Beyond the cloudiness in urinary tract infection: definitions, diagnostics, and strategies for prevention

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Part III

Alternative prophylactic and treatment strategie

Chapter 6

Intravesical aminoglycoside instillations as prophylaxis for recurrent urinary tract infection: patient satisfaction, long-term safety and efficacy

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JAC Antimicrob Resist. 2023 Apr 6;5(2):dlad040

Abstract

Background

Recurrent urinary tract infections (UTI) are common, especially in women. When oral antimicrobial prophylaxis is ineffective or not possible due to allergies or antimicrobial resistance, intravesical aminoglycoside instillations (IAI) are a non-systemic alternative.

Objectives

To assess treatment satisfaction, long-term safety and efficacy of IAI for recurrent UTI.

Methods

We conducted a cohort study using data collected between January 2013 and June 2022 at the Leiden University Medical Center. Adult patients with recurrent UTI who received prophylactic IAI were eligible for inclusion. Treatment satisfaction was assessed through a survey. Data on serum aminoglycoside concentrations, cystoscopy results, and number of recurrences were obtained through chart review. Number of recurrences and UTI characteristics were compared between patients on and off IAI using Poisson and logistic mixed effects models.

Results

Forty-four patients were included (median follow-up time 976 days) and 323 UTIs occurred during follow-up. Overall treatment satisfaction was high (median 79.2/100). All but one patient had undetectable serum aminoglycoside levels and no malignancies were found on follow-up cystoscopy. IAI increased the time to first recurrence (102 days versus 36 days, p = 0.02), reduced the number of recurrences (RR 0.75, 95%CI 0.56 – 0.99, p = 0.04), and the necessity for systemic antibiotics (OR 0.33, 95%CI 0.13 – 0.86, p = 0.02).

Conclusions

In patients with recurrent UTI, IAI was associated with high treatment satisfaction, and was found to be a safe and effective alternative to oral antimicrobial prophylaxis.

Introduction

Recurrent urinary tract infection (UTI) refers to at least three episodes per year or two episodes per 6 months. [1] While morbidity of a single UTI is low, the high incidence and recurrence risk lead to considerable healthcare costs and a reduced quality of life. [2, 3] In patients with high recurrence rates despite behavioural modifications and non-antimicrobial prophylaxis, oral antimicrobial prophylaxis is often initiated. Continuous antimicrobial prophylaxis reduces recurrence risk, including in patients who perform clean intermittent catheterisation (CIC). [4, 5] However, an important disadvantage of continuous oral antimicrobial prophylaxis is the emergence of resistant pathogens, limiting treatment options. [5, 6] This is especially relevant for patients with an increased risk of infections with multidrug resistant organisms (MDRO), e.g. patients with neurogenic bladder and kidney transplant recipients. [7, 8] In addition to antimicrobial resistance (AMR), allergies and side effects may preclude oral antimicrobial prophylaxis as a viable treatment strategy for recurrent UTI. [9]

In an era where AMR is a rising threat to global health, direct instillation of antibiotics in the bladder may be an appealing alternative to systemic antimicrobial prophylaxis. [10] With intravesical aminoglycoside instillations (IAI), high concentrations of aminoglycosides – which exhibit concentration-dependent killing – are achieved in the bladder. Consequently, uropathogens without high-level aminoglycoside resistance can still be treated with IAI as concentrations in the bladder exceed MIC breakpoints. [11] Systemic uptake of aminoglycosides is rare, diminishing the concern for nephrotoxicity and ototoxicity. [11] As aminoglycosides stay in the bladder, it is hypothesised that the commensal flora of the gut, perineum and vagina may remain unaffected. In fact, Stalenhoef et al. [11] showed a reduction in MDRO UTIs, possibly also explained by a decrease in overall systemic antibiotic use. [12] Treatment satisfaction has not yet been assessed with validated tools. Evaluating treatment satisfaction is particularly relevant for patients receiving IAI, as it is more invasive than other prophylactic alternatives, and treatment satisfaction influences treatment-related behaviour (adherence and persistence), ultimately affecting treatment success. [13] Since the study by Stalenhoef et al. [11], the Leiden University Medical Center (LUMC) has implemented IAI in an increasing number of outpatients with recurrent UTI, most of them continuing IAI after 6 months. As a consequence, more long-term data have become available. The aim of this study is to assess treatment satisfaction, long-term safety and efficacy of IAI in patients with recurrent UTI.

