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# Bladder irrigation with povidone-iodine prevent recurrent urinary tract infections in neurogenic bladder patients on clean intermittent catheterization

Mohamad Moussa<sup>1</sup> | Mohamed Abou Chakra<sup>2</sup>  | Athanasios G. Papatsoris<sup>3</sup> | Athanasios Dellis<sup>4</sup> | Baraa Dabboucy<sup>5</sup> | Youssef Fares<sup>6</sup>

<sup>1</sup>Department of Urology, Lebanese Univeristy, Beirut, Lebanon

<sup>2</sup>Department of Urology, Faculty of Medical Sciences, Lebanese University, Beirut, Lebanon

<sup>3</sup>Second Department of Urology, School of Medicine, Sismanoglio Hospital, National and Kapodistrian University of Athens, Athens, Greece

<sup>4</sup>Department of Urology and General Surgery, Areteion Hospital, Athens, Greece

<sup>5</sup>Department of Neurosurgery, Faculty of Medical Sciences, Lebanese University, Beirut, Lebanon

<sup>6</sup>Department of Neurosurgery, Neuroscience Research Center, Faculty of Medical Sciences, Lebanese University, Beirut, Lebanon

## Correspondence

Mohamed Abou Chakra, Department of Urology, Faculty of Medical Sciences, Lebanese University, Beirut 1108, Lebanon.  
Email: [mohamedabouchakra@hotmail.com](mailto:mohamedabouchakra@hotmail.com)

## Abstract

**Aims:** To determine if daily povidone-iodine (PI) bladder irrigation in neurogenic lower urinary tract dysfunction (NLUTD) patients doing clean intermittent catheterization (CIC) can reduce the rate of symptomatic urinary tract infections (UTIs), emergency department (ED) visit for UTIs, and hospitalization for UTIs.

**Methods:** We prospectively reviewed the records of patients with NLUTD on CIC who had recurrent symptomatic UTIs and who were placed on daily intravesical instillations of PI. This trial was conducted from January 2014 to January 2020 on 119 patients.

**Results:** After using daily PI bladder irrigation, the rate of symptomatic UTIs was reduced by 99.2% (incidence rate ratio [IRR]: 0.008, 95% confidence interval [CI]: 0.001–0.059;  $p < .001$ ), the rate of ED visits was reduced by 99.2% (IRR: 0.008, 95% CI: 0.001–0.059;  $p < .001$ ), and the rate of inpatient hospitalizations for UTI was reduced by 99.9% (IRR: 0.0008, 95% CI: 0.0002–0.0035;  $p < .001$ ). There was also a significant decrease in multidrug resistance in UTI organisms with the use of PI bladder instillation.

**Conclusions:** Daily intravesical PI instillation is a well-tolerated approach to prevent UTIs and related ED visits and hospitalizations in NLUTD patients doing CIC.

## KEYWORDS

clean intermittent catheterization, intravesical instillation, neurogenic bladder, povidone-iodine, recurrent, urinary tract infection

## 1 | INTRODUCTION

The incidence of urinary tract infections (UTIs) in patients with a neurogenic bladder or neurogenic lower urinary tract dysfunction (NLUTD) is high. It is estimated that the overall rate of UTI is 2.5 episodes per patient per year. The high incidence of emergency

department (ED) visits and hospitalizations is essentially proportional to the incidence of antibiotic use.<sup>1</sup> A large proportion of patients with neuro-urologic disorders are managed with indwelling catheterization or clean intermittent catheterization (CIC). In a study, the overall incidence of UTI for males on CIC was 0.41.<sup>2</sup> The incidence of UTI for patients doing CIC is affected by the use of

coated or uncoated catheters, single or multiple-use catheters. The single-use hydrophilic catheters reduce the risk of UTI with a reported incidence of 40% and 60%, as compared with 70%–80% for reuse catheters.<sup>3</sup> Another study showed that the annual rate of symptomatic UTI was 26% for quadriplegic patients doing CIC.<sup>4</sup> Regarding UTI in NLUTD patients caused by spinal cord injury or dysfunction, symptomatic UTI reportedly occurs in 22%–45%.<sup>5</sup> Those patients often present without classic symptoms of UTIs but with abdominal or back pain, increased spasticity, and urinary incontinence.<sup>6</sup>

