pain intolerable pain
  - least pain during the last 24 hours: no pain intolerable pain

5.5 Urodynamics
Filling cystometry is helpful in overactive bladder (OAB) for diagnosing detrusor overactivity as IC and OAB may coexist. This might have implications for treatment.

In males, bladder outlet obstruction can be a differential diagnosis. It is therefore recommended to perform filling cystometry with a filling rate of 50 ml/sec (to comply with the revised Potassium Test - see below) to look for overactivity, volume at first desire to void and cystometric capacity.

In females, flow metry, post-void residual urine volume and pressure-flow study are optional.

In males, a flow metry should be done in all, and if maximum flow rate < 20 ml/sec a pressure-flow study and measure of residual urine volume should be done.

The revised Potassium Test has shown prognostic value in bladder irrigation studies, but is considered optional. If performed it should be performed according to Daha *et al.* (J Urol 2003;170:807-9)

5.6 Potassium sensitivity test
Modified KCl test: comparative assessment of maximum bladder capacity

A Foley balloon catheter (14F) is inserted and the bladder drained. Instill into the bladder 500 ml saline (0.9%) at a rate of 50 ml/min via an infusion set until the maximum capacity is reached. Drain the bladder and measure the saline filling volume. Repeat the instillation and measurement with 500 ml 0.2 M potassium chloride at a rate of 50 ml/min (taking care that filling lines are emptied of all saline before KCl instillation), and calculate the filling volume difference.

A difference in bladder capacity > 30% is considered positive. Besides reduction in bladder capacity by 0.2 M KCl, there is a stronger sensation of urgency in IC patients compared to the saline filling, which is also clinically relevant.

5.7 Cystoscopy
Cystoscopy under local anaesthesia might be part of the general urological workup to exclude diagnoses other than IC.
Cystoscopy under anaesthesia, either spinal or general, is mandatory in cases with suspected IC.

– ***Technique***
A rigid cystoscope is preferred to facilitate taking of adequate biopsies. Glycine or corresponding filling fluid should be used to allow for coagulation after biopsies. Infusion height should be approximately 80 cm above the symphysis pubis. A dripping chamber is used and the bladder is filled until fluid dribbling stops. If necessary, a digital block is applied around the urethra to prevent leakage. Pre-distension inspection includes observation for radiating vessels, coagulum or fibrine deposits, white spots, hyperaemia, oedema, cracks, scars or any other mucosal changes. Continuous inspection while filling the bladder is advised.

When maximum capacity is reached, the distension is maintained for 3 minutes. The bladder is emptied and the colour of the fluid checked for the degree of bleeding. The total volume drained is the measured maximum bladder capacity.

During a second filling, the bladder is filled to approximately 1/3rd to 2/3rd of the bladder capacity to achieve optimal vision for inspection and biopsies. The bladder should not be filled to maximum capacity or distended again to avoid further provocation of changes with doubtful reproducibility.

– ***Inspection***
Describe lesions in anterior wall, posterior wall, lateral quadrants and fundus. At the fundus one should be alert for possible artefacts if there is blind introduction of the scope. Bladder mapping by drawing is mandatory. Photographs are recommended but optional.

– ***Classification***
Grade 0 : normal mucosa
Grade I : petechiae in at least two quadrants
Grade II : large submucosal bleeding (ecchymosis)
Grade III : diffuse global mucosal bleeding
Grade IV : mucosal disruption, with or without bleeding/oedema

The highest grade is to be reported and the observations should be detailed. It is recommended to take the biopsies including muscle under good visibility and not at full bladder capacity. A minimum of three biopsies are taken plus a biopsy from an area with maximum post-distension reaction.

– ***Biopsies***
During cystoscopy the bladder is distended to full capacity. After draining the bladder, bladder biopsies are taken at roughly half-full bladder capacity: Biopsy procedures should be performed by using large forceps and include detrusor muscle; alternatively double punch biopsies or resections of lesions can be used.

