Advanced Management of Patients With Ulcerative Interstitial Cystitis/Bladder Pain Syndrome

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OBJECTIVE To describe a stepwise management of patients with interstitial cystitis/bladder pain syndrome (IC/BPS) with Hunner's lesions and present single institution long-term outcomes.

METHODS This is a retrospective review of a single tertiary center experience with management of patients with Hunner's lesions from January 2005 to January of 2015. Patients who met the diagnostic criteria for IC/BPS were included. Systematic approach to treatment of patients with Hunner's lesions is proposed based on our results.

RESULTS Fifty-five patients with IC/BPS and Hunner's lesions were included. Mean age was 65.0 ±12.7 years, 76.4% (42/55) were female, and median symptom duration was 2 years (interquartile range [IQR] 1.7). All patients had a biopsy to rule out malignancy with therapeutic fulguration which resulted in subjective symptom improvement in 81.8% (45/55) and median time to repeat procedures was 12 months (IQR 621). Triamcinolone injection into the lesion was done in 35 patients and 91.4% (32/35) reported subjective improvement. Repeat injections were done for 74% (26/35) and median time between injections was 8 months (IQR 4, 13). AUA symptom scores and quality of life improved significantly with both treatment modalities. Adjunctive treatment with cyclosporine was used in 47.2% (26/55), and 7.2% (4/55) went on to have a cystectomy.

CONCLUSION Patients with Hunner's lesions benefit from early progression from conservative treatments to endoscopic management. Excellent symptom control can be achieved with biopsy/fulguration and triamcinolone injections but recurrence is common and repeat treatments are needed for most patients. UROLOGY 133: 78–83, 2019. © 2019 Elsevier Inc.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic debilitating bladder disorder characterized by a combination of pain and storage lower urinary tract symptoms. Approximately 5%-10% of patients with IC/BPS have Hunner's lesions. While some studies found variations in clinical presentation between the 2 groups, the majority of the literature suggests that it is not possible to diagnose Hunner's lesions based on symptoms alone.[1,2] The pathophysiology of the 2 conditions appears to be distinct, as it is uncommon for established IC/BPS patients without lesions to develop new lesions when followed over time.[3] Many have suggested that there is an autoimmune component to lesion development as suggested by significant inflammatory reaction on the histological studies and positive response to immunotherapy.[4,5]

The American Urological Association (AUA) guidelines for the Diagnosis and Treatment of IC/BPS recommend cystoscopy with biopsy/fulguration or triamcinolone injection for patients with IC/BPS as a third line therapy but suggest reserving the cystoscopy after conservative treatments have failed.[6] Since there are no clinical parameters that can reliably identify patients with Hunner's lesions,[7] the diagnoses is often delayed. We believe that patients with IC/BPS can benefit from early cystoscopy to identify Hunner's lesions and guide therapy. Therefore, the management algorithm for this group of patients should follow an alternative more targeted pathway aimed at lesion destruction. Currently, there is a need for quality evidence to support early cystoscopy and lesion specific intervention. The aim of this work was to describe the techniques and outcomes for advanced management of patients with IC/BPS and Hunner's lesions who failed conservative and pharmacologic treatments.

MATERIALS AND METHODS

Patients with diagnoses of IC/BPS undergoing cystoscopic procedures with a Female Pelvic Medicine and Reconstructive Surgery provider from January 2005 to December 2015 were identified from an electronic medical record including codes for cystoscopy

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with hydrodistention (CPT 52260), biopsy and/or fulguration (CTP 52224, 52235, 52204), or other procedures used to capture any patients having triamcinolone injection (CPT 52283, 53899). The charts were retrospectively reviewed and patients with diagnoses of IC/BPS who were documented to have Hunner's lesions were included in the analysis. Only patients who met the diagnostic criteria for IC/BPS based on the AUA guidelines were included and all patients with history of prior or current pelvic malignancy, pelvic radiation, neurogenic bladder, nephrogenic metaplasia, or eosinophilic cystitis were excluded.[6]

