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Interstitial Cystitis – Present Therapeutic Perspectives

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"There are two objects in medical education: **to heal the sick and advance the science.**"

Charles H. Mayo.

Interstitial Cystitis – Present Therapeutic Perspectives

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Abstract

Context: Interstitial cystitis/bladder pain syndrome (BPS/IC) is a debilitating chronic disease of unknown etiology. Treatment is not well defined and under intense investigation.

Objective: To review existing literature on treatment of BPS/IC and examine current evidence on present and future perspective.

Evidence acquisition: Pub Med data base was researched and publications in English language of the last 2 years were retrieved and analyzed.

Evidence synthesis: Mainstays of oral therapies are still empirical due to lack of knowledge on etiology of this disease. The few oral drugs that showed enough efficacy in placebo controlled trials are amitriptyline, pentosanopolisulfate, hydroxyzine and cyclosporine A. As for intravesical treatments reasonable evidence is available only for dimethylsulphoxide and resection of visible Hunner lesions. Reconstructive surgery can also be recommended in selected cases. Further studies into the causes and mechanisms of the disease are paramount for the development of effective treatments. Foreseeable therapeutic objectives will comprehend oral blockade of sensory nerve receptors, immune system modulation, peripheral nerve fiber inactivation/desensitization, anti-proliferative factor (APF) blockade and pain gene therapy. Identification of BPS/IC phenotypical subgroups should help delineate proper individualized treatment which will be aimed at the disease and its multiple manifestations rather than at focalized complaints.

Conclusions: Present treatment of BPS/IC comprises pain control in conjunction with control of supposed underlying bladder disease. Based on identified possible therapeutic targets several treatment possibilities warrant further investigation. Identification of BPS/IC phenotype subgroups should help delineate proper individualized treatment along with a comprehensive disease approach.

Introduction

Interstitial cystitis (IC), presently known as Bladder Pain Syndrome (BPS) is a disease recognized for over a century but still far from completely understood. A definition with increasingly wider use is that of the European Society for the Study of Interstitial Cystitis (ESSIC) - pelvic pain, accompanied by at least one other symptom, such as persistent urge to void or frequency, in the absence of an identifiable cause [1]. The disease was initially thought to course with chronic inflammation of the bladder wall, leading to the formation of characteristic lesions called Hunner's ulcers, hence the classic name interstitial cystitis.

Hunner described what he saw as ulcers using rudimentary nineteenth century cystoscopes. In fact Hunner's ulcers are not ulcers but distinct inflammatory lesions that rupture across the mucosa and submucosa at cystoscopy if hydrodistention is performed. Therefore they are now referred to as Hunner's lesions. These can be observed mainly in the lateral walls in up to 50% of the patients. Glomerulations and petequiae (frail urothelium) are more frequently observed lesions but none of the above are pathognomonic [1].

However, it was observed that many patients that had symptoms of IC did not present with intravesical lesions and some of them had no documentable inflammation at all [1]. So "classical" interstitial cystitis (with cystoscopic alterations) is now considered to be part of a wider disorder presently called Bladder Pain Syndrome in which there are two different types: the "classic" form which presents with identifiable bladder lesions and/or chronic inflammation features, observed at cystoscopy and histologic exam of bladder wall biopsy and the "non-classic" form in which the symptoms exist but the macroscopic or