Number of biopsies
At least 3 biopsies from the two lateral walls and bladder dome should be taken in addition to biopsies from lesional areas. The biopsies are to be immediately fixed in neutral buffered 4% formalin.

Biopsy handling
Biopsies are treated conventionally according to routine procedure at the Department of Pathology. Six adjacent 3 µm sections are cut and placed with 3 specimens on each of two specimen slides. The first slide is stained with H&E, the next with a connective tissue stain suitable for the individual institute. Twenty-four 10 µm sections are then cut and every third section is mounted on a specimen slide for mast cell counting (see below). The specimens are stained by Leder-stain (naphtolesterase) according to routine procedures. Finally, a 3 µm section is obtained to ensure the presence of detrusor muscle in the specimens.

Mast cell counting
The use of a measuring grid (Leitz periplan 6F 10N ocular containing a standardized grid) is necessary. Previous standardized measurements have been done on a grid containing 25 squares, each square measuring 0.21 mm^2. The counting of mast cells in the detrusor is preferably made in 20 squares, but at least 7 squares should be counted on a magnification of 25. If less than 7 squares with detrusor are represented, the biopsy is insufficient. Only mast cells containing nucleus are included. When counting the cells, those covering or touching the bottom - and a right line - should be excluded, whereas those covering the upper and left line are included. In this way a maximum of 20 squares may be encounted in the total counting i.e. 20 squares: 20 x 0.21 mm^2 = 4.2 mm^2.

At least 3 biopsies must be the subject of mast cell counting and if possible one including a lesional area.

The total number of mast cells per mm^2 is:

$$\frac{\text{the total number of mast cells}}{\text{the number of squares included in the counting} \times 0.21}$$

If biopsies for mast cell counting do not contain detrusor muscle, new biopsies must be obtained.

– ***The pathology report***
- epithelium
  - not present / present
  - dysplasia with grading

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- abnormal but no dysplasia: description is mandatory
- propria
  - normal
  - inflammation: description with a grading
  - other findings are described
- detrusor muscle
  - abnormal muscle cells: describe
- intrafascicular fibrosis
  - not present / present
- mast cell count: at least three biopsies should be included in the counting; only the biopsy with the highest number of mast cells per mm^2 should be reported

The enzymatic (naphtolesterase) staining is, for the time being, recommended since standardized values are available:

< 20 mast cells/mm^2 : no detrusor mastocytosis
20-28 mast cells/mm^2: grey zone
> 28 mast cells/mm^2 : detrusor mastocytosis

The use of immunohistochemical stainings (i.e. antitryptase) is not at the present time recommended since no reference material employing standardized cutting procedures and counting procedures exist. However, it is the aim of this study group to collect a reference/normal material for immunohistochemical staining and, when available, cutting and staining procedures will be changed accordingly.