Risk factors for UTIs among NLUTD patients are indwelling catheters, urinary stasis, high bladder pressure, and bladder stones. In patients with NLUTD, clinical symptoms and leukocyturia must be present together with bacteriuria to qualify as UTI. The spectrum of pathogens differs significantly from that in patients with normal bladder function.<sup>7</sup> In the acute phase of NLUTD, intermittent catheterization is often necessary. After this phase, patients are subject to UTIs leading to febrile diseases. In the chronic phase of NB, febrile infections are often accompanied by hypertonic bladder.<sup>8</sup>

In NLUTD patients, only UTI should be treated; treatment of asymptomatic bacteriuria is not indicated. Before treatment, a urine culture should be obtained. In recurrent UTI, bladder management should be optimized and morphologic causes for UTI should be excluded. If UTIs persist, medical prophylaxis should be considered.<sup>9</sup> Oral antibiotics, methenamine compounds, and bladder instillations of chlorhexidine preparations are often used and have been shown to postpone bacteriuria for short periods in patients managed with CIC.<sup>10</sup>

Instillation of bactericidal solutions into the bladder following catheterization for the prevention of UTI dates back to the early 1960s. Gentamicin remains the best studied of these agents and is the only intravesical treatment that has shown efficacy in both the prevention and treatment of UTI.<sup>11</sup> Instillations of antibacterial solutions in the bladder after catheterization had conflicting outcomes: Kanamycin-colistin decreased the incidence of bacteriuria, but this was not found with neomycin or polymyxin. Studies with gentamicin instillations show a reduction in bacteriuria and UTI in patients with resistant *Escherichia coli*.<sup>12</sup> In 1985, bladder irrigation with povidone-iodine (PI) in the prevention of UTI after single or intermittent urethral catheterization was investigated in a controlled study. The incidence of hospital-acquired bacteriuria fell from 6.9% to 3.7% after using PI.<sup>13</sup>

In this background, our study was designed to assess whether daily bladder instillation of PI solution can help to reduce recurrent UTIs, ED visits, and hospitalization for patients with NLUTD on CIC. We also planned to assess the safety of this modality of treatment.

## 2 | MATERIALS AND METHODS

This study was a prospective trial. The authors reviewed the records of patients with NLUTD on CIC who had recurrent symptomatic UTIs and were placed on daily intravesical instillations of PI. This trial was conducted from January 2014 to January 2020.

The primary outcomes were to determine if daily PI bladder irrigation of NLUTD patients doing CIC can reduce the rate of symptomatic UTIs, ED visit for UTIs, and inpatient hospitalization for UTIs. The secondary outcome was to assess the safety of bladder irrigation with PI in these patients.

Inclusion criteria for this study were NLUTD of any etiology with bladder drainage managed with CIC, age >18 years old, time doing CIC >12 months, not taking antibiotic prophylaxis for UTI. Patients had recurrent UTI (>3 per year), used at least for 6 months the PI solution and with at least a period of follow-up of 12 months.

Exclusion criteria were patients receiving short-term instillations of PI, <12 months follow-up, discontinuation of CIC, <3 UTI episodes during the last 12 months, doing CIC using multiple-use polyvinylchloride catheters, patients unable to report urinary symptoms accurately, patients with hypersensitivity or allergic reaction to PI, patients with pre-existing thyroid disease or patients with creatinine level >2 mg/dL.

Data collection did not stop for any of the participants, so there is no missing data. We used multiple strategies to reduce attrition. The eligibility criteria were excluded from the study patients who may be difficult to retain. We minimized the time between obtaining consent and study allocation. We put contingency plans for locating patients to obtain a close follow-up.

Symptomatic UTIs were defined as a positive urine culture with greater than 10 000 colony-forming units/mL associated with one or more of the following patient complaints: fever, urinary incontinence/failure of control or leaking around the catheter, spasticity, malaise, lethargy, cloudy urine, malodorous urine, dysuria, pelvic discomfort, increased frequency of catheterization/voiding.