even the histologic changes might not [2]. Furthermore BPS is a designation more in line with the present view of the disease as a chronic pain syndrome and not a disease of and necessarily coursing with inflammation in the bladder. Symptoms can be so severe that patients with BPS/IC may have quality of life scores lower than those treated for end-stage renal disease with hemodialysis [3]. Although BPS can affect both sexes at any age, the majority of patients are women. Up to 12% of women experience some symptoms during their lifetime [4]. Clinically confirmed BPS has a prevalence ranging from 230 to 500 per 100000 [5]. Throughout the years of investigation it became clear that pathophysiology of BPS/IC is probably multifactorial [6]. General belief today is that after an initial as yet unknown insult, bladder epithelium suffers some changes related to an impairment of cellular repair mechanisms, probably related to increased levels of antiproliferative factor (APF) which delays urothelium regeneration [7]. A lack of continuity of the glycosaminoglycan (GAG) layer on the outer surface of the urothelium becomes apparent and this contributes to leakage of irritating substances through the bladder wall [6]. This phenomenon in turn induces inflammatory infiltration with mast cell predominance and increased activation – 70% compared to 10% in healthy individuals [7]. Type C sensory nerve fibers become activated and in turn lead to local neurogenic inflammation, neural sensitization and neuroplasticity both peripherally and centrally [8]. The latter phenomena probably relate to bladder hyperalgesia and allodynia [6]. The original insult triggering these mechanisms and hence etiology of BPS has yet to be identified. Auto-immune mechanisms, unidentified infection, central neurogenic mechanisms, defective gag-layer constitution, toxic urinary components are some of the forwarded yet unproven

candidates [9]. Allergy was the most prevalent auto-immune disorder, but rheumatoid arthritis and inflammatory bowel disease were also several times more commonly found in BPS patients than in the general population [10]. An association between BPS/IC and other chronic diseases such as inflammatory bowel disease, systemic lupus erythematosus, irritable bowel syndrome, fibromyalgia and panic disorders, has been described leading to the suggestion that BPS/IC may be but an aspect of a systemic disease [11, 12]. Recently, attention has been drawn to the high prevalence of child abuse experiences, in patients with BPS/IC, a life event known to be linked with chronic pain development [13]. Sisters of IC patients have 17 times greater probability of having the disease pointing also to genetic susceptibility [14]. As the understanding of the disease evolved, several attempts to establish a diagnostic definition were made. The initial definition proposed by National Institutes of Diabetes Digestive and Kidney Diseases (NIDDK) for scientific studies turned out to be too restrictive, as almost 60% of patients diagnosed by clinicians did not fulfill the criteria. This left NIDDK definition unsuitable for clinical application as it may identify only a particular subset of what is increasingly known as BPS [3,8]. The European Society for the Study of Interstitial Cystitis (ESSIC) not only suggested the name BPS but also proposed a definition that allows the inclusion of patients that were until now undiagnosed: chronic (>6 months) pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom such as persistent urge to void or frequency. Confusable diseases must be excluded [1]. The International Consultation on Incontinence (ICI) followed suit and recommended the same terminology [4].

In view of present diagnostic and physiopathologic uncertainties the quest is on for the establishment of disease and disease-activity markers [15].

Antiproliferative factor APF (increased), hemoglobin binding endothelial growth factor HB-EGF (decreased), EGF (decreased), nerve growth factor (NGF - increased) and brain derived nerve growth factor (BDNF - increased) have been proposed as likely candidates [15, 16, 17]. Recent application of microarray technology to BPS patients and animal models has given further thrust to this aspect [18].

Evidence acquisition

The unrestricted fully exploded Medical Subject Heading (MeSH) “interstitial cystitis”, including all related terms was used to fully search PubMed database for the US National Library of Medicine of the National Institutes of Health.

Publications other than in English were excluded. Thorough review of publications in the last two years was performed. Literature update thus achieved was used to update treatment knowledge acquired in the last two years.

Evidence synthesis

Current treatment strategies

Defining the best management approach to a BPS/IC/ patient has been difficult because valid studies are scarce. The current management of IC/BPS is structured so that minimum harming is inflicted to the patient during treatment. Both patient and physician must be aware that some improvement during the evolution of the disease is already a victory as there is no definite curative treatment.

After the initial diagnostic approach, which includes clinical history, physical examination, urine analysis, cystoscopy with hydrodistension and biopsy patients are classifiable according to ESSIC criteria [9]. Conservative treatment is the first step of management. For patients that can identify certain triggers related to food and beverages dietary modifications should be taken. The most common triggers are citrate and drinks that contain caffeine, alcohol or which are carbonated. Patients that refer pelvic floor tenderness during the physical exam are likely to benefit from physical therapy such as myofascial physical therapy that has been proved to improve significantly the patients' global symptoms after 10 sessions [9,6]. During this initial approach pain may be controlled with non-prescription analgesics. When conservative treatment options fail to control the symptoms specific treatments should be considered.