Patient baseline demographics, clinical characteristics, prior behavioral, pharmacologic, or procedural treatments were extracted. Patients' self-reported subjective improvement in overall IC/BPS symptoms at the first follow-up after the procedure was used as the primary outcome. Secondary outcomes included pre- and postprocedure voiding symptoms assessed using the AUA symptoms index and overall urinary quality of life (QoL).[8] The index event was a biopsy performed at our institution. If the first event at our institution was triamcinolone injection the last biopsy prior to triamcinolone injection was used as the index event even if done outside of our health system. While follow-up schedules differed by provider, patients were instructed to contact the providers with symptom recurrence which would then trigger an evaluation and repeat intervention. At our institution, patients with Hunner's lesions with recurrent symptoms after biopsy/fulguration receive Triamcinolone injection as the next intervention. The timing of injection is determined by the timing of recurrent symptoms.

Statistical analysis was performed using JMP pro (Version 13.1, SAS Institute Inc, Cary NC). Means with standard deviations and median with interquartile ranges (25, 75) were reported for continuous variables and percent or proportions for discrete variables. Student *t* test was used to evaluate continuous variables and chi-square tests were used to compare categorical variables. As appropriate, paired *t* test was used to compare pre- and post-treatment outcomes.

Treatment Technique

Biopsy and Fulguration. Diagnostic cystoscopy was done in clinic setting if patient was able to tolerate the intervention. Alternatively, patient was taken to the operating room for possible hydrodistention or biopsy/fulguration if Hunner's lesions are found. Biopsy/fulguration was done in the operating room under anesthesia. During cystoscopy, care was taken not to overdistend the bladder as this can cause significant bleeding in patients with IC/BPS and can make the diagnoses of an Hunner's lesion difficult. For patients with known lesions some hydrodistention can be helpful to make lesions more apparent. Biopsy was done with a cold cup forceps and was limited to the lesions. The area of the biopsy as well the entire lesion was fulgurated exclusive of the surrounding healthy mucosa.

Triamcinolone Injection. The injection was done in the operating room under anesthesia. Similarly to biopsy, care was taken not to overdistend the bladder. Triamcinolone was diluted in saline and injected submucosally into the lesion. Depending on the size of the lesion an injection was done centrally and peripherally. It is the authors preference to use 40 mg/cc of steroid in normal saline. Injections were done in 0.5-1 cc aliquots. The maximum dose injected in this study was 400 mg. After the injection, 20 cc of 2% lidocaine was instilled into the bladder and left indwelling. A belladonna and opium (B&O) suppository was inserted per rectum for additional pain relief.

Cyclosporine. Concurrent cyclosporine therapy was utilized in patients with recurrent symptoms, particularly those with extensive lesions not amenable to complete endoscopic treatment. Cyclosporine was started at 2 mg/kg divided into 2 daily doses usually after biopsy and confirmation of ulcers. Two-hour post-dose serum level was used for monitoring with adjustments recommended for levels >700 ng/mL.[5] The dose was decreased to minimum effective amount or discontinued over time in patients with resolution of symptoms. Drug monitoring evolved during the course of the study and now includes an office visit with blood pressure reading, laboratory evaluation of renal and hepatic function, complete blood count, uric acid and magnesium levels as well as clinical signs or symptoms of immunosuppression at 1 month and then every 3 months while on therapy.

RESULTS

A total of 592 patients with a diagnosis of IC/BPS underwent cystoscopy procedures by an Female Pelvic Medicine and Reconstructive Surgery provider at our institution. A total of 55 patients (9.2%) had an Hunner's lesion on cystoscopic exam and therefore had biopsy and therapeutic fulguration of the entire lesion(s) with electrocautery. Demographic and clinical data is outlined in Table 1. The cohort was 76.4% (42/55) female and the average age was 65.0 ± 12.7 years. The median time since symptom onset to the presentation at our center was 2 years (interquartile range [IQR] 1.7). Overall 36.4% (20/55) reported gross hematuria, 25.5% (14/55) had depression/anxiety, 29.1% (16/55) had IBS/bowel dysfunction, and 43.6 % (24/55) had chronic pain syndromes. All patients had tried and failed multiple treatment modalities, with pentosan polysulfate and anticholinergics being the most commonly used medications (Table 1). Chronic opioid medication use was widespread at 45.5% (25/55). Pelvic floor exam was documented in 32 patients and 34.4% (11/32) had pelvic floor muscle spasm. Overall, 14.5% (8/55) utilized pelvic floor physical therapy. Forty seven percent of patients (26/55) had prior bladder instillations and 42.6% (23/55) had hydrodistentions prior to consultation at our site (Table 1). Patients continued to trial various combinations of multimodal therapy along with bladder centric interventions