Methods

We conducted a cohort study using data collected between January 2013 and June 2022 in our tertiary care hospital for assessment of long-term safety and efficacy. Treatment satisfaction was assessed through a cross-sectional survey (May 2022). This study was approved by the regional ethics committee (METC-LDD) and all patients provided written informed consent for the use of their data and survey participation. This study was registered at clinicaltrials.gov (NCT05376670).

Study population

Adult recurrent UTI patients who were on continuous or postcoital IAI were eligible for inclusion. Patients exclusively using IAI for on-demand treatment of recurrences (no prophylaxis) were excluded. Moreover, we excluded patients receiving IAI for chronic prostatitis and patients with an indwelling catheter. Patients with multiple treatment cycles (on and off IAI) acted as their own controls.

IAI treatment protocol

Patients received training for CIC and the preparation of the solution by a specialised nurse. They were instructed to mix 80 mg of gentamicin with 20 mL of 0.9% sodium chloride (tobramycin 80 mg or amikacin 250 mg were chosen in case of infections with a gentamicin-resistant pathogen within the preceding 6 months). To increase bladder time, patients were advised to administer the solution before bedtime. The standard treatment regimen consisted of daily instillations for 2 weeks, every other day for 10 weeks, and twice weekly for 12 weeks. In case of new-onset lower urinary tract symptoms (LUTS), daily instillations were reinitiated for 5-7 days if signs of systemic infection were absent. If LUTS persisted or systemic signs were present, oral or intravenous antibiotics were started. Patients were instructed to directly contact the outpatient clinic instead of their general practitioner for all new-onset symptoms, regardless of whether they were on IAI at that time. After 6 months of IAI, discontinuation of treatment was discussed with all patients. If treatment was continued, IAI frequency was individualised and based on recurrence rate. Serum aminoglycoside levels were measured in the first month, after an overnight instillation. Cystoscopy was performed every two years.

Data collection

Clinical data were collected from electronic records and included baseline demographics, comorbidities, other prophylactic measures, and previous MDRO UTIs. For safety endpoints we collected cystoscopy and serum aminoglycoside data. To establish efficacy, we recorded the number of recurrences during follow-up. For each UTI, additional information was collected on LUTS, fever (temperature ≥ 38.0 ºC), microbiological results, hospital admission and treatment.

We defined UTI as an episode with new-onset symptoms that was diagnosed as a UTI by a physician and was treated with an antimicrobial agent. Dysuria, frequency, urgency and suprapubic pain were classified as LUTS, other non-genitourinary symptoms were classified as 'non-specific symptoms'. Both conversion to daily IAI and oral/intravenous antibiotics were considered treatment. We considered ESBL and carbapenemase-producing Enterobacterales, Enterobacterales with combined fluoroquinolone and aminoglycoside resistance, and vancomycin-resistant enterococci as MDRO. MIC-breakpoints for resistance and intermediate sensitivity were based on EUCAST-criteria. [14]

Treatment satisfaction

Treatment satisfaction was only assessed in patients who were on IAI at the time of data collection or had been using IAI no longer than one year before the start of data collection. Treatment satisfaction was assessed through a linguistically-validated Dutch version of the Treatment Satisfaction Questionnaire for Medication-version II (TSQM-II) in a paper format. [15] Permission was obtained from IQVIA Inc. (One IMS Drive, Plymouth Meeting, PA-19462). The TSQM-II consists of 11 questions, divided into four domains: effectiveness, side effects, convenience, and global satisfaction. Scores are calculated by adding items in each domain and transforming the composite score into a value ranging from 0 to 100, where a score of 100 corresponds with the highest degree of satisfaction. For the side effects domain, a score of 100 indicates an absence of side effects.

Statistical analysis

Statistical analysis was performed using SPSS version 27.0 (IBM, Armonk, USA) and R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). Data are presented as percentages, means with standard deviations, or medians with IQR based on the type and distribution of the data. To compare UTI characteristics

between patients on and off IAI, a logistic mixed effects model with a varying intercept per patient was used, to take dependencies between observations (recurrences) per patient into account. The Kaplan-Meier method was used to estimate time to first UTI recurrence; results were graphically displayed and compared between patients on IAI and after cessation of IAI using a log-rank test. In case of multiple IAI cycles, only the first IAI cycle was included in the Kaplan-Meier analysis. To compare the incidence of UTI episodes between patients on and off IAI, a Poisson mixed effects model was used (with random intercept per patient). As the duration of treatment cycles markedly varied, 'duration' was log-transformed and included as an offset in the model. For the Poisson model, we assumed that risk of recurrence was constant over time. Since this assumption may not hold true, we performed a sensitivity analysis in which these data were analysed using a Cox frailty model. Prior to data analysis, sample size was calculated for treatment satisfaction. To estimate the mean overall score on the TSQM-II questionnaire with a margin of error indicated by a 95% CI not wider than 20, a sample size of 25 patients was required, given the expected population standard deviation of 25.4. [5] Subgroup analyses were performed based on gender, menopausal status, history of kidney transplantation, and history of CIC prior to IAI. To determine whether effects of IAI treatment differed between subgroups, Poisson mixed effects models with interaction terms were applied.