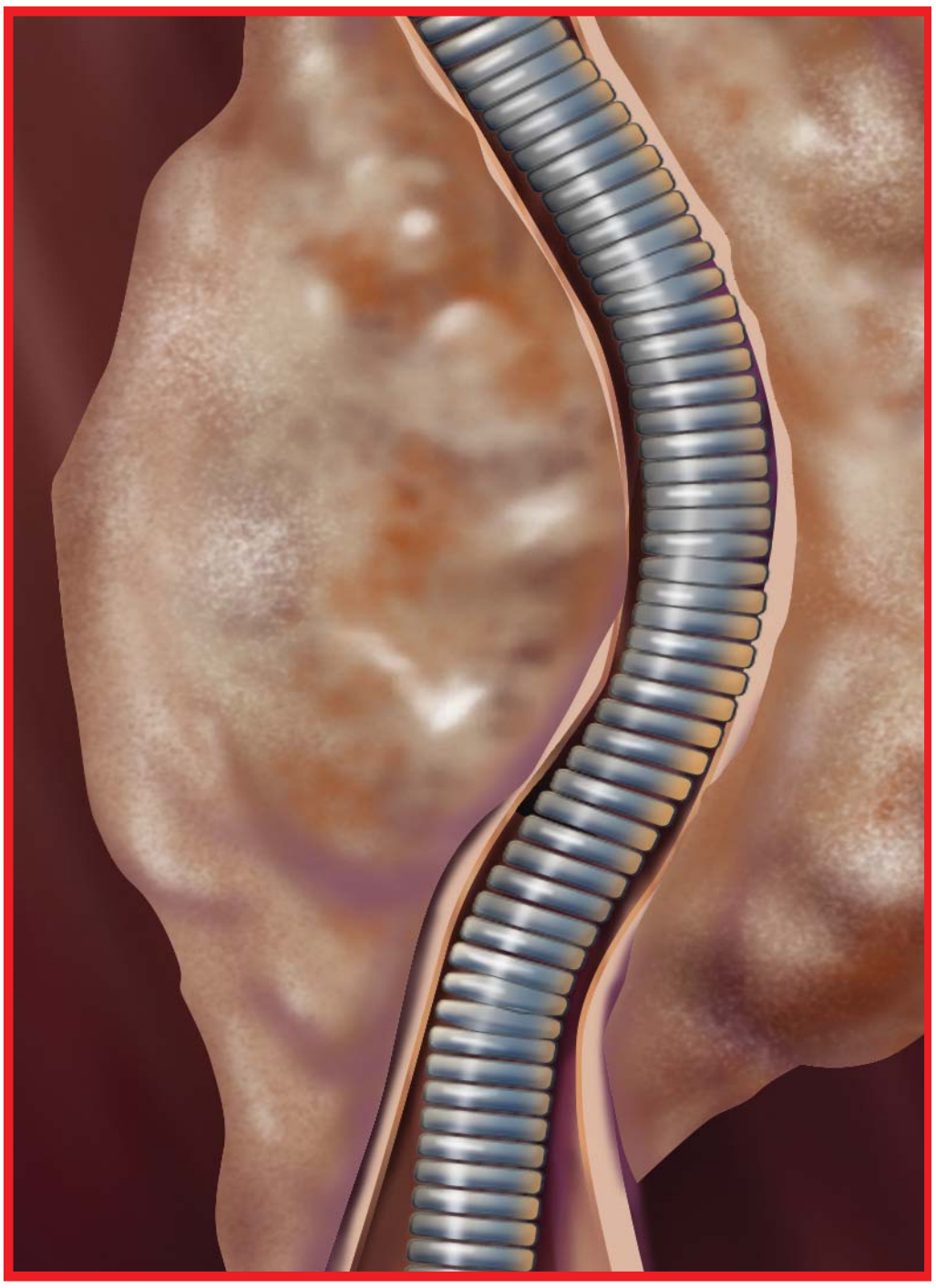
6. Comments

6.1 Comment Prof. Gero Hohlbrugger on the draft version of this report

Prof. Gero Hohlbrugger gave the following comment on the discussions of the Potassium Sensitivity Test.

