Urinary tract infections in the intradetrusor onabotulinumtoxinA population

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Key words: detrusor overactivity; onabotulinumtoxinA; urinary tract infection; antibiotic prophylaxis.

Contributions: EW; design of study, data collection and interpretation, drafting the article, revising the article based on reviewers comments. AB; data collection, analysis, collection of re-audit data, revising the article. TN; concept and design of the study, revising the article.

Conflicts of interest: the Authors declare no conflict of interest.

Ethics approval and consent to participate: no ethical committee approval was required for this case report by the Hospital, because this article does not contain any studies with human participants or animals.

Informed consent: no applicable.

Patient consent for publication: no applicable.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.

Conference presentation: this study has been presented nationally as a poster presentation at the UK Continence Society Conference, Belfast in April 2016 and as an oral presentation at the British Association of Urological Surgeons conference in June 2016. Internationally, it has been presented as an oral presentation at the World Congress of Endourology in Cape Town, South Africa in November 2016.

Acknowledgements: thank you to the microbiologists and antibiotic steering group at our centre who were helpful in attending meetings to review our local guidelines, particularly John Clark. Thank you also to Ahmed Shahzad and Roger Walker who helped with data collection and to steer the project.

Received for publication: 28 January 2023.
Accepted for publication: 27 March 2023.

Urogynaecologia 2023; 35:304
doi:10.4081/uij.2023.304

Abstract

The aim of our study was to determine the incidence of Urinary Tract Infections (UTI) following intradetrusor onabotulinumtoxinA injections within our trust. This was a retrospective study of all patients who underwent intradetrusor onabotulinumtoxinA injections at our trust from August 2005 to 2015. Information was taken from our botulinum database, clinic letters and microbiology results. The primary outcome criterion was a positive urine culture together with symptoms suggestive of infection within 6 months post-procedure. A total of 290 intradetrusor onabotulinumtoxinA procedures were performed on 86 patients. The rate of UTI within 6 months following a procedure was 33%. There was a high resistance rate to our standard antibiotic prophylaxis, which was changed together with the addition of pre-procedure urine cultures and an on the day urine dipstick test. A re-audit was performed between January and June 2016 of 41 procedures and showed a reduction in UTI incidence to 20%. The rate of UTI post procedure within our trust was 33%. Following the implementation of multiple management protocol changes, a re-audit showed a reduction of UTI incidence to 20%.

Introduction

Overactive Bladder (OAB) is defined by the International Continence Society as urgency with or without urinary incontinence, usually associated with frequency and nocturia.[1]

The most recent National Institute for Health and Care Excellence (NICE) evidence based guidelines recommend offering bladder wall injections with botulinum toxin A to women with overactive bladder caused by detrusor overactivity that has not responded to non-surgical management.[2] Specifically, where anticholinergics and or mirabegron have failed, where they are contraindicated, or have intolerable adverse effects. Similarly, the European consensus report published in 2009 recommends the use of botulinum toxin as second line therapy (after pharmacological treatments) for neurogenic detrusor over activity (NDO).[3]

Recognised significant adverse effects following treatment with onabotulinumtoxinA for both NDO and Idiopathic Detrusor Overactivity (IDO) include UTI and urinary retention, with the possible need for CISC.[2,4,5] The incidence of UTI following intradetrusor onabotulinumtoxinA injections quoted in the literature varies considerably ranging from 2-32%.[6,7]

Bacterial colonisation is common for patients following onabotulinumtoxinA injections.[6,7] A small prospective non-randomised study of 42 patients published in the British Journal of Urology International (BJUI) in 2010, looked at the risk of UTI after onabotulinumtoxinA injections for refractory NDO in patients with no antibiotic prophylaxis. It found a 7.1% rate of symptomatic UTI and a urinary colonisation rate of 31% at 6 days post procedure. They concluded that with these high rates of colonisation they deemed antibiotic prophylaxis necessary.[6]

A systematic review and meta-analysis of the use of onabotulinumtoxinA in treating NDO, published in April 2015 in the Chinese Medical Journal, showed a relative risk of UTI of 1.48 when compared to placebo, with a P value of 0.0002.[8] A similar systematic review found the mean UTI rate in those receiving onabotulinumtoxinA was 22.1%, compared to 6.4% in the placebo groups, with the UTI being more severe in the treatment group ($p<0.00001$). In this review a UTI was diagnosed with a urine strip test and leukocyturia defined on urine microscopy as >5 white blood cells per high-powered field. A urine culture was not performed. It did not consider whether the patient was symptomatic, thus could be measuring asymptomatic bacteriuria. Their long-term results, which included studies with follow up results from 4 weeks to 6 months, reported a UTI incidence of 30.1% following onabotulinumtoxinA treatment.[9]