Results

Patient characteristics

In total, 44 patients were included (inclusion flowchart in **Supplementary Figure 1**). Patient characteristics are outlined in **Table 1**. Most patients in our cohort were postmenopausal women receiving IAI due to failure of oral antimicrobial prophylaxis (57%) or the lack of oral options due to AMR (36%). Twenty-eight patients (68%) were already performing CIC prior to the initiation of IAI and 11 patients (25%) had a history of kidney transplantation. Median follow-up duration was 976 days (IQR 468 – 1637) and median number of IAI days was 602 (IQR 402 – 1212).

Treatment satisfaction and (dis)continuation

At 6 months, 80% of patients wished to continue IAI, because of fewer recurrences and an increased quality of life (self-reported). Two patients discontinued after 6-months due to insufficient efficacy, and one patient was switched to oral

Table 1: Baseline characteristics of patients with recurrent UTI starting IAI.

Baseline characteristics	**n = 44**
Age in years	61.9 (14)
Female	31 (71)
Postmenopausal	25/31 (81)
Sexually active	13/21 (62)
Comorbidity	
Previous CIC	28 (68)
Underactive/neurogenic bladder (including spina bifida)	27 (61)
Kidney transplantation	11 (25)
Urethral dilation/meatal dilation/urethrotomy	10 (23)
Diabetes mellitus	8 (18)
Cystocele/rectocele	7 (16)
Nephrectomy	5 (11)
TURP	5 (11)
ADPKD	3 (7)
Urolithiasis	3 (7)
Urological malignancy	0
eGFR mL/min/1.73 m2 prior to start of IAI	
≥ 90	12 (27)
60 – 89	21 (48)
45 – 59	4 (9)
30 – 44	3 (7)
15 – 29	4 (9)
Non-antimicrobial prophylaxis	
Vaginal oestrogen	22/31 (71)
D-mannose	13 (30)
Non-antibiotic irrigations	11 (25)
UTI caused by MDRO in 6 months before IAI	17 (39)
Indication for IAI	
Oral prophylaxis not efficacious	25 (57)
No oral options due to resistance	16 (36)
No oral options due to intolerance	15 (34)
No oral options due to allergy	4 (9)
Other reason	6 (14)
Frequency of IAI at last follow-up	
Daily	7 (16)
Every other day	10 (23)
Twice weekly	13 (30)
No IAI at last follow-up	14 (32)

Age is expressed as mean (SD); all other variables are expressed as n (%). Sexual activity was not reported for 10 women. Other reasons for initiation of IAI: patient preferred IAI over oral prophylaxis, patient already did CIC and had recurrent urinary tract infections. Abbreviations: IAI = intravesical aminoglycoside instillations, CIC = clean intermittent catheterisation, TURP = transurethral resection of the prostate, ADPKD = autosomal dominant polycystic kidney disease, eGFR = estimated glomerular filtration rate, MDRO = multidrug resistant organism.

prophylaxis because resistance to oral antimicrobial therapy was lost. Of the 26 patients that discontinued IAI at some point during follow-up, 18 (69%) restarted IAI. The TSQM-II was filled out by 32 patients (73%), and results are summarised in **Figure 1**. Median scores of the four domains were: global satisfaction 79.2 (IQR 66.7 – 100.0), effectiveness 83.3 (IQR 66.7 – 97.9), side effects 100.0 (IQR 100.0 – 100.0), and convenience 69.4 (IQR 61.1 – 83.3). Two patients completing the questionnaire reported side effects, being painful CIC. Global satisfaction was higher for patients who were already performing CIC before initiation of IAI compared to patients who did not have prior experience with CIC (median score 83.3 versus 58.3, p = 0.03). Discontinuation rates and TSQM-scores did not differ for the specified subgroups (data not shown).

