IL-4 : 招請講演**The Diagnosis of IC : Past, Present, and Future**

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The Past

For most of the 20th century interstitial cystitis was a relatively clearly defined disease characterized by discrete, red, bleeding areas on the bladder wall—Hunner’s ulcers. It was considered a rare condition, almost a clinical oddity. Although others recognized a larger syndrome earlier, credit for modern thinking about IC goes to Messing and Stamey (1978) who described the “early diagnosis” of IC based on cystoscopic identification of glomerulations after bladder distention. From this point forward there has been a steadily increasing appreciation of IC in clinical medicine.

In 1987 the NIDDK sponsored a conference to review the accumulated knowledge of IC—the consensus statement from this meeting (Gillenwater and Wein 1988) included an “official” research definition of IC. This definition encompasses inclusion criteria that describe the syndrome and exclusion criteria that serve to create a relatively homogeneous patient population. The exclusion criteria can be subdivided into two groups—first, other diseases that could engender doubt about the cause of the symptoms and second, a description of symptoms or other factors to eliminate those subjects that might be problematical to evaluate.

This was an important beginning for clinical research. It properly should be viewed as just that, a beginning. The goals of the authors were modest,

“The purpose of these criteria is not to define the disease but to ensure that in any group studies that adhere to these inclusion and exclusion criteria the populations will be relatively comparable.”

Unfortunately, these criteria have been widely used as a de facto definition of the disease in clinical medicine. As reported from the international IC symposium held in Kyoto, Japan in 2003 the majority of investigators outside the US have adopted the NIDDK criteria for diagnosis. In addition, the criteria are also widely used in the US for diagnosis. (Payne 2003)

Little is known about how the NIDDK criteria have performed in practice. Hanno (1999) reviewed the NIDDK IC database study in which expert clinicians enrolled patients based on loose clinical symptoms. The NIDDK criteria succeeded in the purpose stated above as 90% of the database subjects meeting NIDDK criteria were felt to have IC by the experts. However, over 60% of the patients that the experts diagnosed with IC did not meet the strict research criteria. This means that almost 2/3 of the potential subjects are excluded from clinical research at the outset. This impedes research and diminishes its impact because the patient population is clearly not representative of the IC population at large.

The Present :

Because of the controversy the NIDDK charged a committee to examine the evidence supporting current diagnostic strategies and knowledge the gaps to be filled. This was intended to be the first step in moving toward an evidence based definition of IC including specific recommendations for future research to create the necessary evidence. A group of experts to review the literature and presented the findings at the 2003 NIDDK research symposium.

sium. One member was assigned each of five areas for specific focus : urodynamics, biomarkers, potassium sensitivity testing, cystoscopy/distension/biopsy, questionnaires.

The subcommittee found that in the 15 years since publication of the original NIDDK guidelines there has been inadequate evidence to support the routine use of any diagnostic test or combination of tests in defining IC. The key findings and recommendations are summarized below.

Urodynamics :

1. The NIDDK criteria list decreased compliance on cystometry as one of four inclusion criteria for IC clinical research. While diminished compliance appears to occur in a subset of patients this finding has not been adequately characterized to be of clinical value.
2. Involuntary detrusor contractions (IVDC) exclude a patient from a diagnosis of IC by the NIDDK criteria yet IVDC are consistently reported in a subset of IC/PBS patients and correlate with symptom severity. There is no data to suggest that these patients are different from patients who do not have IVDC. IVDC should not be used to exclude the diagnosis.

Biomarkers :

1. Antiproliferative factor (APF) is a very promising potential marker which may characterize a group of patients with a similar biological disorder. APF is a peptide produced by bladder epithelial cells that inhibits growth of the cells in culture. It offers the potential to both identify patients and even explain some of the pathologic factors operating in IC/PBS

Potassium sensitivity testing (PST) :

1. The PST cannot be recommended for general use as a diagnostic tool for IC at this time. However, the test is simple and inexpensive and clearly separates IC patients from normal controls ; it is possible that further research will define a role for the test.

Cystoscopy/distension/biopsy :

1. Cystoscopy—Only required if other disease processes suspected based on endemic areas, other systemic diseases or as per standard evaluation for hematuria, pyuria, etc.
2. Bladder distention—has some value in diagnosis, prognosis, and treatment but neither the sensitivity nor specificity has been established such that this test can be used to routinely establish or refute the diagnosis of IC.

Questionnaires :

1. There is no evidence that any questionnaire can be used to diagnose IC although any of the three published instruments might be used as screening tools

The committee therefore recommended supports the International Continence Society terminology, Painful Bladder Syndrome (PBS), i.e., “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” (NeuroUrology and Urodynamics 21 : 167–178, 2002). The term Interstitial Cystitis is reserved for those patients and research populations with positive cystoscopic findings. The diagnostic approach should be flexible to allow for differences between individual patients as well as in the local expertise and resources available to evaluate them. All the tests listed above have some value and should be used judiciously in the work-up of patients presenting with PBS.

The Future :

As noted above, there is an excellent possibility that antiproliferative factor, another biomarker, or a combination of biomarkers may be used in the near future to define a population with a unifying biologic abnormality. Antiproliferative factor is produced by the bladder epithelium, inhibits urothelial cell growth in vitro, and is associated with abnormalities of other growth factors (low levels of HB-EGF and high levels of EGF). The structure has been elucidated and this may lead to development of an antibody based analysis or some other practical laboratory test in the near future. If abnormal growth factors turn out to define a group of patients with a different prognosis this will be a very important step forward in both clinical treatment and eventual elucidation of the pathophysiology of the disease.

References :

1. Gillenwater JY, and Wein AJ : Summary of the National Institute of Arthritis, Diabetes, Digestive, and Kidney Diseases workshop on interstitial cystitis. National Institutes of Health, Bethesda, Maryland, August 28-29, 1987. *Journal of Urology* 140 : 203-206, 1988.
2. Hanno PM, Landis JR, and Matthews-Cook Y, et al : The diagnosis of interstitial cystitis revisited : lessons learned from the National Institutes of Health Interstitial Cystitis Database study. *Journal of Urology* 161 : 553-557, 1999.
3. Messing EM and Stamey TA. Interstitial cystitis : early diagnosis, pathology, and treatment. *Urology*. 1978 Oct ; 12(4) : 381-92.
4. Payne CK, Terai A, Komatsu K : Research criteria vs. clinical criteria for interstitial cystitis. *Int. J. Urol.* 2003 (10), S7-10.
5. Probert KJ, Payne C, Kusek JW, Nyberg LM : Pitfalls in the design of clinical trials for interstitial cystitis. *Urology*. 2002 Nov ; 60(5) : 742-8.