

INTERSTITIAL CYSTITIS IN 2004

NEED FOR CLARIFICATION

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Interstitial cystitis (IC) is a chronic, inflammatory disorder of the urinary bladder characterized by variable degrees of urinary urgency, frequency and bladder pain.¹ IC is a neglected chronic debilitating disease. Though first recognized as a pathological entity in 1887, it remained a largely unaccepted disease for 100 years. Physicians do not even agree whether it actually exists. What they may agree on, however, is that it is difficult to diagnose and, if diagnosed, that it is difficult to prove and, if proven, that it is difficult to treat. The disease is unique in the sense that although IC patients are numerous and suffer greatly from it, there is not a single symptom, sign or investigation which is diagnostic for IC. To complicate the matter still further, there is no clue to its etiology², its pathology is unknown³ and no treatment has been found to cure the disease.⁴ IC has baffled the scientists and every effort to find a solution has only complicated our understanding of it.

In 1987, the NIDDK formed a consensus definition of IC. The criteria were revised in 1988. The NIDDK established guidelines specifically for research purposes and these guidelines have remained the de facto definition for interstitial cystitis to the present day (Appendix-1). The aim of drawing up these guidelines was to have an international standard to enable a comparison of patients in different geographical areas. Today, some 17 years after these research guidelines were first drawn up, the original aim has not been fulfilled. The guideline has not served its purpose since it was basically a concept of exclusions and not based on evidence. Very few patients with interstitial cystitis fulfilled the criteria and for every patient diagnosed with IC, many remained undiagnosed. It has been estimated that if the guidelines are strictly followed, around 60% of patients will fail to be diagnosed. Hanno *et al.* proved this point by analyzing patients who were enrolled in the multicenter Interstitial Cystitis Database (ICDB) study.⁵

With a general increase in knowledge about the disease and the endeavors of patient support organizations such as the Interstitial Cystitis Association (ICA) and International Interstitial Cystitis Patient Network (IICPN), by 2002 it became evident that there is an urgent need to define the disease. It is also now clear that the 1987 NIH criteria need to be changed since acceptance of them will lead to under-diagnosis. We conducted a survey in 2002–3 in which both the ICA and IICPN also participated. The results of the survey surprised us.⁶ It proved that IC is a global disease. We had responses from 32 countries across the world. The countries included Pakistan, Iran, Indonesia, and Guyana, to name but a few. This survey comprised 24 questions and it was quite a shock to find that there was no consensus on any single aspect of the disease (all 153 scientists who responded had different ideas on all aspects of the disease).⁶ A definite increase in awareness of the disease is evident from the number of papers being published and the number of conferences held around the world to discuss IC.

The year 2003 was a milestone in the history of IC as two very important workshops were organized aimed at reaching some consensus on various aspects of IC. The first meeting was held in Kyoto, Japan in March 2003 and was attended by 25 international urologists and a similar

number of Japanese urologists. This meeting was an attempt to gather the opinion of urologists from all over the world on different aspects of IC. It set the ball rolling and clearly demonstrated that it is very difficult to define the disease and establish criteria. Another workshop was held in Copenhagen in May 2003 and attended by 22 researchers from European countries and one from India. At this European meeting no attempt was made to define the disease, but rather to reach consensus regarding history taking, physical examination, investigations, cystoscopy findings and biopsy reading. It was agreed that every endeavor should be made to evaluate IC patients in the same standard way. This workshop was a great success and a valuable and much appreciated initiative. The NIDDK/ICA International Scientific Symposium on IC research held in Washington in October 2003 also included in-depth discussions on definition and criteria.

RIGID SYMPTOM CRITERIA SHOULD BE DROPPED:

The symptoms of IC patients are by no means uniform. These symptoms are related to urological, gynecological, gastrointestinal and pelvic floor organs. They may originate from the bladder, urethra, prostate, vagina, uterus, rectum and pelvic floor muscles.⁷ Furthermore, in some patients a systemic or generalized disease may affect any part of the body, including the symptoms of IC in the bladder. Studies have been carried out into the possible relationship between IC and systemic autoimmune diseases such as systemic lupus erythematosus (SLE) and Sjögren's syndrome.^{8,9} IC in SLE patients is sometimes referred to as lupus cystitis.