Patients received the intravesical PI solution after drainage of urine was complete and at the patient's last catheterization. Bladder irrigation with 50 cc of 2% PI indwelling for 10 min before catheter removal using Toomey Syringe in an aseptic technique. CIC catheters used by the patients were single-use hydrophilic coated catheters. The teaching of patients and caregivers on bladder instillation was given by a single urologist using oral and written instructions.

Any side effects were reported. Even that systemic side effects are not to be expected but all patients using

bladder irrigation with PI were tested monthly for serum iodine level and TSH level. Values above 250 ng/ml may indicate iodine overload. Urological follow-up was done by the same urologist.

The scientific and ethical content of this study has been approved by our institutional review board and all the patients agreed to enter this study by signing informed written consent.

Descriptive statistics were used to evaluate baseline patient demographic, clinical characteristics, and patient safety measures after PI instillations and UTI characteristics were evaluated before and after PI bladder instillations. For pre-/post- PI comparisons on symptomatic UTI, ED visits for UTI, and inpatient hospitalizations, the Stuart–Maxwell Marginal Homogeneity test was used for paired categorical variables of more than two outcomes.

The relative rate of symptomatic UTI was defined as the incidence rate ratio (IRR), calculated by dividing the UTI rate in the postinstillation group by that found in the preinstillation group. Similarly, the relative rate of inpatient hospitalizations and rates of ED visits for UTI was analyzed with IRR. The absolute mean change in symptomatic UTI visits was calculated by subtracting preinstillation symptomatic UTI from postinstillation symptomatic UTI for each subject so that each subject had its own difference score. Count-based outcomes were analyzed using Poisson regression. Adjustment for symptomatic UTIs by the independent predictors (age, gender, duration of CIC, etiology) was done using multivariate models.

All analyses were performed using SPSS statistical software version 20. The significance threshold was set at 0.05.

### 3 | RESULTS

#### 3.1 | Patients characteristics

During the time period from January 2014 till January 2020, 190 patients with NLUTD were identified who received daily PI bladder irrigation, and 119 met inclusion criteria. Of the 71 excluded subjects, 36 were excluded due to having less than 12 months follow-up, 14 due to short-term use of PI bladder irrigation, 18 due to having <3UTI episodes during the last 12 months, and three due to taking antibiotic prophylaxis for UTI.

Table 1 shows the demographic data of the patients and their clinical characteristics. The mean age of the patients was 36 years. 76.5% of the patients were males. The etiologies of NLUTD was primarily spinal cord injury (62.1%), spina bifida (8.4%), multiple sclerosis (7.6%),

**TABLE 1** Patient demographics and clinical characteristics (*n* = 119)

Gender, <i>n</i> (%)	
Male	91 (76.5%)
Female	28 (23.5%)
Class age, <i>n</i> (%)	
(18–25)	27 (22.7%)
(25–35)	36 (30.3%)
(35–45)	31 (26.1%)
>50	25 (21%)
Duration of CIC, <i>n</i> (%)	
<2 years	9 (7.6%)
2–5 years	53 (44.5%)
5–10 years	53 (44.5%)
>10 years	4 (3.4%)
Etiology of NB, <i>n</i> (%)	
Spinal cord injury	74 (62.1%)
Spina bifida	10 (8.4%)
Multiple sclerosis	9 (7.6%)
Cerebrovascular accident	9 (7.6%)
Parkinson's disease	9 (7.6%)
Degenerative disc disease	8 (6.7%)

Abbreviations: CIC, clean intermittent catheterization; NB, neurogenic bladder.

cerebrovascular accident (7.6%), Parkinson's disease (7.6%), and degenerative disc disease (6.7%). The duration of CIC was less than 2 years in 7.6% of patients, between 2 and 5 years in 44.5% of patients, between 5 and 10 years in 44.5% of patients, and >10 years in 3.4% of patients.

#### 3.2 | Outcomes

Outcomes are presented in Table 2 and Figure 1. Before the initiation of PI bladder irrigation 33.6% of NLUTD patients doing CIC had 4 episodes per year of symptomatic UTIs, 47.1% of patients had 5 episodes per year and 19.3% had >5 episodes per year. After using daily PI bladder irrigation, the number of episodes of symptomatic UTIs per year decreased significantly (*p*-value < .001). 53.8% of patients had 1 episode of symptomatic UTI per year and 32.8% of patients had 2 episodes of symptomatic UTI per year, while 12.6% of patients did not have any symptomatic UTI.