Oral treatments

Oral treatments have been widely studied but sodium pentosane polysulphate (PPS) is the only FDA approved one [8]. PPS's effect is elicited by replacement of the GAG layer as well as the inhibition of mast cell degranulation, thus counteracting two supposed physiopathologic mechanisms of the disease [6]. For patients that initially responded to oral PPS it was shown that adding a small subcutaneous heparin dose is more effective than administering PPS alone [8].

Other oral agents used in BPS, with reasonable evidence, include amitriptyline, histamine-receptor antagonists and cyclosporine A. Amitriptyline was confirmed to be a useful agent by a controlled randomized study from Germany in 2004. It improves the symptoms as it acts as an anticholinergic and sedative by decreasing 5-hydroxytryptamine reuptake which also stabilizes mast cells [20, 2]. However, an RCT by the Interstitial Cystitis Collaborative Research Network (ICCRN) demonstrates that only doses above 50 mg/day are effective [21].

Hydroxyzine is a H1-receptor antagonist that inhibits mast cells by blocking serotonin release in the bladder. It was proven to decrease the severity of the symptoms in 40% and in 55% in patients that had personal history of allergies [21].

H2-receptor antagonists have also been used with significant benefit relative to placebo reported for cimetidine in a RCT [22].

Cyclosporin A, an immunosuppressive agent that inhibits T-cell activation, and cytokine release, when compared to PPS in a randomized controlled study, was

proven to be significantly more effective. However, it was also shown to have more and more significant adverse effects [23].

Various other oral agents have been used albeit with limited success and are thus not mentioned in the present work.

Intravesical treatments:

Intravesical treatments are the next step in the recommended management pathway, since the use of intravesical agents allows exposure to high concentrations of a given agent with limited side-effects [21]. Current possible intravesical therapies include: intravesical dimethyl sulphoxide (DMSO), PPS, neurotoxins, hyaluronic acid and chondroitin sulphate. DMSO is the only FDA approved drug for intravesical use in BPS. It inhibits mast cells and has analgesic, anti-inflammatory, muscle relaxant and collagen-dissolution effects [24]. Subjective and objective improvement was observed in 53 and 93% of patients respectively, in a randomized controlled study of DMSO against placebo [25].

PPS is used intra-vesically to achieve higher concentrations in the bladder, since a RCT showed significant advantage of simultaneous PPS oral and intravesical use over placebo or oral PPS alone [26].

Sensory type C fibers are responsible for pain transmission in BPS/IC. Thus this symptom might be controlled by C fiber desensitization [24]. Several studies showed a beneficial effect of resiniferatoxin (RTX) applied intravesically in patients with BPS/IC [21]. However Payne et al in a RCT involving 163 patients concluded that RTX was not superior to placebo. Since RTX was never commercially available and had to be prepared in laboratory for immediate

application, many doubts aroused in the scientific community about preparation, container used for drug transport and time elapsed between preparation and application in the various studies [27]. However in view of the inconclusive results the drug is since not recommended for BPS.

Besides PPS, GAG layer restitution has been attempted with hyaluronic acid and chondroitin sulfate. Good evidence however, is scant for either.

Intravesical sodium chondroitin sulphate efficacy and safety were recently evaluated in a multicentric, placebo controlled but underpowered RCT. The results show that the treatment is safe. There was no significant difference between the two groups regarding the improvement of symptoms. However, while only 22.6% of the vehicle control patients reported moderate or marked improvement, in the active group the percentage went up to 39,4% [28].

A prospective study by Riedl et al, performed in order to verify the long term effect of intravesical hyaluronic acid therapy involved 126 patients followed for 6 years. Overall positive response to treatment was 87%. Fifty percent of patients were asymptomatic after the observation period. 41,7% reported initial improvement with recurrence during the first year. Only 8,3% were refractory to this treatment. However results were for a subset of patients who had a positive modified potassium test [29].