Table 1. Cohort demographic and clinical information

	Total ($n = 55$)
Patient characteristics	
Age (y)	65.0 ± 12.7
Female	76.4% (42/55)
BMI	27.9 ± 5.5
Chronic pain	43.6% (24/55)
Depression/anxiety	25.5% (14/55)
IBS/bowel symptoms	29.1% (16/55)
History of gross hematuria	36.4% (20/55)
Time from diagnoses to presentation (y)	2 (IQR 1, 7)
Prior or current medications	
Anticholinergics	60.0% (33/55)
Pentosan polysulfate	56.4% (31/55)
Tricyclic antidepressants	27.3% (15/55)
Neuroleptic medications	18.1% (10/55)
Cystoprotek	14.5% (8/55)
Opiods	45.5% (25/55)
Prior or current treatments	
Bladder instillations	47.2% (26/55)
Hydrodistention	40.7% (22/55)
Pelvic floor physical therapy	14.5% (8/55)

throughout the study period. Prior to the index biopsy/fulguration 34.5% (19/55) had previously undergone cystoscopy with biopsy/fulguration but outcome data was limited as these were done prior to a referral to our institution.

With biopsy/fulguration 81.8% (45/55) reported subjective improvement in overall IC/BPS symptoms. Urinary symptoms also improved significantly after intervention as described by pre- and post-treatment AUA symptom scores (21.1 ± 7.3 vs 14.6 ± 8.0, $P<0.001$) and QoL scores (5.2 ± 1.1 vs 4.0 ± 1.8, $P = 0.003$) (Fig. 2). The most common reported pathological description was denuded urothelium with chronic inflammation. Complications were rare and occurred in one patient who developed gross hematuria with clot retention requiring cystoscopy and repeat fulguration. After biopsy/fulguration patients were optimized on medical therapy and were instructed to contact the providers with symptom recurrence. Median follow-up was 3 years from the first biopsy (IQR 2, 6). Clinical symptoms remained stable in 10 patients after injection at that follow-up and they were managed conservatively, 3 patients with recurrent symptoms declined intervention, and 76.4% (42/55) went on to have secondary cystoscopic procedures due to recurrent Hunner's lesions at a median of 12 months (IQR 6, 21) after biopsy/fulguration.

Triamcinolone injection was used in 63.4% (35/55) of patients with recurrent lesions after biopsy/fulguration. After first triamcinolone injection 85.7% (30/35) reported subjective overall improvement, while 5.7% (2/35) had marginal improvement, and 8.6% (3/35) reported no improvement in pain symptoms. This was not statistically different from the rate of improvement with biopsy/fulguration (81.8% vs 91.4%, $P = 0.726$). Mean AUA symptom scores and QoL improved significantly after triamcinolone injections (18.9 ± 10.7 vs 12.3 ± 7.8, $P = 0.004$ and 4.6 ± 1.5 vs 3.1 ± 2.0, $P<0.001$, respectively) (Fig. 2). Complications were rare occurring in 5.7% (2/35) patients and included hematuria with clots that resolved spontaneously, and elevated blood pressure requiring an ER visit. Seventy-four percent (26/35) had repeat injections. The median number of injections was 1.5 (IQR 1, 3.3) with a median time between injections was 8 months (IQR 4, 13) (Table 2). At the last follow-up 34.3% (12/35) patients were planning for repeat injections for symptom recurrence.