**TABLE 2** UTI characteristics, ED visit, and inpatient hospitalization before and after povidone-iodine bladder instillations

	Before povidone- iodine	After povidone- iodine	<i>p</i> *
Symptomatic UTIs/ year, <i>n</i> (%)			<.001
None	0 (0%)	15 (12.6%)	<i>p</i> -value
1 episode	0 (0%)	64 (53.8%)	
2 episodes	0 (0%)	39 (32.8%)	
3 episodes	0 (0%)	1 (0.8%)	
4 episodes	40 (33.6%)	0 (0%)	
5 episodes	<b>56 (47.1%)</b>	0 (0%)	
>5 episodes	23 (19.3%)	0 (0%)	
ED visits for UTI, <i>n</i> (%)			<.001
None	0 (0%)	20 (16.8%)	<i>p</i> -value
1 visit	0 (0%)	69 (58%)	
2 visits	0 (0%)	29 (24.4%)	
3 visits	5 (4.2%)	1 (0.8%)	
4 visits	35 (29.4%)	0 (0%)	
>4 visits	79 (66.4%)	0 (0%)	
Inpatient hospitalizations for UTI, <i>n</i> (%)			<.001
None	0 (0%)	34 (28.8%)	<i>p</i> -value
1 hospitalization	2 (1.7%)	<b>74 (62.2%)</b>	
2 hospitalizations	9 (7.6%)	10 (8.4%)	
3 hospitalizations	41 (34.5%)	1 (0.8%)	
>3 hospitalizations	67 (56.3%)	0 (0%)	

Abbreviations: ED, emergency department; UTI, urinary tract infection.

Before the initiation of PI bladder irrigation, 66.4% of NB patients had >4 ED visits for UTIs per year, 29.4% of patients had 4 ED visits per year and 4.2% had 3 ED visits per year. After using daily PI bladder irrigation, the number of ED visit for UTIs per year were significantly reduced ( $p$ -value < .001). A total of 58% of patients had only 1 ED visit for UTIs per year, 24.4% of patients had 2 ED visits per year and one patient had 3 ED visits per year. Otherwise, 16.8% of patients never visited the ED for UTIs.

Before the initiation of PI bladder irrigation, 56.3% of patients had >3 hospitalizations for UTI per year, 34.5% of patients had 3 hospitalizations for UTI per year, 7.6% of patients had two hospitalizations per year, and 1.7% of

patients had only one hospitalization per year. After using daily PI bladder irrigation, the number of hospitalizations for UTI per year was significantly reduced ( $p$ -value < .001). A total of 62.2% of patients had only one hospitalization for UTI per year, 8.4% of patients had two hospitalizations per year. We noted that 28.8% of patients had never been hospitalized for UTIs during the last year.

In summary, after using daily PI bladder irrigation, the rate of symptomatic UTIs was reduced by 99.2% (IRR: 0.008, 95% confidence interval [CI]: 0.001–0.059;  $p$  < .001), the rate of ED visits was reduced by 99.2% (IRR: 0.008, 95% CI: 0.001–0.059;  $p$  < .001), and the rate of inpatient hospitalizations for UTI was reduced by 99.9% (IRR: 0.0008, 95% CI: 0.0002–0.0035;  $p$  < .001). Incidence rate ratios compared between preinstillation and postinstillation of intravesical PI are presented in Table 3.

There are no significant differences in mean change of a number of UTI episodes in the multivariate model adjusted for age, gender, duration of CIC, and etiology of NLUTD, neither in the multivariate model adjusted only for NLUTD. The pairwise comparisons revealed no significant differences in any of these etiologies of NLUTD.

