Optimizing triage and treatment strategies in urinary tract infection

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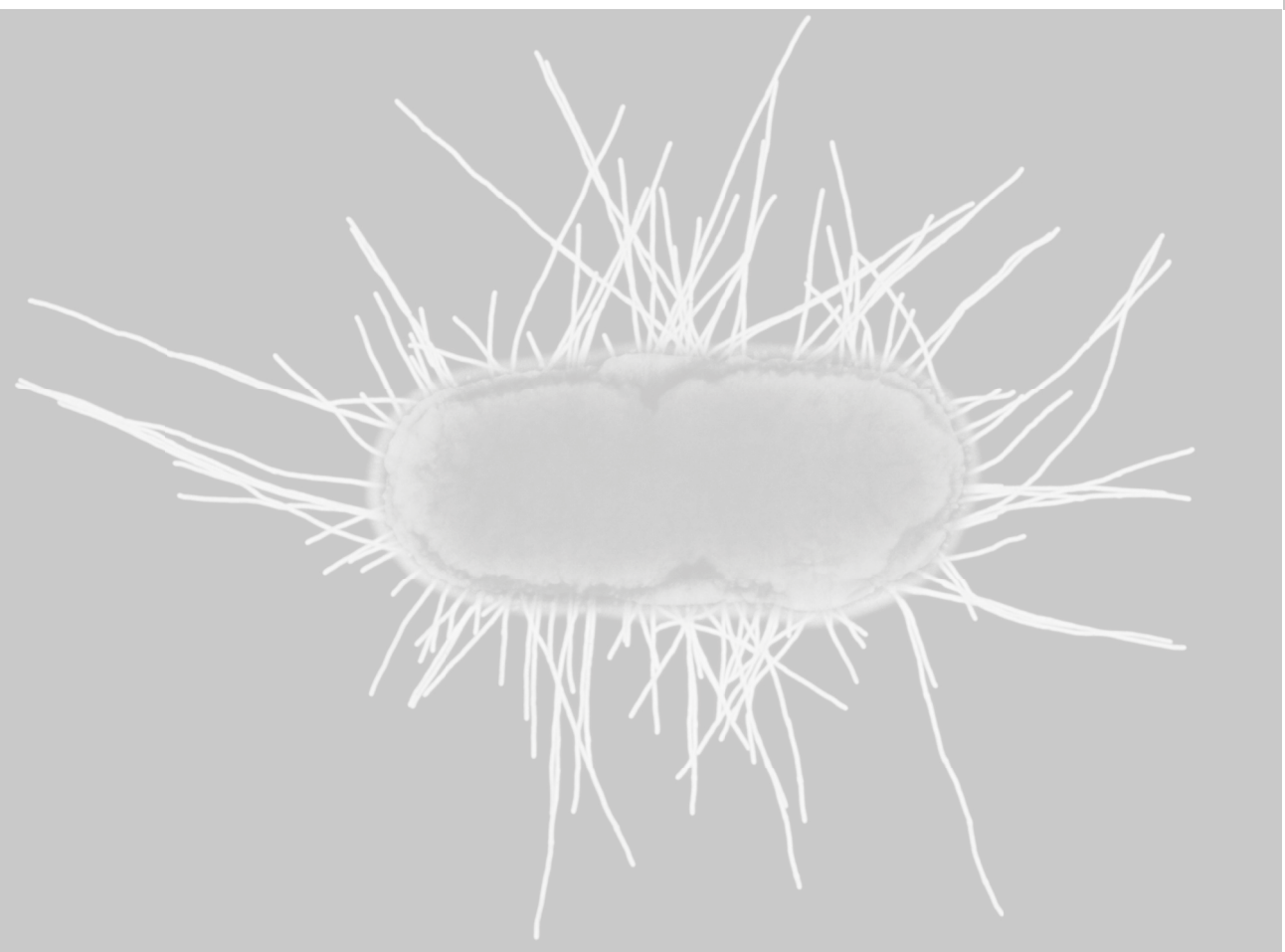

CHAPTER 6

Intravesical gentamicin treatment for recurrent urinary tract infections caused by multidrug-resistant bacteria

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ABSTRACT

Background

Antimicrobial resistance leads to complications in the management of recurrent urinary tract infections (rUTIs). In some rUTI patients with limited treatment options, intravenous therapy with reserve antibiotics is often required.

Objective

To assess the effectiveness, safety, and feasibility of prophylactic treatment with intravesical gentamicin in patients with refractory rUTI caused by multidrug-resistant (MDR) microorganisms.
Design, setting, and participants
Prospective trial of 63 adults with rUTI caused by MDR pathogens, enrolled at one academic and one general hospital in the Netherlands between 2014 and 2017, and a retrospective analysis of 27 adults with rUTI treated with intravesical gentamicin between 2009 and 2014.

Intervention

Overnight intravesical instillations of gentamicin for 6 months. In the retrospective cohort, the frequency and duration varied (predominantly once daily).

Outcome measurements

The primary outcome was the recurrence rate of UTIs compared to that in the preceding 6 months. Secondary objectives included the assessment of the safety of intravesical gentamicin instillation and its influence on the development of antibiotic resistance in uropathogens.