Interventional therapies:

Hydrodistension (HD) not only allows the visualization of Hunner's lesion but is generally considered to have therapeutic effect by itself. In fact HD increases HB-EGF and decreases APF, two important disease and disease-activity potential bio-marker molecules in BPS [7]. However clinical evidence for its use beyond initial BPS evaluation procedures is scant at the most [30].

Neuromodulation

Long-term results were investigated by Gajewski et al. 72% of the patients (n=78) referred improvement after a median follow-up of 61.5 months. However, high rates of revision were observed and in 28% of the patients explantation was necessary. Neuromodulation should therefore be considered for persistent cases and before advancing to more invasive interventions such as surgery [31, 32].

Transurethral resection of Hunner's lesion induces a good response in 90% of the patients. Aiming at lesser morbidity transurethral lesion destruction has also been obtained both by fulguration and by laser application with success.

Transurethral intervention has good results and patients remain symptom-free for up to two years. The obvious setback of this invasive treatment is that it is only effective in a subset of BPS patients [33, 34].

Major surgery is viewed as a last resort. Different types of surgery are available: urinary diversion with bladder conservation, supratrigonal cystectomy, subtrigonal cystectomy or radical cystectomy including excision of the urethra. Supratrigonal cystectomy with enterocystoplasty is the most attractive option. Careful patient selection is of major importance and available evidence

identifies end stage classic ulcerative disease with bladder contraction as the ideal indication for surgery [35].

Since such a large portion of patients will be or are become refractory to treatment or will respond only partially to it, the practicing clinician dealing with BPS must work join in close contact with pain specialist units. The disease will be approached even more as a chronic pain picture *per se*, rather than a supposed organ disease and will follow habitual protocol. Any previous treatment presenting with some effect will be maintained.

Future trends in the treatment of BPS

The previously described approach to BPS treatment is a step by step method where often every patient is submitted to the same kind of treatment without considering the different kinds of symptoms or associated diseases of each patient. However no one treatment is effective in all patients and up to now, no means are devised to understand who will respond to which treatment.

Patel et al suggested a treatment algorithm in which the management was based on the patient phenotype dividing the patient's symptoms into six categories: urinary, psychological, organ specific, infection, neurologic and tenderness (UPOINT). Treatment in patients with urinary symptoms (frequency, urgency outlet problems, incontinence) should include urinary analgesics, anticholinergics, alfa-blockers, botulinum injection and neuromodulation. Those with psychological diseases that need to be treated with antidepressants should receive serotonin- norepinephrine reuptake inhibitors. Organ-specific treatment includes DMSO, PPS, bladder instillations, urinary analgesics and herbal agents. Infection should be treated with culture-specific antibiotics. Patients with

other diseases such as fibromyalgia, irritable bowel syndrome benefit from physical and alternative therapies and neuromodulation. When tenderness is identified physical therapy, massage, local anesthetics and muscles relaxants are appropriate [6].

Another way to approach BPS treatment/research might be to take into consideration specific subsets of patients according to ESSIC criteria and try to link them to responder subsets as exemplified by Riedl et al with modified potassium testing [4]. Further management approaches can include treatments such as intravesical botulinum toxin and other treatments still in an experimental context and dependent on clarification of etiology of BPS.

BPS treatment – future perspectives

Antibiotics?

Bacterial etiology hence antibiotic treatment is periodically reappraised. Presence of nanobacteria (NB) was investigated in twenty-seven BPS patients. NB were present in eleven of these patients. For these tetracycline treatment was performed; both oral and intravesical treatments were given for 3 months. After this period NB levels decreased and 36.35% of the patients considered themselves cured, 54,55% referred subjective improvement and only one patient did not refer any improvement [36].

New pharmacologic targets

Rudick et al used a murine model of BPS, obtained by pseudorabies virus infection, in order to identify potential therapeutic. Type 2 histamine receptor and neurokin type I receptor blockade elicited best reduction in pain parameters in this model [37].