Some IC patients have symptoms of pain, urgency and frequency, some may experience pain as their main symptom with minimal frequency and urgency, while other patients may complain of only frequency and urgency. Absence of nocturia has been considered to be an exclusion criterium in the NIDDK guidelines, but many IC patients may in fact experience no nocturia. In 2004, it is now becoming clear that pain is most important characteristic symptom of IC. Nocturia is not essential for the diagnosis of IC. It is also believed that patients with normal frequency but with pain and urgency can also have IC. This indicates that IC patients can present with a wide spectrum of different permutations and combinations of symptoms.

PAIN SHOULD BE FURTHER DEFINED

It is regrettable that the NIDDK criteria make no reference to the different types of pain or its severity.¹⁰ In clinical practice, patients have different ways of expressing pain. Some patients will talk of pain, some will describe it as burning while others will say they feel discomfort, heaviness and pressure. These symptoms may or may not be relieved by micturition. In 2004 researchers feel that IC should be suspected in all patients who come with urinary discomfort, suprapubic pressure or heaviness or burning micturition with or without pain, in the absence of bacterial infection. There is a need to redefine the pain in IC patients and to consider the possibility of IC in all patients who present with the above-mentioned symptoms.

3 MONTHS SUFFICIENT TO DIAGNOSE IC

Taking a look at the severity of symptoms and the suffering of the patients, it is not understood why we should wait for 9-12 months to diagnose IC. The consensus in 2004 is 3 months. IC should be suspected in a patient if the symptoms are present for 3 months. This very significant point should be borne in mind when the criteria for the disease are drawn up in the future. This will go a long way towards decreasing the suffering of IC patients.

INVESTIGATIONS

Any article written on IC will list numerous investigations, but none will mention the minimum investigations needed or their significance. IC is currently diagnosed on the basis of clinical features. The recommended tests include urinalysis, urine culture, cytology, urodynamics and cystoscopy under anesthesia with bladder distension.² In 2004 there is consensus on the need for

urine analysis, urine culture, and a voiding diary. It is believed that urodynamics do not serve any fruitful purpose and can better be omitted. Cystoscopy under anesthesia is the most controversial investigation as there are some who believe it to be indispensable, while others believe it to be unnecessary and feel that a diagnostic office cystoscopy can be performed under local anesthesia to rule out malignancy in patients with hematuria. It is also unclear whether investigations such as X-ray KUB, USG KUB and urinary cytology should be performed or not as these tests rule out other diseases. We strongly believe that there is a need to define the investigations in two types: mandatory and optional.

URINARY MARKERS

This is one of the most researched topics in IC. All the markers initially look very promising, only to prove disappointing at a later stage of research. In 2004 there is as yet no urinary marker which can diagnose IC. If we succeed in finding a urinary marker with high sensitivity and specificity, it will be very easy to define the disease and draw up the criteria.

GLOMERULATIONS /HUNNER'S ULCER: CONFUSING TERMINOLOGY

Glomerulations have long been considered the hallmark of IC.² If certain conditions are excluded, the presence of glomerulations will point to a diagnosis of IC. However, many IC patients will not have glomerulations on cystoscopy and hydrodistension.¹¹ Glomerulations have also been found in normal women undergoing tubal ligation.¹² Although the term glomerulations is associated with IC, there is no correlation between them and the degree of histological inflammation¹³ and symptoms¹⁴. In 2004, there is increasing consensus that the terms Hunner's ulcer and glomerulations should be dropped as they create more confusion. At the European workshop in Copenhagen, these two terms were omitted from the description of the cystoscopic findings.

Copenhagen cystoscopic classification of bladder mucosa (May 2003)

- **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**

DISEASE UNDER-DIAGNOSED:

In the ICDB study it was demonstrated that the disease is under-diagnosed. It is generally believed that IC should be suspected in bacterial cystitis patients who do not respond to antibiotic therapy.¹⁵ Patients with OAB who do not respond to anticholinergics should also be suspected of having IC.¹⁵ Furthermore, there is every chance that patients with chronic abacterial prostatitis may also be suffering from IC. A cystoscopic appearance of IC was found in 70% of men with symptoms of abacterial prostatitis and prostatodynia when scoped under anesthesia.¹⁶ In 2004 there is a substantial difference of opinion concerning the concept that IC may be the same as abacterial prostatitis, even though there is growing evidence favoring both as the same disease.

