

Mini-Reviews

Interstitial Cystitis in Adolescents and Children: A Review

T.F. Mattox, MD, FACOG

Department of Obstetrics and Gynecology, Division of Urogynecology, Greenville Hospital Systems, University of South Carolina, Greenville, South Carolina, USA

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Introduction

Interstitial cystitis (IC) is a disease of the bladder. Often considered to be a problem in adults (over age 18), its cause(s) are unknown, diagnostic criteria are debatable, and treatment options are limited. As it currently stands, there is no cure, but science and medicine are making steps in the right direction. The purpose of this review article is to expand the current thinking of practitioners who treat pediatric girls and young women to consider IC by understanding the current pathogenesis, diagnostic options and treatment modalities available.

There are several hurdles to appreciate when considering if an adolescent has interstitial cystitis. The first hurdle is that the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) diagnostic criteria for interstitial cystitis excludes anyone under the age of eighteen. To the naive, this suggests that no child could possibly have this disease. However, the astute practitioner should realize that the NIDDK criteria are used to select a uniform group of people into study trials, and there is little doubt among experts that these criteria select only the most severe cases of IC.¹ Moreover, there are liability and consent issues for patients under the age of eighteen, which can hamper patient enrollment into trials.

The second hurdle is that there is a paucity of articles on IC in the pediatric population. Using the

keywords “interstitial cystitis” and “pediatrics” to search Pubmed, only four articles were found to be devoted to the subject in the past ten years.^{2–5} Going back over forty years yielded an additional three articles devoted to children with interstitial cystitis.^{6–8}

Demographics and Presentation

The initial symptoms of IC mimic other diseases so that a patient often sees a number of physicians before the problem is properly diagnosed. The classic triad of IC is urinary frequency, bladder pain, especially with bladder filling, and relief of pain with voiding. The stealth of this disease is that it often presents with a single symptom. Looking specifically at presentation for all age groups and sexes, Driscoll et al. found that 89% of patients present with a single symptom, and the median time to have all three symptoms of classic IC was about 2 years.⁹ Moreover, the mean time for all symptoms was over 5 years, suggesting there are outliers at all age ranges. When looking at symptom progression, 73% presented with either frequency/urgency or pain and crossed over or expanded into other symptoms (nocturia). Close et al. looking only at children, noted 88% and 81% of children presented with either frequency or pain, respectively.⁵ This suggests that despite age differences at onset, the presentation of the disease appears to be uniform and progression is common.

While both the Driscoll and Close studies employed chart reviews and/or telephone follow up, recall and observer bias may be present. Yet even with these considerations the underlying theme is that patients with IC have symptom creep. Common misdiagnoses were bacterial cystitis, endometriosis, and chronic pelvic pain. A patient who presents with a prior diagnosis of “urethral problems;” specifically, urethral stenosis, urethral syndrome, urethrotrigonitis, urethritis,

Address reprint requests to: T. F. Mattox, MD, 890 West Faris Road, Suite 470, Greenville, SC 29605

Synopsis: Interstitial cystitis is an uncommon problem in children and adolescents; however, its symptoms and treatment appear to be the same as in adults.

and chronic urethritis may be warning flags that suggest IC may be the culprit. Since cystitis symptoms are the most common presentation, it is interesting to note that 13 of 17 patients in the Driscoll study had documentation of a negative urine culture in light of the urinary tract infection diagnosis. Patients with repeated negative cultures for cystitis symptoms should strongly be suspected of having IC, even when the patient appears to respond to antibiotic therapy.

On a positive side, IC is not a disease of the young; most studies quote the mean age of onset to be in the early forties. The actual age of onset in children is unknown since there are so few cases published, but children as young as 2, 3, and 4 years of age have been reported,^{5,6} and, as with adults, the majority of patients (~90%) are female.⁸⁻¹⁰ Prevalence rates for adults vary widely from approximately 4 to 900 per 100,000 individuals.^{1,10-13} Perhaps the best estimate of prevalence in children comes from the work of Close et al., noting that sixteen children had presented over a 12-year time span from a total population of approximately 20,000 pediatric patients at a tertiary pediatric urology clinic.⁵ This suggests that physicians in either a tertiary pediatric urology or gynecology clinic should anticipate one or more cases of IC annually.