Tanezumab, a humanized monoclonal antibody that specifically inhibits nerve growth factor was investigated in a proof of concept RCT. After 1 single IV injection patients evaluated at 6 weeks showed significant better results with tanezumab compared to placebo. Doses, treatment regimes are yet to be delineated [38]. APF antagonists were shown experimentally to revert tight junction damage in laboratory models presenting also a therapeutic possibility [39]. Sanchez Freire have forwarded evidence implying that epigenetic alterations and their reversal may be key in understanding and treating BPS. In fact the authorsshowed that MicroRNAs may mediate down-regulation of NK-1 receptor in BPS. Thus Micro-RNA manipulation might present also a therapeutic option in the future [40].

Gene therapy

Opioids are known to diminish pain and hyperactivity, however, these drugs induce dependence, bowel and cognitive side effects that are prohibitive to their long term use. Gene therapy presents a valid option since it delivers anti-nociceptive factors directly to bladder afferents. Both viral and non-viral vectors have been studied. Non-viral vectors are significantly less immunogenic but they do not have an efficient gene delivery as the viral vectors. Yokoyama et al studied the effect of targeted and localized expression of enkephalin in afferent

nerves that innervate the bladder by gene transfer using replication-defective herpes simplex virus (HSV) vectors expressing preproenkephalin, in a rat model of bladder hyperactivity and pain. This study showed that the therapy reduced the bladder irritation induced by capsaicin and the nociceptive freezing behavior was reduced when capsaicin was applied to un-anesthetized mice [41]. Human studies are underway with technology in human cancer patients [42].

Acupuncture is a well-known technique widely used for chronic pain diseases e.g rheumatoid arthritis. In a double-blind, randomized clinical trial comparing acupuncture with sham acupuncture therapy in 90 asian patients, 20 treatment sessions of acupuncture were twice as effective as sham acupuncture at easing symptoms of chronic prostatitis/chronic pelvic pain syndrome. After 10 weeks, the acupuncture group improved 4.5 points more on average in NIH-CPSI total score than the sham group. No demographic or clinical characteristic was associated with response [43].

Intravesical therapies

Hydrodistension under local anesthesia was undertaken with 71% patients showing success at one month follow-up and remaining well for medium 20 weeks. If confirmed this approach would avert the economic and personal burden of multiple operating room procedures [44].

The alkalinized form of lidocaine (able to penetrate urothelial barrier) was used by Nickel et al intravesically in a RCT. Alkalinized lidocaine had an immediate effect on symptoms: mean pain scores measured with a visual analogue scale decreased significantly from 6 to 1,8 after the first instillation. Despite being

significantly positive, these results again were limited to a subset of patients thus justifying phenotyping efforts [45].

In order to better understand the responsiveness to intravesical DMSO, Kim et al developed a new transgenic cystitis model that resembles BPS histopathology. Both chronic and acute phases of inflammation were studied. Results confirmed DMSO is capable of reducing both acute and chronic multiple inflammatory manifestations. DMSO or DMSO-derived improved compounds might thus have an enhanced role in BPS treatment [46].

Intravesical botulinum toxin A injection

Intravesical botulinum toxin A (Onabotulinum A) injection has been studied as a possible treatment as it may have an anti-nociceptive effect on bladder afferent pathways and diminishes muscle contractility. Although the results of several studies suggest a beneficial effect there is no irrefutable evidence of its role as an effective treatment yet. Placebo-controlled studies are needed. The injections have been associated with some adverse effects such as urinary retention and to decrease this event small doses of toxin should be used and it should be injected into the submucosa or at the bladder trigone [47].

In a RCT study the difference between hydrodistension and hydrodistension plus intravesical botulinum toxin A was analyzed. Of the 67 patients, 44 were divided in two groups that received the injections (one group received 200 U and the other 100 U) and cystoscopic hydrodistension was performed after two weeks. The remaining 23 patients received hydrodistension only. There was symptomatic improvement in all groups. However, in the hydrodistension group, 70% had returned to their previous symptoms after the first month whereas in

the OnabotA- treated groups there was improvement of VAS, FBC and cystometric bladder capacity at 3 months. At 12 and 24 months the results in the active group were 55 and 30% versus 26 and 17% in the hydrodistension group [48].