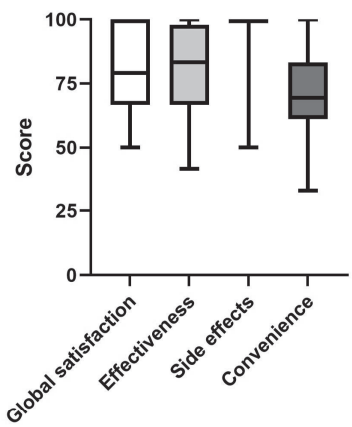

Figure 1: Box and whiskers plot of Treatment Satisfaction Questionnaire for Medication version II (TSQM-II) scores in patients with current or recent IAI treatment (n = 32). Median values are represented by the black line within the boxes; the median value of the side effects domain was 100.

Safety

Cystoscopy was performed in 29 patients (66%) after a median of 768 days (IQR 363 – 1327) since the start of IAI. No malignancies were found. Other cystoscopy findings included bladder trabeculation (n = 6), diverticula (n = 3) and cystitis cystica/glandularis (n = 2). Serum aminoglycoside levels were available for 40 patients (91%). All but one patient had undetectable serum aminoglycoside levels. The patient with a detectable aminoglycoside level (serum tobramycin 0.5 mg/L) had macroscopic haematuria (due to a recent bladder biopsy for a suspected fungal cystitis) at the time of measurement.

Efficacy

Recurrences and antimicrobial consumption

In total, 323 UTIs (207 during IAI prophylaxis, 116 after IAI prophylaxis) were reported in 44 patients. UTI characteristics are outlined in **Table 2**. LUTS were present in 209/268 (78.0%) episodes and fever in 44/323 (13.6%) episodes. Median time to first recurrence was longer for patients on IAI compared to after cessation of IAI (102 days versus 36 days, p = 0.02), as summarised in **Figure 2**. Moreover, IAI significantly decreased the number of recurrences (rate ratio 0.75, 95%CI 0.56 – 0.99, p = 0.04). A positive effect of IAI was also consistently seen in various Cox frailty models (**Supplementary Table 1**). In patients on IAI, 75.2% of recurrences were treated with systemic (oral or intravenous) antibiotics, compared to 92.2% of recurrences after cessation of IAI (OR 0.33, 95%CI 0.13 – 0.86, p = 0.02).

Table 2: Characteristics and treatment of UTIs in patients with IAI and after cessation of IAI.

	IAI n (%)	No IAI n (%)	OR (95%CI)	p-value
New-onset LUTS	122/169 (72.2)	87/99 (87.9)	0.43 (0.16 – 1.18)	0.10
Fever	30/207 (14.5)	14/116 (12.1)	1.23 (0.45 – 3.34)	0.68
UTI caused by classic GNR	101/164 (61.6)	75/102 (73.5)	0.66 (0.31 – 1.43)	0.29
UTI caused by enterococci	26/164 (15.9)	5/102 (4.9)	4.45 (1.40 – 12.88)	0.01
MDRO (including ESBL)	22/155 (14.2)	18/99 (18.2)	0.78 (0.28 – 2.19)	0.64
Hospital admission	30/206 (14.6)	10/116 (8.6)	1.09 (0.34 – 3.56)	0.88
Necessity for systemic (oral/ intravenous) antibiotics	155/206 (75.2)	107/116 (92.2)	0.33 (0.13 – 0.86)	0.02

E. coli, *Proteus mirabilis* and *Klebsiella pneumoniae* were defined as classic Gram-negative rods. Missing data: new-onset LUTS (n = 55), hospital admission (n = 1), necessity for systemic antibiotics (n = 1). In 54 UTI episodes, no urine culture was performed. Odds ratios were calculated using a logistic mixed effects model with a varying intercept per patient. Abbreviations: OR = odds ratio, 95%CI = 95% confidence interval, UTI = urinary tract infection, LUTS = lower urinary tract symptoms, GNR = Gram-negative rods, MDRO = multi-drug resistant organism, ESBL = extended spectrum beta-lactamase.

The results of the subgroup analyses are provided in **Supplementary Table 2**. In the subgroup of women, the time to first recurrence was 98 versus 23 days, p = 0.02 and the rate ratio of recurrences was 0.59 (95%CI 0.43 – 0.81, p = 0.001).