Pathogenesis

The exact etiology of IC is unknown. A number of theories have been put forth and it is now agreed that IC is probably a multifactorial disease.¹⁴ Infection of any type is not thought to play a role.¹⁵

Looking at histologic biopsies of bladder walls of patients with interstitial cystitis, it has often been described as hypertrophy of the bladder wall with an infiltration of mast cells. Fibrosis, edema, and vasodilation in the submucosa have been described as well.¹⁶ However, the disease can be disproportional to the symptoms, as noted by Denson et al. where a significant proportion of patients had no histological evidence (31%) or mild histological evidence of inflammation (41%) on bladder biopsy despite meeting the NIDDK criteria for both symptoms and cystoscopic findings.¹⁷ Not to be discounted, the work by Hofmeister et al. should not be dismissed. Going a step farther, Hofmeister also looked at mast cell density and nerve fibers. In an earlier publication, these authors found destruction of nerve fiber endings near mast cell proliferation, suggesting a relationship between the two.¹⁸ Pang et al. also found that substance P, a neuropeptide thought to trigger mast cell secretion, was increased in patients with interstitial cystitis.¹⁹ Additional work by this latter group also suggested that mast cells in patients with IC may be due to a progesterone/estrogen imbalance,

which may explain why the disease is more prevalent in women.²⁰ It is this potential interaction between mast cells and nerve endings that is the rationale behind some long-term treatment modalities for patients with interstitial cystitis.

Much attention has been given to the mucous layer of the bladder. Parsons, who has and still continues to perform a significant amount of research in this area, has done much of this work. The theory suggests that the bladder is coated with a mucous layer in normal patients; however, in patients with interstitial cystitis, this layer is somehow lost. In an elegant study of bladder wall permeability, Lilly and Parsons showed that the mucous lining could be removed with protamine sulfate and then "regenerated" with heparin.²¹ More significant was that all of the patients experienced pain and urgency with the protamine solution with partial or complete relief with the heparin solution. Research on why this mucous layer/bladder permeability is deranged and how it can be regenerated is ongoing.

Diagnosis

Patients with IC should have an urgency/frequency syndrome or pain in the bladder or pelvic area without any other obvious cause for their symptoms. These two symptoms are actually NIDDK inclusion criteria for IC and it is no different with children. There are two instruments, patient questionnaires, that have been validated in the adult literature, the O'Leary-Sant questionnaire and the pelvic pain and urgency/frequency questionnaire.^{22,23} While neither have been used in children, both could be modified for a pediatric population. Children who score high on either test should be suspected of having IC and further diagnostic tests pursued.

An additional clue that a patient may have IC is their voiding history. Most patients will easily void in excess of eight times a day, so a voiding diary, recording the time and amount of a child's voiding, can be helpful. For the older and observant child, she may report that the syndrome is worse around her menses (confusing the diagnosis with endometriosis) and may be aggravated by caffeine, fruit drinks, tomatoes and tomato products (pizza and pasta), and most notably with diet soft drinks. Sexual activity is also known to exacerbate symptoms;²⁴ hopefully, most of the pediatric population will not be able to answer this question either way.

A pelvic exam in a child or young woman can be difficult and traumatic. In young patients suspected of having IC, this can be deferred until the patient is asleep in the operating room. For the adolescent who will assent to an exam, the bladder base may be tender; there are

no findings on physical exam that are pathognomonic for IC.

A child who is suspected of having IC should undergo cystoscopy, but recent publications have questioned the validity of cystoscopic findings.²⁵ Not only is this a diagnostic procedure, but also it can be therapeutic. Depending on the experience of the physician, the procedure can be done in the office with topical anesthesia and sedation or in an operating suite; our preference is the latter since there are potential unknown psychological effects with conscious sedation of children in the office. Once adequate anesthesia has been obtained, the bladder is catheterized for a urine specimen. Cystoscopy is performed, distending the bladder to approximately 70–100 cm of water; this is done by gravity by raising the infusate the appropriate height above the pelvis. Patients and parents should be cautioned that bladder rupture is a possibility, although uncommon; using a pump to fill the bladder may increase this risk. Initial cystoscopic findings suggestive of IC are a hypervascular bladder mucosa as well as areas of linear scarring. The bladder is emptied and the mucosa scanned for signs of tearing, glomerulations and ulcers; bladder biopsy is not recommended because of its very low yield in detecting cancer.⁵ Furthermore, there are no histological findings that are diagnostic for interstitial cystitis. Since IC affects the entire bladder, the epithelial disruptions should be seen in all quadrants; otherwise, the damage seen may be from the cystoscope or instrumenting the urethra. Hematuria is often seen after the procedure and the patient and parents should be counseled that this is self-limiting.

Confounding the cystoscopic debate, Waxman et al. performed cystoscopy on normal women undergoing tubal ligation.²⁵ Forty-five percent of their patients had cystoscopic findings consistent with interstitial cystitis. While the number of patients in this study was small ($n = 20$) and obviously did not contain any pediatric patients, the consideration that glomerulations may not be diagnostic of interstitial cystitis must be considered. It should be emphasized that IC is based primarily on symptoms and is a diagnosis of exclusion from other processes. Readers interested in color pictures of bladder abnormalities suggestive of IC should review this article.