There are no national or international guidelines regarding the use of antibiotic prophylaxis for intradetrusor onabotulinumtoxinA. A systematic review of antibiotic prophylaxis in urologic procedures published in European Urology, concludes that there is a lack of well-performed studies investigating the need for antibiotic prophylaxis for many urological surgeries. There is moderate evidence to suggest antibiotics are not required for cystoscopy alone.[10] EAU guidelines updated in March 2022 state there is strong evidence to screen and treat asymptomatic bacteriuria prior to urological procedures breaching the mucosa and that bacteriuria is a definite risk factor for infections.[11] However, antibiotic prophylaxis prior to onbotulinumtoxinA is not specifically mentioned.

A further relevant study was a retrospective study of 111 women who underwent onabotulinum toxin A injections.[12] It included two cohorts, one which were given ciprofloxacin 1 day before the procedure and the other where ciprofloxacin was given after the procedure. Adjusted analysis showed the pre-procedure antibiotic group had a significant reduction in post-procedure UTI. This could therefore be used to support the use of pre-procedure prophylactic antibiotics. Pharmacologically the timing of antibiotics is very important, as ciprofloxacin reaches maximum serum concentrations 1-2 hours after oral administration. This timing differs for different antibiotics and is an important consideration for clinicians when using antibiotic prophylaxis for procedures. For example, for co-amoxiclav the time to peak concentration in the circulation occurs after just 1 hour, whereas for Trimethoprim this is longer at approximately 3 hours.

Regional discussions anecdotally have revealed that local guidelines for prophylactic antibiotics before onabotulinumtoxinA procedures vary. The aim of this study was to investigate the rate of symptomatic culture proven urinary tract infection following onabotulinumtoxinA injections used as treatment for NDO and IDO.

Materials and Methods

Data was collected retrospectively for all patients who received onabotulinumtoxinA injections from August 2005 to August 2015 within a single centre in the UK. All patients were having the injections for clinical use. Patients included both NDO and IDO, 100 and 200 units of onabotulinumtoxinA, with a mixture of General Anaesthetic (GA) and Local Anaesthetic (LA) cases. Two patients were excluded as there was insufficient documentation and missing clinic follow up letters.

This centre has a centralised electronic botulinum database, designed to record information regarding the severity of patient's OAB symptoms pre-procedure, the procedure itself and all follow up information. This database was created in October 2013. Entries for patients operated on prior to this were therefore retrospectively entered on to the database. Patients routinely have a clinic follow up at 3 months after their first procedure; in addition to a telephone consultation from a specialist nurse at 2 weeks post procedure. At this consultation the urology nurse specialist also discusses the need for CISC. If patients feel they are not emptying their bladder completely when voiding, or if they report any voiding difficulties then they are brought in for face-to-face review and post-void residual measurements are performed. CISC was recommended for those patients who were found to have post void residuals of 200ml or greater and this information was recorded in their clinical notes. Information regarding which patients were already using CISC and those who were newly started on CISC following their procedure was all collected from the clinical notes. Information regarding symptoms of post procedure urine infections, where available, were taken from clinic follow up letters and database entries. Symptoms suggestive of infection included suprapubic pain, dysuria, worsening urinary frequency and fever.

All available urine cultures within 6 months of onabotulinumtoxinA treatment were retrospectively reviewed, recording any specific bacterial growth and the antibiotic sensitivities. The growth of other microorganisms was also noted, for example fungal infections. The hospital laboratory follows the UK Standards for Microbiological Investigation for examination of urine, reporting a urine culture as positive when caused by a single organism that is present in a concentration of $\geq 10^5$ CFU/ml.[13] Urine culture results were available for those urine tests sent by the hospital and by the majority of local general practices who are geographically near the hospital and as such utilise the hospital laboratory. Most patients referred to our hospital live within the catchment area for the hospital laboratory.