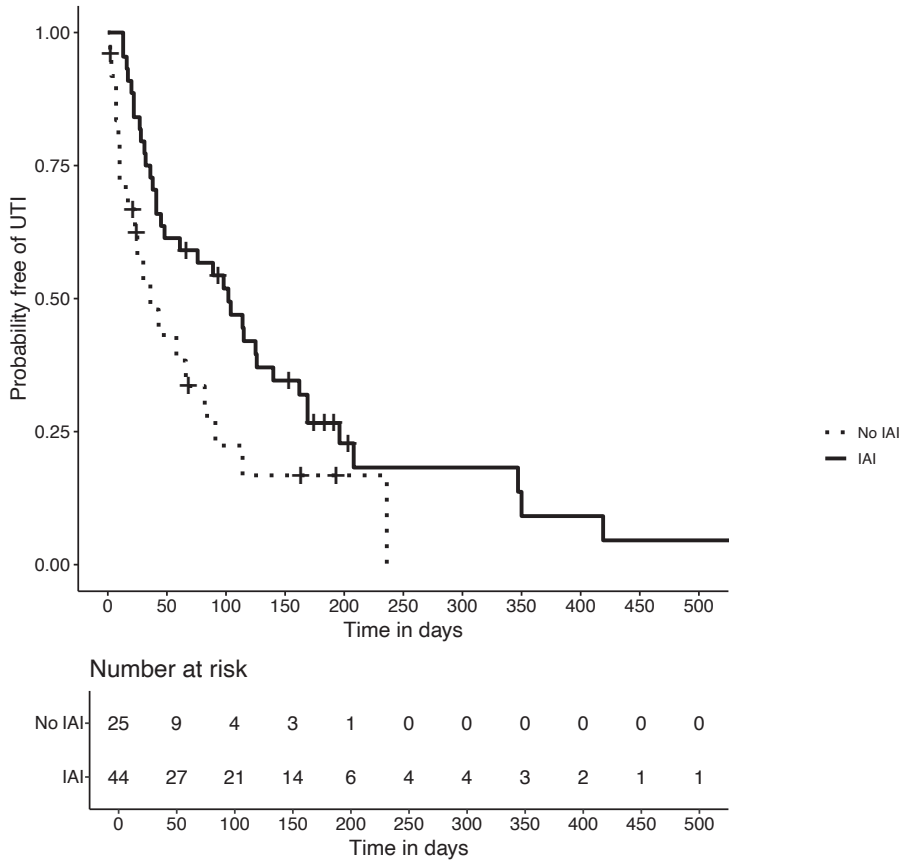

Figure 2: Kaplan-Meier curve of time to first recurrence (UTI) in patients with IAI and after cessation of IAI. Patients on IAI treatment are indicated by the solid line, and patients that have stopped IAI by the dotted line. Abbreviations: IAI = intravesical aminoglycoside instillations.

Microbiological characteristics

A urine culture was performed in 267 episodes (82.7%). In 216 cases (80.9%) a single uropathogen was found, while in 20 cases (7.5%) two uropathogens, in 21 cases (7.9%) mixed flora, and in 10 cases (3.7%) no uropathogens were found. Recurrences that occurred during IAI were more often caused by enterococci than recurrences that occurred after cessation of IAI (OR 4.45, 95%CI 1.40 – 12.88, p = 0.01). No differences were found in the same comparison for classic Gram-negative rods (*E. coli, Klebsiella pneumoniae,* and *Proteus mirabilis*). In the 6 months before initiation of IAI, 17 patients had a UTI caused by an MDRO (5 were aminoglycoside

resistant). Three of these 17 patients experienced a recurrence with the same MDRO in the 6 months after initiation of IAI.

Sensitivity analysis

Eight patients (18%) in our study had also participated in the study by Stalenhoef et al.[11] Including only the remaining 36 patients (82%) in our Poisson model produced a rate ratio of 0.75 (95%CI 0.53 – 1.05). Furthermore, results of our logistic mixed effects model were not affected by missing clinical and microbiological data (**Supplementary Table 3**).

Discussion

In patients with recurrent UTI, IAI is associated with high treatment satisfaction and continuation rates, and it appears to be a safe and effective alternative to oral antimicrobial prophylaxis.