Trigonal only injection seemed effective and long lasting since 87% of patients (n=23) reported improvement after a 3 month follow-up period in a study by Pinto et al. Over 50% referred continuity of the beneficial effect nine months after the first treatment. When retreatment was needed similar results were obtained. The authors concluded that this treatment is safe, effective and can be repeated [17].

Laboratory engineered Onabotulinum toxin A, allowing for a more selective binding of the toxin to sensory fibers, will represent a major advance in this field. Basic work to this end is underway.

Conclusions:

Present treatment of BPS comprises multistep pain control in conjunction with control of any underlying bladder disease. Available treatments are largely insufficient. However, results are probably undermined by the lack of common terminology among researchers and especially by lack of clear disease subtype identification. Even so e.g. amitriptyline, PPS, hydroxyzine, DMSO, cimetidine, cyclosporine A, transurethral resection and surgery have been proven effective. Several treatment hypothesis warrant further investigation, based on identified therapeutic targets. Such is the case for alkalized lidocaine, neurokinin, histamine and nerve growth receptor blockers, intravesical botulinum toxin type A and preproenkephalin viral vector carriers. Identification

of BPS phenotype subgroups, be it through clinical or physiopathological criteria, should help delineate proper individualized treatment along with a more comprehensive disease approach.

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Take home message

BPS is in urgent need of uniformed phenotyping in order to maximize effect of presently known therapies and results of new therapeutic target research.

Exciting new armamentarium (neurotoxins, channel blockers, gene therapy) will benefit patients with a clear aiming.

Anexo

Normas para submissão de manuscritos da revista “European Urology”

“Review Articles

These are reviews that systematically find, select, critique, and synthesize evidence relevant to well defined questions about diagnosis, therapy, and prognosis. Review articles are in principle solicited by the editorial board. Authors who would like to submit unsolicited review articles should first write to the editorial office describing the content of the review article they wish to submit. Review articles should not be submitted in full without prior approval from the editors.

The format of the review article should be as follows:

Abstract

Provide a structured abstract no longer than 300 words with the following sections: Context, Objective, Evidence Acquisition, Evidence Synthesis, Conclusion (see abstract structure details below.)

- Context: Include one or two sentences describing the clinical question or issue and its importance in clinical practice or public health.
- Objective: State the precise primary objective of the review. Indicate whether the review emphasizes factors such as cause, diagnosis, prognosis, therapy, or prevention and include information about the specific population, intervention, exposure, and tests or outcomes that are being reviewed.
- Evidence Acquisition: Describe the data sources used, including the search strategies, years searched, and other sources of material, such as subsequent reference searches of retrieved articles. Methods used for quality assessment and inclusion of identified articles should be explained.
- Evidence Synthesis: The major findings of the review of the clinical issue or topic should be addressed in an evidence-based, objective, and balanced fashion, with the highest quality evidence available receiving the greatest emphasis.
- Conclusions: The conclusions should clearly answer the questions posed if applicable, be based on available evidence, and emphasize how clinicians should apply current knowledge.

See example of a [structured abstract](#).

Text

The text of the manuscript should be divided as follows: Introduction, Evidence Acquisition, Evidence Synthesis, Conclusions.

- Maximum word count is 4000, including the abstract but not including the references, tables, figures, or legends.
- Number of references should be limited to 50.

Take Home Message

Two or three sentences (no more than 40 words) summarizing the main message expressed in the article must be uploaded as a separate file.

Manuscript Preparation and Submission Requirements

Manuscript Submission

Original manuscripts written in English should be submitted through the web site of our online submission system, EES (<http://ees.elsevier.com/eurorol>), in Word, WordPerfect, or LaTeX formats for text and EPS or TIFF for illustrations. Authors may also check the status of submitted articles at this site. At the time of submission, complete contact information (postal/mail address, e-mail address, telephone and fax numbers) for the corresponding author is required. First and last names, e-mail addresses, and institutional affiliations of all coauthors are also required. Manuscripts submitted through the online system should not also be submitted by mail or e-mail. Once the manuscript is submitted online, the corresponding author will receive a manuscript number and will be able to follow the status of the manuscript through the online system.

Manuscript Components

Include a title page, abstract, text, references, and as appropriate, figure legends, tables, and figures, take home message (for original and review articles) and authorship form (authorship form can be downloaded at [authorship form](#)).