Table 2. Triamcinolone injection details

	Total ($n = 35$)
Baseline characteristics	
Age (y)	66.0 ± 11.1
Female	82.9% (29/35)
Time from diagnoses to injection (y)	3 (IQR 1, 5)
Injection	
Number of ulcers	2 (IQR 2, 3)
Total dose injected	193.4 ± 16.8
Complications	5.7% (2/35)
Outcomes	
Improved	85.7% (30/35)
Marginally improved	5.7% (2/35)
No change in symptoms	8.6% (3/35)
Proportion with repeat injections	74.2% (26/35)
Time to repeat injection (mo)	8 (IQR 4, 13)
Number of repeat injections	1.5 (IQR 1, 3.3)
Follow-up	
Follow-up (y)	3 (IQR 2, 6)
Patients planning for repeat injections	34.2% (12/35)
Cyclosporine A	34.3% (12/35)
Cystectomy/diversion	2.9% (1/35)

In addition lesion targeted treatments patients continued to trial behavioral and pharmacologic therapies. Specifically, cyclosporine therapy was utilized in patients with recurrent symptoms, particularly those with extensive lesions not amenable to complete endoscopic treatment. Cylcosporine was started after biopsy and confirmation of ulcers in 23.6% (13/55) and after triamcinolone in another 23.6% (13/55). Median duration of treatment was 14.5 months (IQR 7.3, 35.3) and it was used alongside triamcinolone injections. At the last follow-up, 46.1% (12/26) patients treated with cyclosporine were still on the medication; 3 were also receiving repeat triamcinolone injections. The reasons for cyclosporine discontinuation were side effects ($n = 6$, recurrent sinus infections, lung infections, nausea or acid reflux disease, muscle spasms, elevated creatinine, and hyperuricemia), no improvement ($n = 2$), noncompliance with monitoring ($n = 2$), resolution of IC/BPS symptoms ($n = 3$), and in one case a diagnosis of malignancy, in which the patient discontinued cyclosporine while undergoing treatment.

Overall 7.2% (4/55) patients progressed to cystectomy after a median of 10 years (IQR 9.16) since IC/BPS diagnoses. Two of these patients reported subjective improvement in pain and urinary symptoms, 1 had persistent pain and 1 was lost to follow-up.

DISCUSSION

IC/BPS is a chronic condition that requires long-term management and multimodal therapy. There is significant variability in symptom distribution between pain and urinary domains and inconsistent treatment responses. This is especially true for patients with Hunner's lesions, where bladder centric etiology of disease is supported by the evidence of mucosal changes and lesion formation. For patients with Hunner's lesions targeted treatments to address ulcers and prevent recurrence can provide optimal results. In this manuscript, we describe a systematic approach to management of patients with ulcerative IC/BPS with Hunner's lesions (Fig. 1), report long-term single center outcomes, and emphasize the need for early cystoscopy.

At initial presentation a brief trial of behavioral modifications and symptom-targeted pharmacologic therapy is a reasonable initial approach to patient with IC/BPS however, cystoscopy should not be delayed for patients with persistent symptoms of bladder pain or hematuria. In this study, there was about a 2-year delay from symptom onset to endoscopic intervention, thus emphasizing a significant delay in the community practice to the start of targeted treatment. In addition, over 1/3 of patients with Hunner's lesions reported gross hematuria which alone should warrant a cystoscopy. As patients with IC/BPS suffer from significant decline in QoL with persistent symptoms in our practice we offer cystoscopy within a few months of presentation if there is no significant response to behavioral modifications and pharmacotherapy.

Once diagnosis of a benign inflammatory lesion is confirmed and malignancy is ruled out patients should be offered lesion targeted treatments for recurrent symptoms in addition to multimodal behavioral and pharmacologic therapy. In this cohort 34.5% (19/55) of patients had prior biopsy/fulguration at outside institutions prior to referral. While a few of these patients had lesion targeted