This problem of under-diagnosis clearly means that there is a need to change and expand the definition of IC. Others have also raised similar concerns.^{17, 18} It is believed that until the cause(s) of and risk factors for IC are known, a more inclusive definition of this symptom complex may be appropriate to allow a more accurate assessment of its prevalence in the general population. IC is still greatly under-diagnosed in Europe because outdated criteria are applied for diagnosis.¹⁹

IS IC LIMITED TO THE BLADDER?

It is difficult to believe that we are dealing here with a disease in which we are not even entirely sure of the organ where the symptoms originate. Nor are we confident that IC is in fact a disease, or whether it may not perhaps be a syndrome. Even in 2004 it is not clear if the disease is limited to the bladder only, or whether it involves other pelvic organs.

CHANGE OF NOMENCLATURE: IC/CPPS or IC/PBS

At a meeting of BAUS (2000), it was proposed that the term "painful bladder syndrome" might be more appropriate.¹⁸ "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."²⁰ "The ICS believes this to be a preferable term to "interstitial cystitis". Interstitial cystitis is a specific diagnosis and requires confirmation by typical cystoscopic and histological features.²⁰ In the investigation of bladder pain it may be necessary to exclude conditions such as carcinoma in situ and endometriosis.²⁰ But again there are conflicting views on this issue too. Painful bladder syndrome may be a different entity to IC, or it may be the same entity but with different grades of severity. The pain may stem from the bladder or from the different organs of the pelvis. In some patients, the pain is mediated by more centralized pain mechanisms in the spinal cord. In such patients the entire pelvis is painful and the symptoms worsen with urination and sexual intercourse. It is difficult to determine whether the pain is coming from bladder or elsewhere, as even removal of the bladder in some IC patients has failed to lead to resolution of pain.²¹ Some IC patients appear to present with more than one pain syndrome in the urogenital region.

Some scientists do not wish to change the name of the disease as the term interstitial cystitis has now become well-known. The terminology is a misnomer as it denotes inflammation which may or may not be present in a case of interstitial cystitis. IC is also considered by some to be part of a chronic pelvic pain syndrome and one possibility is that IC may be known by the terminology IC/CPPS in future. However, at the NIDDK/ICA scientific symposium on IC in Washington in 2003, people tended to be in favour of IC/PBS as the term to use. On the other hand, at the ICICJ meeting in Kyoto in 2003, researchers tended to favor IC/CPPS. The final chapter in nomenclature has not yet been written. It is hoped that this confusion regarding terminology will be brought to an end in 2004 and that the same name will be used worldwide.

SUBTYPE OF IC

Though the disease has not been defined, it has in recent years been considered to have two subtypes: ulcerative (Hunner's ulcer) and non-ulcerative types. Ulcerative or classic IC is considered to be a rare type accounting for 5-10% of cases.²² It is claimed that the two subtypes differ in clinical presentation, age distribution, histopathological and immunological findings and response to treatment.^{22,23,24} In 2004 there is concern about the term Hunner's ulcer. Scientists are of the opinion that this term should be scrapped. While there are some researchers who firmly believe in Hunner's ulcers, there are others who swear that they have never seen Hunner's ulcers in a single patient in their entire career. The terms Hunner's ulcer and glomerulations have not been used in the Copenhagen cystoscopic classification. If the term Hunner's ulcer is to be omitted, the classification of IC into two subtypes is nullified.

POTASSIUM SENSITIVITY TEST

The potassium sensitivity test was introduced in 1994.²⁵ This test has been shown to be positive in 75% of patients with IC and is also positive in patients with detrusor instability, radiation cystitis and bacterial cystitis. The potassium sensitivity test is not very popular. The consensus in 2004 is that it can be included as an optional test.