As per hospital policy, patients receiving onabotulinumtoxinA injections under GA have a pre-procedure urine culture sent at their pre-operative assessment. If this is positive, they are given a treatment course of antibiotics and their procedure is deferred until the infection cleared. For the procedures completed under LA, there is no set policy for pre-procedure urine cultures. Patients receiving onabotulinumtoxinA injections under LA received 1 dose of 200 mg oral trimethoprim 15 minutes pre-procedure followed by a 3 day course of 200mg twice daily. Patients undergoing the procedure under GA were given a single induction 1.5g dose of cefuroxime intravenously (IV) during their anaesthetic induction immediately before their procedure. Deviation away from this policy was only in cases where previous cultures showed resistance to the guideline recommended antibiotic. The guidelines differ for GA and LA procedures to avoid the necessity for IV access in LA procedures completed in the outpatient setting.

The primary outcome measure was the overall incidence of culture proven UTI following onabotulinumtoxinA injections together with patient reported symptoms of infection. The secondary outcomes included the type of organism colonised, sensitivities across all isolates to each of the commonly used antibiotics in urology, infections with respect to the aetiology of DO, gender and use of CISC.

Results

Initial audit

There were a total of 290 onabotulinumtoxinA procedures performed during the 10 year period on 86 patients. 81% (70) of patients were female. The overall mean age across both sexes was 56 years (range 21-86 years). The patient characteristics are summarised in Table 1.

Patients developed a culture proven UTI following 33% of all the onabotulinumtoxinA procedures (95). Of the total 290 procedures, 70.3% (204 procedures) were for IDO and 29.7% (86 procedures) were for NDO. The incidence of UTI was 31.8% amongst the patient cohort with IDO and 34.8% of those treated for NDO. The incidence of culture proven UTI following LA procedure was 43% (25 procedures) and following GA procedure was 29.7% (69 procedures).

The 85% (247) of all 290 procedures were completed for female patients. The incidence of culture proven UTI following all procedures amongst the male patients was 28% (12/43), compared to 36% in the females (89/247). Data regarding the use of CISC was missing from 8 procedures, due to missing clinic letters or data not recorded. Of the 282 procedures with available data, CISC was used post procedure in 169 cases (60%). Of these, 42% developed a culture proven UTI. Of those patients who never required CISC, the incidence of UTI was 18%. A further secondary end point was to assess the isolates grown in the urine cultures. Of all isolates, 79% of growth was Gram negative bacteria, 11% mixed growth, 9% Gram positive and 1% yeast. The most commonly identified Gram-negative bacteria were Coliforms, at 88%.

Figure 1 shows the susceptibility of single agent antibiotics against all isolates. The antibiotics with the highest sensitivity to all isolates grown were gentamicin, nitrofurantoin, co-amoxiclav and cefalexin, with sensitivities of 87.2%, 83.9%, 82.6% and 71.6% respectively. The antibiotic with the lowest sensitivity against all isolates was trimethoprim, with a sensitivity of 43%. Sensitivities to amoxicillin and ciprofloxacin were 46.4% and 51.1% respectively.

Table 1. Patient characteristics from initial audit.

Time period	2005 – August 2015
Total number of procedures	290
Total number of patients	86
Anaesthetic	GA 80.0% (232/290) LA 20.0% (58/290)
Indication	IDO 70.3% (204/290) NDO 29.7% (86/290)

Change in local antibiotic policy and operation note

Following a review of these results, joint meetings were held with microbiologists, urologists and pharmacists at the trust to determine the best antibiotic policy. At the antibiotic steering group meeting, it was decided to change the prophylaxis from trimethoprim to a single dose of co-amoxiclav. With sensitivities of over 80%, both nitrofurantoin and co-amoxiclav were deemed to have sufficient antibacterial cover for the local ecology. Discussions amongst microbiologists, urologists and pharmacists at the antibiotic steering group meetings enabled a considered decision for co-amoxiclav (625mg single oral dose) to be the new first line choice of prophylaxis for LA cases, in preference to nitrofurantoin because of its greater efficacy in patients with renal impairment. Where a patient was penicillin allergic, then 100mg nitrofurantoin orally was given, with the caveat that if their eGFR was less than 45 mL/min/1.73 m^2 then 500mg oral cefalexin was given instead.

The new prophylactic antibiotic protocol used by the department is illustrated in Figure 2. We also implemented a mandatory pre-operative mid-stream urine for culture two weeks prior to the procedure for all patients. Patients found to have bacteriuria were given a treatment course of antibiotics and their procedure was postponed until a repeat urine culture was clear of bacteriuria.