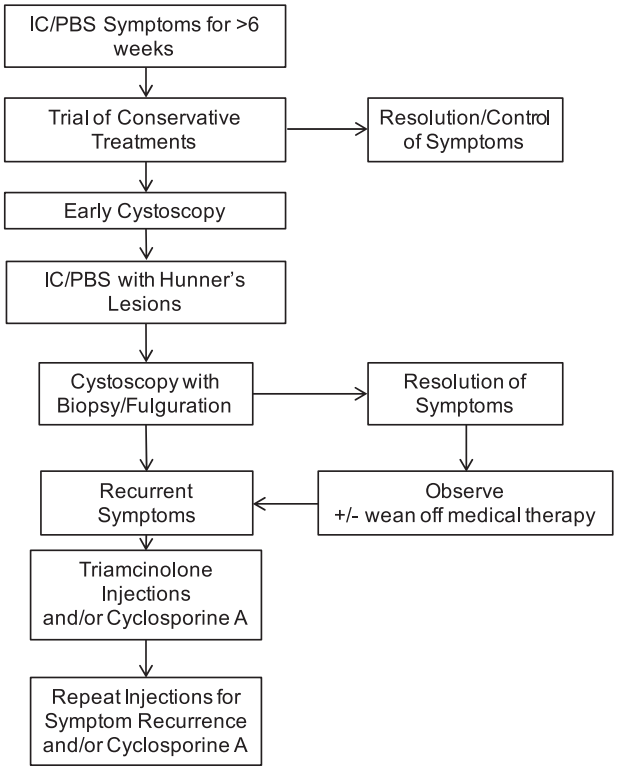

Figure 1. Proposed Treatment Algorithm.

interventions, many were managed conservatively with suboptimal results. This presents another point of delay in care and need for patients with lower urinary tract symptoms and pain who have benign bladder lesions to be referred for targeted lesion treatment.

Biopsy and Fulguration

In this cohort success rates with biopsy/fulguration were around 80% which is in line with prior studies reporting rates of success ranging from 78% to 90%.[9-11] Alternatively, laser Nd:Yag laser has been used successfully for lesion destruction in small studies with 78%-100% response rates [12,13] but is associated with increased cost. Repeat biopsy should be considered any time there is significant change in the ulcer appearance or uncertainty of diagnosis. While effective, biopsy/fulguration will not regularly achieve a permanent response, making repeat procedures necessary in 76.4% (42/55) at a median time of 12 months (IQR 6, 21). These results are consistent with previous studies demonstrating repeat procedure rates of 50%-70% at time points ranging from 2 to 23 months[9-11,14] and can be used to guide patient expectations.

Triamcinolone Injection

Patients with recurrent symptoms after biopsy/fulguration should be re-evaluated for lesion recurrence with cystoscopy and can be managed with either a repeat biopsy/fulguration or triamcinolone injection. The injection of a steroid into the ulcer is meant to serve a dual purpose: diminish scar formation and decrease inflammatory response. There is a theoretical concern that multiple repeated biopsy/fulgurations can expedite bladder scarring and functional deterioration, but this has not been confirmed to date.[11] There are currently no studies that have directly compared fulguration to triamcinolone injection outcomes but both have been shown to be effective. Since it is our preference is to perform triamcinolone injections once the diagnosis of Hunner's lesions has been established we are not able to directly compare these 2 treatment modalities.

This study supports the safety and effectiveness of triamcinolone injections in IC/BPS with Hunner's lesions with over 85% of patients reporting improvement in pain symptoms with a median duration of benefit of 8 months (IQR 4, 13) and 74% continuing with repeat injections. This is in line with prior limited evidence demonstrating symptom improvement in 70% of patients and a quarter of patients having repeat injection at about 11 months.[15,16] Another study of 20 patients demonstrated 70% retreatment rate at >8 months of follow-up.[17] In this cohort, urinary symptoms and QoL also improved significantly (Fig. 2). Specifically, improvement in nocturia and frequency was most pronounced (Fig. 2). This is consistent with a recent larger study of a heterogenous IC/BPS population treated with triamcinolone that reported decrease in frequency and nocturia.[18] While the authors did not find a statistically significant decrease in pain at 12 weeks it may be because authors did not limit the population to patients with Hunner's lesions, but also included patients with mucosal cracks after bladder was hydrodistention.[18]

Role of cyclosporine

A limited number of studies have supported the use of cyclosporine for the treatment of IC/BPS, with superior results observed in patients with Hunner's lesions.[4,5,19] In this study, 26 patients used cyclosporine for a median of 15 months and it was used safely along with triamcinolone injections. At the last visit, 12 were continuing use and 3 reported resolution of symptoms at the time of discontinuation. Patients should be carefully monitored for side effects as in our cohort 23% of patients had to discontinue medication use due to possible side effects. We reserve this systemic treatment for patients who are not amenable to endoscopic treatment due to diffuse disease or those who have frequent recurrences. Since cyclosporine was used selectively for patients with severe symptoms we are not able to assess additive benefit of this medication and further studies are needed.