### 3.3 | Patients safety after using bladder irrigation with povidone-iodine

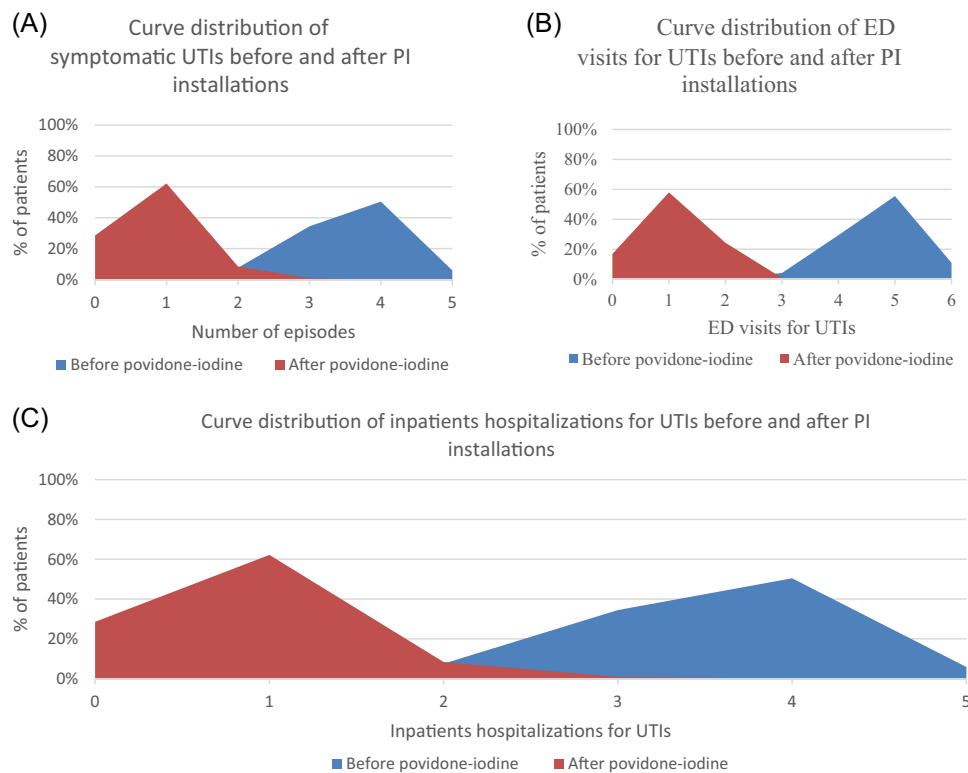
Reported adverse events of intravesical PI instillation are documented. A total of 65.6% of patients did not report any side effects of PI intravesical instillation. A total of 26.8% of patients reported mild new irritative symptoms, 5.9% of patients reported itching around the genital area, and 1.7% of patients reported hematuria.

The monthly TSH level and serum iodine level were normal for patients using daily PI bladder irrigation.

### 3.4 | Microorganisms and multidrug resistance

Agents isolated from urine cultures before and after PI instillation are mentioned in Table 4. Among the 782 urine cultures associated with UTIs, 583 urine cultures (80%) were positive before PI instillation, and 145 were positive after PI instillation (20%). The most prevalent organism preinstillation and postinstillation of PI for individual urine cultures was *E. coli* (348/583 urine cultures, 60%, vs. 75/145 urine cultures, 52%). The number of all germs was significantly reduced after PI therapy. There was also no change in the microorganisms obtained in urine cultures.

Before PI instillation, 145 of the 583 isolates were multidrug-resistant. After PI intravesical instillation,



**FIGURE 1** Curve distribution of symptomatic UTIs per year, the rate of ED visits, and the rate of inpatient hospitalizations for UTI before and after using PI bladder irrigation. ED, emergency department; PI, povidone-iodine; UTI, urinary tract infection

**TABLE 3** Incidence rate ratios compared between pre-instillation and postinstillation of intravesical povidone-iodine

Count outcomes	Unadjusted		p-Value
	IRR	95% CI	
Symptomatic UTIs/year	0.008	(0.001–0.059)	<.001
ED visits for UTI	0.008	(0.001–0.059)	<.001
Inpatient hospitalizations for UTI	0.0008	(0.0002–0.0035)	<.001

Abbreviations: CI, confidence interval; ED, emergency department, IRR, incidence rate ratio; UTI, urinary tract infection.

patients had a significantly lower number of multidrug-resistance strains (60 strains vs. 145 strains before PI therapy).