IC IN CHILDREN

Patients under the age of 18 years were automatic exclusions in the 1987 NIDDK research criteria. The diagnosis of IC in children is controversial. 25% of IC patients report that they had chronic urinary tract problems in childhood.²⁶ Children do indeed present with dysfunctional voiding. There is no theoretical reason why IC cannot exist in children. In 2004 it is agreed that IC can present in children and exclusion criteria based on age does not hold true.

NEED FOR INTERNATIONAL COMMON PROTOCOL:

It is clear to us that an evidence-based definition of IC is not currently possible and that further specific research is necessary for this to be achieved. However, what can be done now is to develop a common protocol so that all patients with *suspected* IC are dealt with in the same standard way. This common protocol should have two sets of procedures: one mandatory and one optional. This will mark the start of an era in which we will examine, investigate and treat patients worldwide in the same way. Optional steps can be followed by those who believe in them and have the necessary facilities to carry them out. This protocol should be reviewed periodically (possibly annually) and revised where necessary. We believe that this will simplify the task of defining the disease and criteria.

TABLE

SUMMARY OF THE ARTICLE

INTERSTITIAL CYSTITIS	SITUATION IN 2004
NOMENCLATURE	IC or IC/PBS or IC/CPPS or PBS. NO CONSENSUS
DURATION OF SYMPTOMS	3 MONTHS
FREQUENCY	8 IS NOT A FIXED NUMBER, CAN BE MORE OR LESS
PAIN	MOST IMPORTANT SYMPTOM, PRESSURE, BURNING HEAVINESS URINARY DISCOMFORT SHOULD ALSO BE CONSIDERED AS PAIN
NOCTURIA	NOT ESSENTIAL
HUNNER'S ULCER	CONFUSING TERMINOLOGY
GLOMERULATIONS	CONFUSING TERMINOLOGY
URINE CULTURE AND SENSITIVITY, VOIDING LOG	MANDATORY INVESTIGATIONS
URODYNAMIC, CYTOLOGY POTASSIUM TEST,	OPTIONAL
ULTRASONOGRAPHY, X-RAY KUB	NO CONSENSUS
CYSTOSCOPY UNDER ANESTHESIA	NO CONSENSUS
BLADDER BIOPSY	NO CONSENSUS
IC IN CHILDREN	POSSIBLE
URINARY MARKERS	NOT YET

CONCLUSION

In 2004 there is consensus that considerable change is required in the IC world. There is a need to draw up a definition and establish criteria for the disease. It is also believed that the new definition and criteria should be evidence-based and not merely opinion-based. All researchers agree that it is very difficult task, but that a start has to be made. 2003 was truly a landmark in the history of IC. Until final diagnostic criteria are established, there is a need for international cooperation and collaboration. There is a need to follow a common algorithm so that a large amount of data can be collected and compared. There should be a working algorithm for history taking, physical examination, investigations cystoscopy, biopsy and treatment. We should establish an INTERNATIONAL ALGORITHM for the disease and review it periodically. At any event, clarification regarding interstitial cystitis, its definition and criteria, is now a matter of urgency. The medical world cannot continue in the present limbo for much longer.

APPENDIX-1

NIDDK 1987 CRITERIA FOR INTERSTITIAL CYSTITIS

Automatic exclusions: < 18 yrs old Benign or malignant bladder tumors Radiation cystitis Tuberculous cystitis Bacterial cystitis Vaginitis Cyclophosphamide cystitis Symptomatic urethral diverticulum Uterine, cervical, vaginal or urethral Ca Active herpes Bladder or lower ureteral calculi Waking frequency <5 times in 12 hrs. Nocturia <2 times Symptoms relieved by antibiotics, urinary antiseptics, urinary analgesics (for example phenazopyridine hydrochloride) Duration <12 mos. Involuntary bladder contractions (urodynamics) Capacity >400 cc, absence of sensory urgency Automatic inclusions: Hunner's ulcer Pos. factors : Pain on bladder filling relieved by emptying Pain (suprapubic, pelvic, urethral, vaginal or perineal) Glomerulations on endoscopy Decreased compliance on cystometrogram
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Bladder distension is defined arbitrarily as 80 cm water pressure for 1 minute.

Two positive factors are necessary for inclusion in the study population.

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