Cystectomy

Cystectomy and urinary diversion is reserved as the last resort treatment for patients with IC/BPS as it carries a significant risk of complications at the expense of incomplete response in about ¼ of patients.[20] In our study, only 4 patients, including 1 patient who failed triamcinolone, went on to have a cystectomy with urinary diversion. Only 50% reported improvement which further underscores the unclear benefit of cystectomy in IC/BPS.

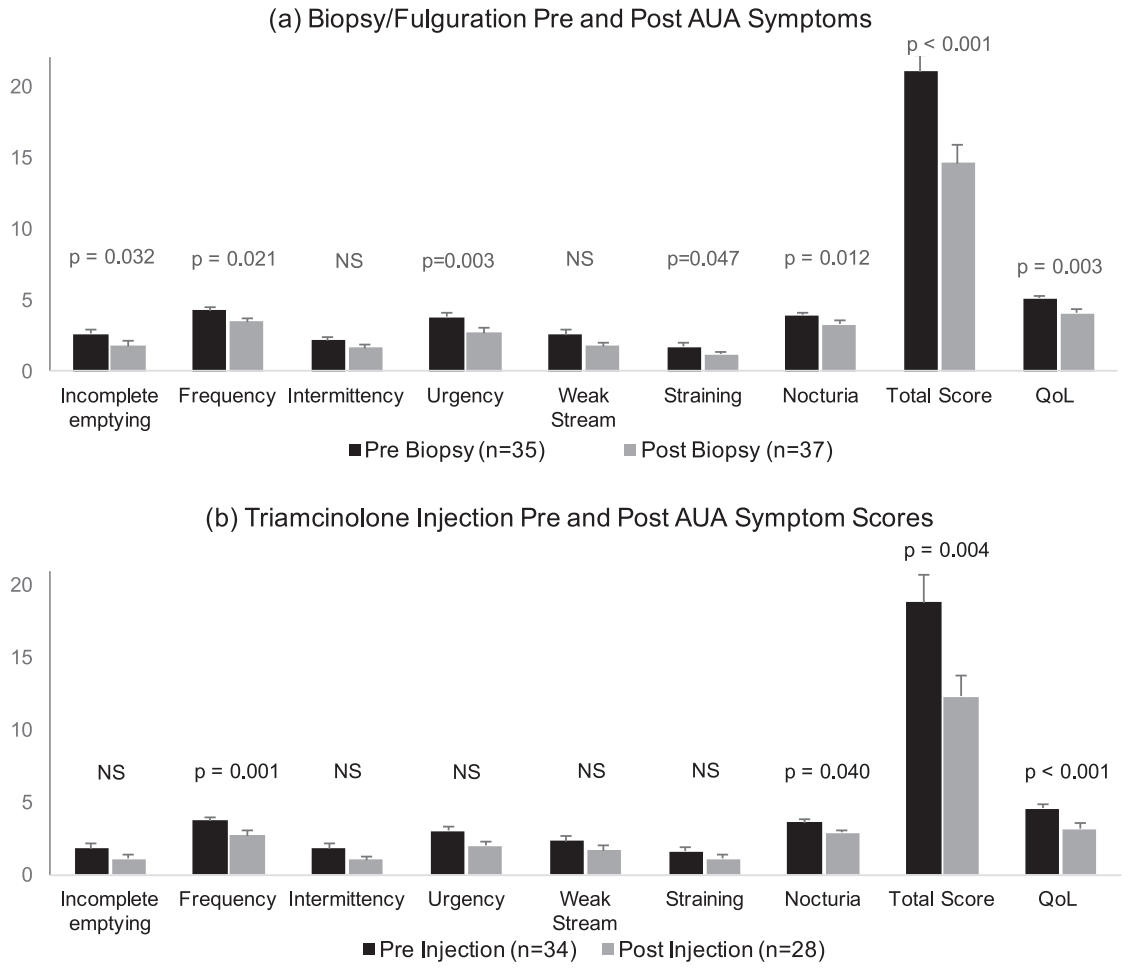

Figure 2. AUA Symptom and QoL scores pre- and postbiopsy/fulguration (**A**) and pre- and posttriamcinolone injection (**B**).