Treatment satisfaction

Thus far, treatment satisfaction for IAI has not been assessed with a validated questionnaire. Stalenhoef et al. [11] requested patients to grade their satisfaction by providing a score between 0 and 10 and found a mean score of 8 (SD 1.2) after 24 weeks of IAI. This score is similar to the overall satisfaction score that was found in our study (median 79.2 out of 100). However, an overall score does not give insight into the different domains of treatment satisfaction. The highest satisfaction scores were observed in the 'effectiveness' and 'side-effects' domains. In fact, only two patients reported any side effects (painful catheterisation). Contrary to previous studies, no gastro-intestinal complaints or vaginal infections were reported. [11, 12] The validated questionnaire that we used in our study was also used in a randomised trial evaluating oral antimicrobial prophylaxis in patients with recurrent UTI and CIC use. [5] Scores for effectiveness were comparable to our IAI cohort. However, convenience scores were lower in our patients with IAI (mean 71.2, SD 16.1) compared to patients in the oral prophylaxis study (mean 88.9, SD 13.9). Lower convenience scores for IAI are unsurprising as CIC is necessary for administration of the drug. In the oral prophylaxis study, all patients were already performing CIC and questions focused on convenience of oral therapy alone.

Safety

Serum aminoglycoside levels were undetectable in all but one patient, confirming results of previous studies that systemic uptake is very rare. [11, 16-18] In treatment of non-muscle-invasive bladder cancer, systemic uptake of intravesical agents occurs more frequently in case of mucosal damage, due to recent transurethral resection, traumatic catheterisation or an active UTI. [19] In an infected rat bladder model, systemic aminoglycoside absorption was observed in 3/7 rats, but serum aminoglycoside levels were all in the non-toxic range. [20] The serum concentration that was found in one patient (0.5 mg/L) was likely related to disruption of the epithelial barrier due to recent bladder biopsies. This concentration is considered non-toxic as it falls below the usual trough levels for systemic aminoglycoside treatment. [21] We propose that routine measurement of serum aminoglycoside concentration should no longer be performed in patients using IAI, except in patients with macroscopic haematuria.

Neither in our study, nor in the study by Stalenhoef et al. [11] were malignancies found on follow-up cystoscopy. Our study had markedly longer follow-up times, with a quarter of patients having a follow-up cystoscopy more than 3.5 years after initiation of IAI. However, caution is warranted when interpreting these findings, as our sample size was relatively small, bladder cancer incidence is generally low, and the median age of our cohort lies below the median age at bladder cancer diagnosis.

Efficacy

In our study, IAI significantly reduced the number of recurrences and necessity for systemic (oral/intravenous) antibiotics. These findings are consistent with previous studies, most of them including patients with neurogenic bladder. [11, 12, 17, 22, 23] In subgroup analyses the effect of IAI seemed to be most pronounced in women, which is in contrast with the results of two previous studies that also investigated the effect of gender. [11, 22] However, caution should be applied when interpreting results of subgroup analyses, as the subgroups were small and other determinants had a skewed distribution. For instance, 54% of men were kidney transplant recipients, compared to 13% of women.

The majority of studies compared the number of recurrences in the 6 months prior to IAI to the number of recurrences in the 6 months after initiation of IAI. However, Stalenhoef et al. [11] showed that recurrence rates in the 6 months after

cessation of IAI remained low. In this study, follow-up started at the initiation of IAI and recurrence rates were compared between on and off IAI cycles, meaning that patients off IAI had already used IAI in the past. It is possible that the reduction in recurrence rate would have been even more pronounced had we compared recurrence rates between patients on IAI and prior to initiation of IAI. A comparison between self-reported recurrence rate (before IAI) to physician-reported recurrence rate was not deemed ideal. In patients receiving IAI, we observed that fewer recurrences had to be treated with systemic antibiotics. This observation underestimates the reduction of the total antibiotic burden, as recurrence rates are also lower in patients with IAI use.

It is incompletely understood which mechanisms contribute to the efficacy of IAI. Worby et al. [24] have shown that gut microbial richness is significantly lower in women with recurrent UTI. In this study, 1 in 4 recurrences were treated with daily IAI only. We hypothesise that a reduction in systemic antibiotic use (due to a decrease in recurrence rate as well as treating recurrences with IAI only) may promote a recovery of a dysbiotic gut microbiome, thereby potentially reducing recurrence risk. Another hypothesis is that IAI may eradicate intracellular bacterial reservoirs that can seed recurrent infection. [25]

Implications for clinical practice

Despite a lower recurrence rate on IAI, breakthrough infections do occur. If signs of systemic infection are absent, primary management with daily IAI is preferable, to avoid the drawbacks of systemic antimicrobials. If symptoms persist despite daily IAI, and systemic antimicrobial therapy is necessary, the different pathogen distribution among IAI-users is relevant for empirical therapy. We observed that most patients who had had a UTI caused by an MDRO in the 6 months prior to IAI did not have a recurrence with that same pathogen. Moreover, recurrences that developed during IAI prophylaxis were more frequently caused by enterococci, which is likely explained by the fact that enterococci are frequently intrinsically resistant to high levels of aminoglycosides.