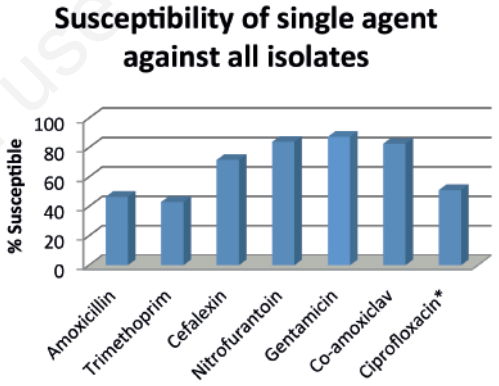

Figure 1. The susceptibility of single agent antibiotics against all isolates. *Ciprofloxacin sensitivity was not tested routinely.

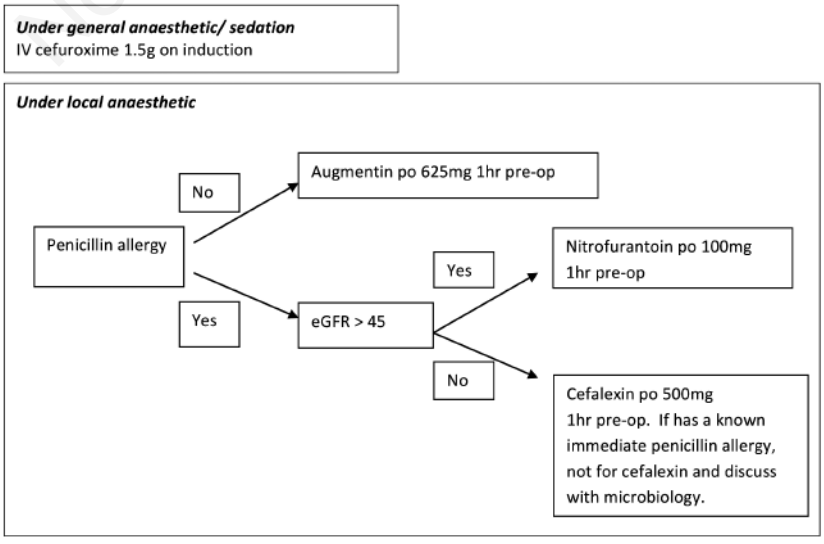

Figure 2. Antibiotic guidelines for intradetrusor onabotulinumtoxinA procedures.

For patients with a history of 3 or more recurrent symptomatic urine infections, we prescribed a one month course of post-procedure low dose antibiotic prophylaxis guided by the patient's previous culture sensitivities and through liaising with microbiology.

A standardised operation note was devised to ensure that UTI symptoms were noted pre-procedure and to ensure good clear documentation.

Re-audit

One year later, data was prospectively collected from 41 patients who were scheduled to receive intradetrusor onabotulinumtoxinA injections between January and June 2016. We collected the data using the same methods as for the first cycle of the audit, from the same department botulinum database. The proportion of patients with NDO and IDO remained the same. The proportion of procedures performed under LA increased from 20% to 59%. This increase in LA procedures was in line with the development of an outpatient based service. Pre-operative protocols designed following results from the initial audit were implemented. This included the introduction of a mandatory pre-operative mid-stream urine for culture two weeks prior to the procedure. This identified 10 patients with a pre-operative positive urine culture. 70% of these positive cultures were growths of Coliform species. These patients were treated appropriately according to the available antibiotic sensitivities and the procedure was postponed until a repeat culture showed no bacteriuria. The new changes also included commencing patients on a 1 month course of low dose antibiotic prophylaxis if they had a history of 3 or more proven UTI within the prior 12 months. This policy was implemented for 5 of the 41 patients, 12.2%. Every patient underwent a urine dipstick test of their urine on the day of the procedure. This extra step, which was added following the initial audit, identified 1 patient who had a positive urine dip in addition to UTI symptoms and this patient's procedure was therefore postponed until treatment completion and until a further negative urine culture was obtained.

Eight of the 41 patients included in the re-audit had a proven post-op UTI, which was defined as UTI symptoms and a positive urine culture (>10^5 CFU/ml). This showed a reduction in our UTI incidence from 33% to 20%. The main organisms grown were Coliforms (62%). The trimethoprim resistance rate found in the re-audit was 43%, compared to 57% in the initial study. The culture proven symptomatic UTI rate in this cohort was interestingly unaffected by CISC or by being in the IDO or NDO groups.