## 4 | DISCUSSION

Many patients with NLUTD performed CIC to assist with bladder emptying. However, these individuals still have a 4-fold-increased risk of UTI compared to those who do not perform CIC.<sup>14</sup>

A study conducted by Lucas et al. to compare the type and virulence of microorganisms recovered from the urine of patients that use either a hydrophilic or

**TABLE 4** Microorganisms present in total urine cultures performed before and after povidone-iodine bladder instillations

Urine microorganisms based on individual positive urine cultures (total n = 728)	Before PI instillation (n cultures = 583)	After PI instillation (n cultures = 145)
Organism, n (%)		
<i>Escherichia coli</i>	348 (60%)	75 (52%)
<i>Acinetobacter</i>	32 (5%)	8 (6%)
<i>Enterococcus</i>	45 (8%)	12 (8%)
<i>Pseudomonas</i>	46 (8%)	20 (14%)
<i>Klebsiella pneumonia</i>	39 (7%)	12 (8%)
<i>Enterobacter</i>	27 (5%)	5 (3%)
<i>Proteus mirabilis</i>	36 (6%)	6 (4%)
Multiple organisms	5 (1%)	2 (1%)
Others	5 (1%)	5 (3%)

Abbreviation: PI, povidone-iodine.

conventional polyvinyl chloride (PVC) catheter for CIC. It was concluded that there was a trend for reduced recovery of potentially pathogenic bacteria with the use of



hydrophilic catheters. The reduction in potentially pathogenic species will reduce antibiotic exposures.<sup>15</sup> Madero-Morales et al. determined whether single-use PVC would reduce UTI compared to reused PVC catheters in patients with NB due to spina bifida. No statistical difference was found between the single-use versus reused catheter groups in the frequency of UTIs (35.2% vs. 36.8%,  $p = .877$ ).<sup>16</sup>

Many authors tested if daily bladder instillations of antibiotics or other substances can reduce the rate of symptomatic UTIs in NLUTD patients doing CIC. Huen et al. determine if daily neomycin-polymyxin or gentamicin bladder instillations reduce the rate of symptomatic UTIs in those patients. 90.4% and 9.6% of patients received neomycin-polymyxin and gentamicin instillations, respectively. After initiation of intravesical antibiotics, the rate of symptomatic UTIs was reduced by 58% (IRR: 0.42, 95% CI: 0.31–0.56;  $p < .001$ ), the rate of ED visits was reduced by 54%, and the rate of inpatient hospitalizations for UTI was reduced by 39%.<sup>17</sup> Cox et al. tested if the use of gentamicin bladder instillations reduces the rate of symptomatic UTI in NLUTD patients on intermittent self-catheterization who have recurrent UTIs. Twenty-two patients met the inclusion criteria. Patients had fewer symptomatic UTIs (median 4 vs. 1 episode;  $p < .004$ ) and underwent fewer courses of oral antibiotics after initiating gentamicin (median 3.5 vs. 1;  $p < .01$ ). The proportion of multi-drug-resistant organisms in urine cultures decreased from 58.3% to 47.1% ( $p = .04$ ).<sup>18</sup>

Haldorson et al. evaluated the regular instillations of 0.1% neomycin after each catheterization. One group of 53 patients was included in the study. There was no difference in the incidence of bacteriuria between the neomycin-treated group and the control group (53 vs. 49%, respectively).<sup>19</sup> Pearman et al. testing the value of kanamycin-colistin bladder instillations in reducing bacteriuria during intermittent catheterization of patients with acute spinal cord injury. Twenty-two patients had kanamycin-colistin solution instilled into the bladder at the end of each catheterization, and 25 patients were not given these instillations. The incidence of significant bacteriuria during intermittent catheterization of both males and females receiving the instillations was only half the incidence of those not receiving the instillations.<sup>20</sup> Wikström et al.<sup>21</sup> demonstrated that bladder irrigation with chlorhexidine, using intermittent self-catheterization, reduced bacteriuria in patients with spinal cord injury and bacteriuria.