Strengths and limitations

Strengths of our study include the long follow-up time, the use of a validated questionnaire to assess treatment satisfaction, and the inclusion of subgroup analyses. Furthermore, the results regarding efficacy were consistent across

different statistical approaches. Our study has several limitations. Firstly, the TSQM-II questionnaire was administered at the same time for all patients, which led to a variable timing of the questionnaire in relation to treatment duration. Most respondents were on IAI at the time of the survey, which might have led to an overestimation of treatment satisfaction. Secondly, due to the observational nature of this study we did not use an existing reference standard for UTI, which might have contributed to misclassification of UTI. However, this effect will have occurred in both 'groups' (on and off IAI) and biased results are therefore unlikely. Another limitation is the unblinded nature of this study. Finally, a limitation that is inherent to observational studies is unmeasured confounding.

Conclusion

In conclusion, IAI is a safe and effective non-systemic alternative for UTI prophylaxis with a high degree of treatment satisfaction. It should be considered in patients who fail oral antimicrobial prophylaxis or have allergies and resistance patterns that preclude oral prophylaxis as a viable strategy. Future studies should focus on elucidating the best regimen in terms of dosage and frequency.

Acknowledgements

The authors would like to thank P.H. Verbeek-Menken and I.G.A. Nellen for instructing patients on IAI use. Moreover, we thank B.E.L. Vrijsen for his valuable contribution to the statistical analysis of the data.

Funding

This study was carried out as part of routine work.

Transparency declaration

None of the authors have an association that might pose a conflict of interest.

Author contributions

Conceptualisation and methodology M.P.B., M.M.C.L., L.G.V., and R.H.H.G.; writing – original draft preparation M.P.B.; data interpretation M.P.B., M.M.C.L., L.G.V., and R.H.H.G.; writing – review and editing M.P.B, M.M.C.L., J.I.M.U., J.E.S., C.N., L.G.V.; supervision M.M.C.L. and L.G.V. All authors have read and agreed to the final version of the manuscript.

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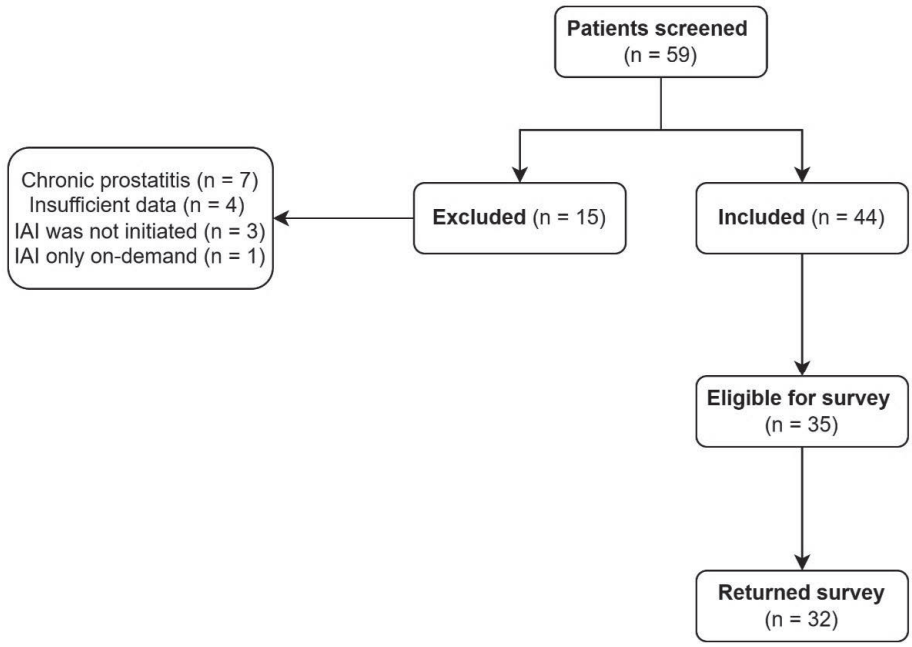
Supplement



Supplementary Figure 1: Flow chart of screening and inclusion process

Supplementary Table 1: Cox regression analysis.