Limitations

Since our institution serves as a regional referral center patients were often referred late in the course of the disease and data on prior interventions is limited. Based on the data available we found a significant delay from symptom onset to the initiation of Hunner's lesion targeted treatment which is concerning considering the significant disease burden of IC/BPS. While robust long-term follow-up was available within our system, we did not have IC/BPS specific questionnaire assessing pain available over the last 10 years and had to rely on subjective patient reported outcomes for overall improvement. This can be associated with recall bias and does not offer a measurement scale of improvement. We did however have a robust assessment of urinary symptoms with a validated AUA score demonstrating clear benefit of lesion targeted treatments. Additionally, due to a retrospective nature of the study, the follow-up schedule varied by provider with most patients having at least 1 visit per year. Regardless of the follow-up schedule, the strength of the study is that patients triggered additional treatment events by contacting the provider to report symptom recurrence which is a valuable representation of symptom bother and severity.

CONCLUSION

While there is a significant overlap in symptom and presentation of IC/BPS, patients with Hunner's lesions have the greatest benefit from ulcer targeted treatments. Cystoscopy should not be delayed for IC/BPS patients with incomplete response to behavioral and medical therapy in order to identify patients with ulcerative lesions. This study demonstrates that sequential approach to diagnostic cystoscopy, followed by biopsy/fulguration, and maintenance therapy with triamcinolone and/or oral cyclosporine can offer good symptom control in the long-term and lead to improvement in urinary QoL.

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EDITORIAL COMMENT

Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) is a heterogeneous condition best treated by mulimodal therapy driven by clinical phenotyping. An established clinically relevant subtype are patients with Hunner's Lesions (HL) which are visible during cystoscopy. Not only does finding HL establish the bladder as a likely pain driver, it also opens additional therapies including fulguration, direct injection of steroids, and a higher rate of response to cyclosporine.

In this retrospective study, the authors describe their outcomes in Interstitial Cystitis/Bladder Pain Syndrome patients who had HL and were treated with fulguration, triamcinolone injection, or cyclosporine while continuing their other baseline therapies. Improvement with bladder directed therapies was high but retreatment was often required. What lessons can we draw from this experience? First that delay in diagnosis of the HL was 2 years. Current AUA guidelines have cystoscopy at a third line therapy once conservative treatments have failed. The authors and I disagree with this stance. It does not make sense to deprive patients with HL of highly effective therapies which could and should be provided up front, especially that 46% of the patients were requiring chronic narcotics. The second lesson is that HL directed therapies are simple to perform, effective, and should not be confined to academic centers of excellence. Finally, although cyclosporine is firmly established in the guidelines as a fifth line therapy it can be effective and bladder preserving, especially in the HL population. While many Urologists may be reluctant to use it due to its side effect profile it can be safely given at this dose with a minimum of patient monitoring.

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AUTHOR REPLY

The editorial comment provides an excellent summary of the major take away points we hoped to portray in this retrospective review. Specifically, in our practice patients with IC/PBS and Hunner's lesions often experience delay to lesion targeted therapy which is most beneficial for them. This delay occurs at multiple management points along the IC/PBS management pathway. Initially, it happens at the time of diagnosis as AUA guidelines do not recommend cystoscopy until patients have failed multiple conservative treatments and thus patients with Hunner's lesions are not identified until much later. Another delay occurs after cystoscopy is done, pathology is found to be benign, and no further lesion targeted treatments are offered. Finally, we demonstrate that ¾ of the patients will need repeated treatments for their lesions and should be offered this when clinical symptoms recur or worsen.

This work demonstrates our long-term experience and safety of lesion targeted treatment with direct triamcinolone injection and its use alongside with cyclosporine. Over 80% can expect overall improvement with lesion targeted therapy and side effect profile is low. As more evidence accumulates on the efficacy of lesion targeted treatment for patients with Hunner's lesions, a modification in the AUA guidelines may be warranted to address management of this distinct phenotype of IC/BPS as noted by the editorial comment.

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