Conclusion:
To test the effect of urinary K^+ on the bladder wall, there are two options: Parsons' potassium sensitivity test (PST) with 0.4 M KCl, or our comparative evaluation of maximum cystometric capacity with normal saline vs. 0.2 M KCl. We nicknamed the potassium impact on capacity PIC. In the symptomless bladder with normal capacity and without post-void residual urine, negative PST/PIC might show a normal "impermeable" blood-urine barrier. A number of arguments support the idea that it is not the upregulated urothelial C-fiber endings, but rather K^+-induced depolarization of the detrusor and the associated firing of the Adelta fibers and myogenic C-fibers that lies at the root of a positive PST/PIC in IC. Urothelial hyperpermeability together with relative ischemia of the bladder wall enable urinary K^+ to reach the detrusor. It is highly probable that it is not the GAG deficit that is directly responsible for the urothelial hyperpermeability of the IC bladder, but rather sympathetic hyperactivity that is triggered by a defective mucus layer and by abnormal firing of A-delta fibers. Accordingly, the interpretation of the positive PST/PIC should be extended to include the following: it is a triad of relative ischemia due to urothelial hyperpermeability and despite sympathetic hyperactivity.
The negative PST/PIC of the small capacity bladder can then be explained as the result either of urothelial impermeability as a consequence of sympathetic hypoactivity and/or of a silencing of the A-delta fibers as a consequence of sustained depolarization of the muscle nerve unit. The fact that the PST/PIC yields a relatively high percentage of negative outcomes makes it unsuitable as a reliable diagnostic tool for IC. Moreover, it does not help in identifying patients who may not at all benefit or those likely to benefit only for a short period, from GAG substitution therapy. To be able to screen such patients, specific skin, blood or urine tests need to be developed by future research. To ensure that a sub-group of PST/PICpositive IC bladders do not progress to a completely different pathophysiological infrastructure in endstage disease with negative PST/PIC, the currently available diagnostic and therapeutic guidelines are not adequate. Because it is totally painless, we prefer to evaluate the PIC. When it is supplemented with EMG flow metry, the method enables easy identification of the vesicogeneity of the painful pelvic floor. Despite proven shortcomings, it must be mentioned that PST as well as PIC still have a considerable role in the investigation of IC and most likely other bladder diseases.

e-mail Gero Hohlbrugger, 15 August 2005



Announcement

European Association of Urology

6th Central European Meeting (CEM)
Prague, Czech Republic, 15–16 September 2006

Dear colleagues,

It is a great pleasure and honour to invite you to the 6th Central European Meeting, which will take place in Prague September 15th-16th, 2006.

On behalf of the Czech urologists I can assure you that we secured a wonderful congress venue and that the scientific programme will be enhanced with some very interesting social activities. The scientific programme clearly relies on the quality of the abstracts submitted and maybe the awards established for f.i. Best-Poster presentation are an added incentive to submit high-quality material in time for the deadline of **18 June 2006!**

The 6th Central European Meeting will also feature world-experts giving state-of-the-art lectures on a range of topics, among which prostate cancer, neurogenic bladder and urethral surgery.

Do remember that 15 September 2006 coincides with European Prostate Day!
Join us, present your papers, see your friends from other Central European countries and enjoy 'tasty' Prague.

We are looking forward to seeing you all in the heart of Europe in September 2006.

T. Hánuš, Chairman of the EAU 6th Central European Meeting and President of the Czech Urological Association

Dear all,

It also gives me great pleasure to invite you to the 6th Central European Meeting in Prague.

Objective of this EAU regional meeting is to develop a platform, where new experimental and clinical work from the region is presented to an international audience. It is the ideal forum for urologists to meet colleagues with similar interests and to develop urological networks within the region.

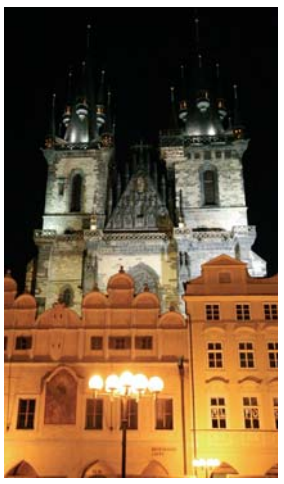
We herewith invite you to submit abstracts. The Advisory Board will make the final selection. There will be prestigious awards for the best presentations. In addition state of the art presentations by invited speakers will highlight topics of current controversy.

M. Marberger, Chairman of the EAU Regional Office

Topics that will be covered in the plenary session are:
- Prostate cancer
- Renal cell cancer
- Female urology
- Neurogenic bladder dysfunction
- State of the art lectures on Paediatric urology (hypospadias), Transplant surgery, Reconstructive surgery (of the urethra)

Call for Abstracts!

Authors are invited to submit abstracts for poster presentation on these topics or any other clinical or experimental recent work, prior to the deadline of 18 June 2006.
Submission of abstracts can be made on-line through www.uroweb.org in the 'meetings and events' section.



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