Discussion

Given the increasing popularity of intradetrusor onabotulinumtoxinA injections it is essential that the safety profile is optimised. UTI following this procedure is a recognised complication. To the best of our knowledge there are no current guidelines determining which antibiotic prophylaxis to use, despite literature suggesting that antibiotic cover is deemed necessary.

The UTI rate following intradetrusor onabotulinumtoxinA injections in the initial audit was 33%. The rate of UTI was found to be higher following procedures completed under LA. These patients were given a different pre-procedure antibiotic. There was no statistical difference in the incidence of infections according to patient gender or by aetiology of the detrusor overactivity. These results were also seen in the data from the re-audit.

The initial results from this study found that CISC may be associated with developing UTI following intradetrusor onabotulinumtoxinA injections. There are however many confounding factors amongst these patients that were not studied. There is currently no consensus on what represents a significant post void residual or when CISC should be started. Revising the technique of patients using CISC to ensure a clean non-touch technique of self-catheterisation could also be a useful tool to try to reduce symptomatic infections.

Gentamicin is a commonly used induction antibiotic in urology and this study found it to have the highest sensitivity to all isolates. However, at the time of these procedures there was a concern that aminoglycosides may theoretically potentiate the neuromuscular activity of onabotulinumtoxinA and it was therefore felt to be best avoided from our protocol. Furthermore, because an increasing number of intradetrusor onabotulinumtoxinA injections are completed under LA in the outpatient setting, an oral antibiotic was thought to be more appropriate.

During the re-audit only a small number of cases were completed under GA, as this was limited to those patients who cannot tolerate the procedure under LA. These patients received a single dose of IV cefuroxime 1.5 g at induction. The sensitivities of all isolates to cephalosporins were deemed acceptable.

This study showed a resistance rate against all isolates to trimethoprim of 57%. We recognise that this is a very high rate of resistance to what was previously our standard antibiotic prophylaxis for LA procedures and as a department we have discussed that this could have been recognised earlier, for example by an earlier audit. With this knowledge of the local bacterial resistance profiles several changes were made. The resistance rate to trimethoprim goes some way to explain the higher incidence of UTI following LA procedures compared to GA procedures who received IV Cefuroxime pre-operatively. The timing of administration of the antibiotic was not altered after the audit, however the time to maximum serum concentration following oral administration of co-amoxiclav is less than that for trimethoprim, which could be a contributing factor to the reduced rates of UTI observed. We propose that antibiotic prophylaxis should be adapted in accordance with local ecology, but that it should be active against *E.Coli* the most common organism grown.

Limitations of the study

Asymptomatic bacteriuria

The diagnosis of UTI can be challenging in this patient group, as symptoms of infection such as haematuria and dysuria are also recognised symptoms following intradetrusor onabotulinumtoxinA injections. For this reason we used urine cultures to determine infection together with records of patient symptoms. A limitation of our study is that we may have over diagnosed UTI through identifying Asymptomatic Bacteriuria (ASB). Information regarding symptoms was collected retrospectively and as such may not have been accurately recorded. Our rates of UTI were found to be very high at 33% and overdiagnosis of UTI with ASB is likely a contributing factor to this. Conversely, our laboratory diagnosis of a positive urine culture uses a cut off point of ≥10^5 CFU/ml, therefore we may have underdiagnosed UTI in some patients if they had bacteriuria below this CFU cut-off criteria.

We have only collected data from the urine cultures which were positive for infection. It would have been interesting to have recorded results for all urine cultures sent from all patients in the 6 months' timeframe, regardless of the result, to see what proportion of all patients had a urine culture sent. Given that most of our patients live locally to the hospital, we expect that the majority of urine culture results were available to review.

A further limitation of this study is that we do not know the proportion of urine cultures that were sent from planned follow up,

versus those sent unplanned from the emergency department or GP. However, it may be reasonable to assume that the majority were sent from the latter due to the patient presenting with symptoms. There is a recent systematic review published in European Urology Focus in August 2021 regarding the challenges of defining UTI. It concludes that specific definitions for UTI using both clinical and laboratory criteria used for large clinical studies are heterogeneous. The review concludes that a generally accepted UTI definition for neurourological patients is urgently needed.[XIV] It is difficult to compare our UTI rates with other studies given the differences in criteria and methodology. However, a key point of our study was comparing the rates of UTI within our different patient groups, both before and after our implemented changes. We were therefore able to use the same criteria throughout.