For the more mature adolescent, a potassium challenge test can be performed.²⁵ This is an office procedure that requires catheterizing the bladder and instilling a solution of either saline/water or potassium chloride. Patients are asked to rate both urgency and pain on a scale of 0 to 5 when either solute is instilled into the bladder and allowed to remain for several minutes. A change in two or more units (e.g., 2 to 4) is considered a positive test; however, our experience suggests that patients who are positive for

the potassium solution have almost immediate pain or urgency. Patients with equivocal results can be offered cystoscopy at the discretion of the physician. In an adult population, Parsons et al.²⁶ found 85% of patients with chronic pelvic pain to have a positive potassium test, suggesting that interstitial cystitis may be more common in patients with this problem. Research is sorely needed on the teenage population to corroborate these numbers using the potassium challenge test.

Treatment

Hydrodistention appears to be the mainstay of both diagnosis and treatment in children. The actual mechanism of action of hydrodistention is unknown, but is felt to be disruption of the afferent nerve endings within the bladder.²⁷ Close et al. found that 13 of 14 patients undergoing hydrodistention had relief of their symptoms, but 50% of these recurred.⁵ In our teenage population with IC, these findings have been true as well. When symptoms recur, the patient can undergo subsequent hydrodistentions or institute other medical therapies. Autodistention, a term referring to having patients hold their urine for longer periods of time between voids, has been shown to be effective in adults.²⁸ Close et al. have suggested that children do this naturally after hydrodistention when they are out playing.⁵

Several bladder instillation therapies have been suggested with modifications of these “cocktails” to include local anesthetics, steroids, and heparin. Silver nitrate bladder instillations have a long history of use in the adults, but have not been suggested for the pediatric population. While we have not instituted bladder instillation therapy in our adolescent population, Close et al. instilled a combination of DMSO (dimethylsulfoxide) and/or heparin into three of their patients with intractable pain and recurrent symptoms with good results.⁵ Patients should be cautioned that the modality is a temporary one, and repeat instillations are the norm. In our adult population with IC, instillation treatments are given weekly for 4 weeks and continued for 6 weeks if improvement is seen. The need for more frequent instillations can be seen in some patients, and these same patients will usually become “resistant” to this regimen. Patients and parents should be warned that the person treated will have a garlic odor breath. Moreover, the long-term effects of DMSO on children are unknown.

As previously mentioned, heparin has had therapeutic benefit in patients suffering from symptoms of IC. It is thought that heparin can replace the glycosaminoglycan (GAG) layer that is thought to be lost in patients suffering with this syndrome.²⁹ Parsons has advocated doses of heparin ranging from 10,000 units to 40,000

units.³⁰ Unfortunately, this has to be done on a daily basis, and it may be difficult to do in younger patients.

Oral therapy, primarily pentosanpolysulfate (PPS), has had some promise in patients suffering from IC. Going by the trade name, elmiron, this substance is excreted into the urine and is supposed to correct the GAG defect within the bladder wall. It is taken in divided doses on a daily basis, starting at levels of 100 mg taken three times a day. There are no reports on using this medication in children. In our teenage population, all three patients have responded to hydrodistention and oral elmiron therapy, but this group is too small to draw any conclusions other than that there have been no adverse side effects. The best results with PPS have come from Parsons et al., where the treated groups had about a 30% improvement of symptoms.^{31,32} Patients are cautioned that it takes 3 to 6 months of daily therapy before benefit is seen. Intravesical therapy with elmiron has been advocated, but this has not been reported in children. Our current recommendation is that therapy is considered to be lifelong; however, patients that appear to be symptom-free for a long period of time can have their PPS daily doses lowered.

Dietary modifications have been implemented in our practice and they are regularly purported to help patients with their symptoms. Unfortunately, scientific data to support this is lacking. Anecdotal accounts from our pediatric and adult populations suggest that some foods do appear to trigger symptoms. In general, caffeine, artificial sugars, and acidic juices appear to trigger some exacerbations; patients are cautioned to keep a dietary log of what they eat and avoid foods that potentiate bladder symptoms. "IC diets" and their modifications are available on a number of websites using either a yahoo or google search engine.

More aggressive therapy has been recommended in adults with IC; however, it would be unlikely that a child would have such severe symptoms to warrant removing their bladder or having an implantable neurostimulator. These modalities should be considered for the more mature patient who would better understand the impact of such invasive therapies would have on their overall lives. As more is understood about the disease and newer medications become available, patients will hopefully have a better array of choices for therapy.

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