Start each of these sections on a new page, numbered consecutively, beginning with the title page. Please check the instructions per article type listed above.

Manuscript File Formats

For submission and review, acceptable manuscript file formats include Word, WordPerfect, EPS, Text, Postscript, or RTF format. Use 12-point font size, double-space text, and leave right margins unjustified with margins of at least 2.5 cm. Each page should be numbered in the upper right corner, beginning on p. 2. Add continuous line numbering.

Title Page

The title page should include a word count for the text and abstract separately. Authors full names, highest academic degrees, and affiliations should also be included (see list below). If an author's affiliation has changed since the work was done, the new affiliation also should be listed. For indexing purposes, 3-10 key words should be supplied in alphabetical order (see example below)

- Title
- Authors (first name and initials followed by surname, e.g., Juan X. Alvarez)
- Affiliations (if multiple affiliations are listed, indicate with lowercase letter footnotes following the respective authors names)
- Contact information for corresponding author, including full mailing address, telephone number, fax number, and e-mail address
- For indexing purposes, 3-10 keywords should be supplied (in alphabetical order) as follows: Keywords Benign prostatic hyperplasia; Doxazosin; Lower urinary tract symptoms
- Word count of text: include the abstract but not the references in this count
- Word count of the abstract (please remember Abstracts cannot exceed 300 words)

Abstracts

Include a structured abstract of no more than 300 words for original, review and surgery in motion articles. (See instructions above for preparing structured abstracts.) Abstracts are not required for editorials. No information should be reported in the abstract that does not appear in the text of the manuscript.

Headings

Do not use automatically generated numbering or bulleting systems or hidden text (e.g., for headings, references, footnotes, lists).

Units of Measurement

Units of measurements must conform to the Systeme International (SI): year(s), yr; month(s), mo; days, d; hours, h; minutes, min; seconds, s; grams, g; liters, l; meters, m; sample size, n; degrees of freedom, df; standard error of the mean, SE; standard deviation, SD; probability, p.

Numerals and Abbreviations

Use numerals for all values greater than ten and those followed by a unit; otherwise, spell out (e.g., 18 patients, 0.8 g/ml, 47%, 37.8°C, six cases). Spell out numbers at the beginning of a sentence. Abbreviations must be defined at first use in each of the following: text, tables, and figure legends.

Acknowledgments

The "Acknowledgments section is the general term for the list of contributions, credits, and other information included at the end of the text of a manuscript but before the references. Authors should obtain written permission to include the names of individuals in the Acknowledgment section.

References

In the text, references should be cited in numerical order, with citation numbers placed in square brackets.

Personal communications (pers. comm.) and unpublished data (unpubl. data) are mentioned only in the text: (pers. comm., A. Brown, Ithaca, New York, USA).

Each reference number should correspond to a single published source.

List all authors up to six; for more than six authors list the first three followed by "et al.

Use Index Medicus abbreviations for journals. Provide full page ranges, using the abbreviated format shown below.

[1] MacDonald R, Fink HA, Huckabay C, Monga M, Wilt TJ. Botulinum toxin for treatment of urinary incontinence due to detrusor overactivity: a systematic review of effectiveness and adverse effects. *Spinal Cord* 2007;45:535-41.

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Book chapter

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Thesis or Dissertation

[1] Kato H. Neuroendocrine cells: their effect on the development of benign prostatic hyperplasia. Ph.D. diss. [MS thesis], University of Tokyo Medical School, Tokyo, 1997.

Tables

- Compose tables in a word-processing program; do not insert as graphic elements. Number tables with Arabic numerals in the order they appear in the text. Place each table on a separate page.
- Provide a title at the top of each table.
- Explain abbreviations and include any other comments in a note at the bottom of each table.

Figures

- Figures must supplement, not duplicate, the tables and text.
- Illustrations must clearly convey their message and be of high quality and sufficient size and clarity (especially lettering, arrows, and data points) to be interpretable when reduced for publication.
- Number figures with Arabic numerals in the order they appear in the text.
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