The data for the re-audit following implementation of our changes was collected prospectively by one clinician. It is likely that in part the notable decrease in post-procedure UTI rates for those patients in the re-audit may be due to more comprehensive recording of information regarding patient symptoms. Possible reasons for this improvement in documentation could be due to the clinician's heightened awareness of the recent changes in protocol and the knowledge that the new process would be audited. Urine cultures were only sent by the urologist if the patient was symptomatic, as such, there may have been less asymptomatic bacteriuria mistakenly recorded as UTI, unlike in the first loop of the audit review where all information was collected retrospectively. This is a recognised limitation of our study. Urine cultures sent by the emergency department and GP from both audit cycles were not influenced by the urologist and in the re-audit urine cultures could still have been sent if the patient had no urinary symptoms, for example if they presented with an alternative complaint.

Study size and patient group

Our study is limited by its small size and the retrospective nature of the data collection. The information gathering was limited by the follow up letters available. We recognise that we did not have access to all midstream urine (MSU) results sent by general practitioners within the community and as such it is possible that there is missing urine culture data. Urine samples sent from general practices within proximity to the hospital are processed through our laboratories and therefore it is likely that only a small proportion of MSU results for our patients were not available.

A further limitation of this study is the heterogeneity of the patient group. The small patient size had a mixture of NDO and IDO, those that were already established on CISC and those that were not. In addition, there was a mixture of LA and GA procedures. We also did not record patient's other co-morbidities, such as diabetes or history of prior UTI which could also alter their susceptibility to further infections. This heterogeneity results in multiple confounding factors which could have affected our results in ways that we were not able to determine or measure.

In this study we did not look at the effectiveness of the procedure itself, or whether having bacteriuria pre-operatively impacted the effectiveness of the treatment.

Clean intermittent self catheterisation

Our results show a higher risk for developing UTI amongst those patients using CISC. Although CISC may be a risk factor for developing UTI, we recognise that there may also be unknown confounding factors amongst this patient cohort which could increase their susceptibility to infections which were not studied. Furthermore, higher rates of ASB amongst patients using CISC may not have a clinical impact for them.

The rates of use of CISC following injections with onabotulinumtoxinA varies considerably. A systematic review published in 2018 in a Brazilian journal had secondary endpoints which looked at rates of CISC and UTI after 100 units of onabotulinumtoxinA.[XV] Urinary retention was the main complication reported in the studies. They found the incidence of CISC ranged from 0-72% which was dose dependent and dependent on the definition used for retention; commonly the presence of post-void residual ≥200 mL. The need for intermittent catheterisation at the 100 units dose ranged from 6.9–30%. The lower figures for CISC rates were in a paper where the study used 350ml residual as the cut off to instigate CISC.

Time interval

We looked at urine cultures and reviewed patient letters for a period of 6 months following each procedure. This time frame was decided by the clinicians designing the study to allow us to review the incidence of UTI in the longer term post-operative period for our patients. This longer timescale was of interest to us as it is an area which has not been as closely reviewed in the literature and can impact our patients. There may be other factors affecting the patient and their susceptibility within that 6-month time frame which were not studied. Many patients had multiple procedures, however we did not look at the time interval between each of these. A further element we could study would be to look at the time interval between patient's treatments and whether this impacted the overall rates of symptomatic UTI post-procedure.

Conclusions

In conclusion, our initial study found that the UTI rate following intradetrusor onabotulinumtoxinA injections within our trust was 33%. With the change of antibiotic prophylaxis, use of pre-operative urine cultures and the introduction of a urine dipstick test on the day, this rate has fallen to 20%. The fall in post-procedure UTI symptoms is likely to be clinically significant to our patients who undergo these procedures on a regular basis. This study has been very useful on a local level and has helped with tailoring our antibiotic prophylaxis to local pathogens. It has also demonstrated the importance of audit of antimicrobial resistance patterns and how subsequent adjustments to prescribing guidelines can improve outcomes for patients.

Symptomatic UTI are a debilitating adverse event of intradetrusor onabotulinumtoxinA and require prospective studies to determine which prophylactic antibiotics are of benefit in this cohort, with due consideration to local bacterial resistance patterns and antibiotic stewardship.

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