	Hazard ratio (95%CI)	p-value
Cox ME model (no other variables)	0.52 (0.33 – 0.82)	0.005
Cox ME model (including age, gender, and oral prophylaxis)	0.50 (0.31 – 0.79)	0.003
Cox ME model (only first on and off IAI cycle)	0.36 (0.18 – 0.70)	0.003
Cox ME model (extra variable: time between second/third/ fourth IAI cycle and start of first cycle)	0.47 (0.29 – 0.77)	0.002

A mixed-effects model was used to account for multiple (dependent) observations within a patient. Cycle = one 'on' or 'off' treatment period. Abbreviations: ME = mixed effects, IAI = intravesical aminoglycoside instillations

Supplementary Table 2: Subgroup analysis for gender, menopausal status, kidney transplantation and prior CIC.

Subgroup	N	Median time to first recurrence (days)			Number of recurrences on IAI versus off IAI		Interaction term*
		On IAI	Off IAI	p-value	RR (95% CI)	p-value	p-value
Female	31	98	23	0.02	0.59 (0.43 – 0.81)	0.001	0.007
Male	13	114	74	0.90	1.66 (0.87 – 3.18)	0.13	-
Premenopausal	5	89	14	0.06	0.53 (0.25 – 1.11)	0.09	0.85
Postmenopausal	26	98	23	0.04	0.62 (0.44 – 0.87)	0.006	-
Kidney transplant	11	45	82	0.40	1.71 (0.91 – 3.19)	0.10	0.002
Prior CIC	28	104	39.5	0.10	0.82 (0.55 – 1.24)	0.35	0.59

The Kaplan-Meier method was used to estimate time to first recurrence. To compare the incidence of UTI episodes between patients on and off IAI within the stratum, a Poisson mixed effects model was used (with random intercept per patient). * Poisson mixed effects models were made with an interaction term for gender, menopausal status, kidney transplant status and prior CIC status. Menopausal status was evaluated in the stratum of women, all other interaction terms were evaluated in the entire population. Abbreviations: IAI = intravesical aminoglycoside instillations. CIC = clean intermittent catheterisation.

Supplementary Table 3: Sensitivity analysis.

	IAI n (%)	No IAI n (%)	OR (95%CI)	p-value
New-onset LUTS n (%) Not reported = LUTS	160/207 (77.3)	104/116 (89.7)	0.43 (0.18 – 1.06)	0.07
New-onset LUTS n (%) Not reported = no LUTS	122/207 (58.9)	87/116 (75.0)	0.65 (0.32 – 1.32)	0.23
UTI caused by classic gram-negative rods n (%) No culture performed, mixed flora or not reported = gram-negative rods	157/220 (71.4)	96/123(78.0)	0.82 (0.41 – 1.65)	0.58
UTI caused by classic gram-negative rods n (%) No culture performed, mixed flora or not reported = gram-negative rods	101/220 (45.9)	75/123 (61.0)	0.76 (0.41 – 1.42)	0.39
UTI caused by enterococci n (%) No culture performed, mixed flora or not reported = enterococci	82/220 (37.3)	26/123 (21.1)	2.04 (1.11 – 3.75)	0.02
UTI caused by enterococci n (%) No culture performed, mixed flora or not reported = no enterococci	26/220 (11.8)	5/123 (4.1)	3.76 (1.24 – 11.38)	0.02
MDRO/ESBL resistance n (%) No culture performed, mixed flora or not reported = resistance	78/211 (37.0)	39/120 (32.5)	1.06 (0.57 – 1.97)	0.86
MDRO/ESBL resistance n (%) No culture performed, mixed flora or not reported = no resistance	22/211 (10.4)	18/120 (15.0)	0.82 (0.30 – 2.22)	0.69
Hospital admission n (%) Not reported = hospital admission	31/207 (15.0)	10/116 (8.6)	1.13 (0.35 – 3.65)	0.84
Hospital admission n (%) Not reported = no hospital admission	30/207 (14.5)	10/116 (8.6)	1.08 (0.33 – 3.52)	0.90
Number of systemic (oral/intravenous) antibiotics n (%) Not reported = systemic antibiotics	156/207 (75.3)	107/116 (92.2)	0.33 (0.13 – 0.86)	0.02
Number of systemic (oral/intravenous) antibiotics n (%) Not reported = no systemic antibiotics	155/207 (74.9)	107/116 (92.2)	0.32 (0.13 – 0.83)	0.02

Abbreviations: LUTS = lower urinary tract symptoms, UTI = urinary tract infection, MDRO = multidrug resistant organism, ESBL = extended spectrum beta-lactamase, IAI = intravesical aminoglycoside instillations, OR = odds ratio, 95%CI = 95% confidence interval