The use of intravesical PI to prevent symptomatic UTIs while performing CIC has been described in the literature with variable success. Van den Broek et al.<sup>13</sup> reported that the use of bladder irrigation with PI after

intermittent urethral catheterization can reduce bacteriuria. A preliminary study was conducted by Sharpe et al. to evaluate diluted solutions of PI as urinary bladder irrigants for the treatment and prevention of UTI. The diluted PI solutions had no efficacy in either the treatment or prevention of UTI when used as indwelling urethral or suprapubic catheter irrigants.<sup>22</sup>

In this study, we demonstrated that daily intravesical PI installation was successful in decreasing the rate of UTIs per year, the ED visits for UTIs per year, and the hospitalization for UTI in NLUTD patients with recurrent UTIs and practicing CIC.

The watertight barrier between blood and urine formed by the urothelium represents the toughest barrier to drug delivery known to man. The drastic reduction in the incidence of systemic side effects by the intravesical route allows the use of very toxic agents. Conversely, transvesical transport can be adversely affected by dilution of instilled drug solution by residual urine in the bladder.<sup>23</sup> Regarding the safety of the intravesical gentamicin, systemic absorption was not reported.<sup>24</sup> However, caution is still warranted when using intravesical therapy. De Jong et al.<sup>25</sup> reported a case of perception deafness in a boy with end-stage renal disease who underwent neomycin bladder instillations. Gerharz et al.<sup>26</sup> reported complete irreversible deafness of three patients with end-stage renal disease who had undergone bladder irrigation with neomycin solution.

Concerning the safety of bladder irrigation with PI, data are lacking. Miller et al. conducted a study to ascertain the toxicity of PI on the catheterized rat bladder and to measure the systemic absorption of iodine. Bladder catheters were surgically placed into each of three groups of rats: Group 1, catheters only; Group 2, irrigation with phosphate buffer solution every 8 h; and Group 3, irrigation with a 1:3 dilution of a 10% polyvinylpyrrolidone iodine (PVP-I2) I2 solution every 8 h. Protein-bound iodine was higher in Group 3 rats at the conclusion than Group 1 and 2. There was no difference in T3 or T4 levels. Iodine is absorbed from rat bladder mucosa, but thyroid function as determined by serum T3 and T4 values did not change.<sup>27</sup> In certain susceptible individuals, including those with pre-existing thyroid disease, the elderly, and the risk of developing iodine-induced thyroid dysfunction might be increased.<sup>28</sup> In general, PI irrigation should not be used in patients with iodine sensitivity, burns, thyroid disease, or renal disease until more research has been conducted.<sup>29</sup> In our study, the monthly serum TSH and Iodine levels were normal during all periods of therapy.

PI bladder irrigation had mild adverse events. About 20% of patients reported mild new irritative symptoms and only two patients reported a new-onset of hematuria

after each instillation. Moreover, there are no data that address the side effect of such a modality of therapy to compare it to our results.

Our study has several limitations. First, it is an observational study that could impact the generalizability of the results, we are unable to compare the efficacy of antibiotic instillation to placebo. Second, we did not determine how bladder irrigation with PI can change the type of germ isolated in the urine of infected patients. Third, patients were selected by their urologist, this could induce a selection bias.

## 5 | CONCLUSION

While many strategies are used to prevent symptomatic UTI for NLUTD patients doing CIC. Daily use of intravesical PI solution has shown efficacy in decreasing the rate of symptomatic UTI's per year, the ED visits for UTI, the inpatient hospitalization for UTI's in these patients.

## CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

## AUTHOR CONTRIBUTIONS

*Study conception and design and critical revision of the manuscript and its final approval:* Mohamed A. Chakra, Mohamad Moussa, Athanasios G. Papatsoris, Athanasios Dellis, Baraa Dabboucy, Youssef Fares. *Data acquisition:* Mohamed A. Chakra, Mohamad Moussa. *Data analysis:* Mohamed A. Chakra, Mohamad Moussa, Athanasios G. Papatsoris, Baraa Dabboucy. *Drafting of the manuscript:* Mohamed A. Chakra, Mohamad Moussa, Athanasios G. Papatsoris.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## ORCID

Mohamed Abou Chakra  <http://orcid.org/0000-0002-4293-3314>

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