Results and limitations

The mean number of UTIs during the treatment reduced from 4.8 to 1.0 in the prospective trial. The mean number of UTIs in the retrospective cohort was 0.6 during treatment. The resistance rate of the uropathogens dropped from 78% to 24%. No systemic absorption or clinically relevant side-effects were observed. Limitation: lack of a control group.

Conclusions

Intravesical gentamicin instillation reduced the number of UTI episodes and the degree of antimicrobial resistance.

Patient summary

We studied the effect of administration of gentamicin into the bladder after self-catheterisation in patients with frequent urinary tract infections caused by multidrug-resistant bacteria. The treatment reduced the incidence rates of infection and resistance to antibiotics, without relevant side-effects.

INTRODUCTION

The management of patients with recurrent urinary tract infections (rUTIs) is more complex in this era of rising antibiotic resistance.[1] Guidelines on the management of rUTI recommend the consideration of continuous antimicrobial prophylaxis after counselling, and behavioural modification has been attempted in patients without a source of bacterial persistence.[2,3] Continuous antibiotic prophylaxis reduced the number of clinical and microbiological recurrences in healthy, young women with rUTI in trials conducted in the 80s and 90s, when the resistance rates were considerably lower.[4]

Nowadays, patients are often refractory to the above-mentioned measures, as the availability of oral antibiotic agents is either limited or absent due to resistance, allergies or side-effects.[1] The use of systemic antimicrobial prophylaxis augments the emergence of resistant organisms, further limiting the antimicrobial treatment options.[5,6] Particularly, in patients with complex urological histories, such as those with neurogenic bladder disorders necessitating intermittent catheterisation and renal transplant recipients, the spectrum of uropathogens and their sensitivity patterns differ from those of the general population.[5,7] In rUTI patients with limited treatment options, intravenous therapy with reserve antibiotics is often required, which affects health-related costs and the quality of life.

Intravesical treatment with gentamicin may be a reasonable treatment option for rUTIs in some patients.[8] Aminoglycosides have concentration-dependent antimicrobial activity and by direct intravesical instillation, high concentrations can be achieved at the site of infection, well (>10 times) above the minimum inhibitory concentration (MIC) of even uropathogens with lower susceptibilities. Antimicrobial resistance is unlikely to occur in the urinary tract due to high urinary drug concentrations and a lack of selective antibiotic pressure on the commensal flora at other sites of the body including the intestines, perineum and vagina. With the local use of gentamicin, the recovery of this commensal flora may even lead to the clearance of multidrug-resistant (MDR) microorganisms. Concerns regarding systemic uptake and, therefore, the side-effects associated with parenterally administered aminoglycosides (nephrotoxicity and ototoxicity) are minimal, although long-term data are lacking.[8,9]

This prospective study aimed to assess the effectiveness, safety, and feasibility of treatment with intravesical gentamicin in patients with refractory rUTI. Furthermore, we described a retrospective cohort of patients treated with intravesical gentamicin. These data were combined as the treatment and follow-up were almost similar to those in the prospective trial.

MATERIAL AND METHODS

Design and study population

Competent adults with a history of rUTI were recruited from the Leiden University Medical Center (LUMC) and the Haga Teaching Hospital, the Netherlands, after referral by urologists from across the Netherlands, between May 2014 and March 2017. Recurrent UTI was defined as ≥3 episodes of UTI in the last 12 months in women and ≥2 episodes of UTI in the last 12 months in men. UTIs in the preceding year were defined by self-report, but ≥1 episode of UTI had to be documented

by urine culture with the isolation of ≥10^3 CFU/mL of an identified MDR pathogen. Multidrug resistance was defined as acquired non-susceptibility to ≥1 agent in ≥3 antimicrobial classes.[10] Exclusion criteria were a glomerular filtration rate <15 ml/min, abnormalities of the upper urinary tract including the presence of urinary stones, a permanent urinary catheter, complete urinary incontinence, known hypersensitivity to gentamicin, pregnancy or lactation and a positive urinary culture for high-level gentamicin-resistant Enterobacteriaceae or enterococci (MIC >128 mg/L) in the preceding 6 months. Before enrolment, urological evaluation was performed, and modifiable behavioural practices were addressed in all patients.

The original study was designed as a randomized trial (registered at www.trialregister.nl NTR4646), but because of the lack of patients willing to participate in a randomized trial that beheld the risk of being assigned to standard treatment (oral prophylaxis) that had failed them before, the study design was converted to a prospective non-controlled trial. The study protocol, including the conversion to a non-controlled trial, was approved by the local ethical committee (#P13.254). The patients in this study provided written informed consent for the publication of their case details.

The retrospective study included a cohort of adult patients treated with intravesical gentamicin to treat rUTIs, between June 2009 and April 2014, in the infectious diseases outpatient clinic of the LUMC. All data were collected from electronic patient files.

Treatment

Patients were trained on self-catheterisation and the preparation of a gentamicin solution by a specialised nurse during outpatient clinic visits. When patients were unable to perform self-catheterisation, instillations were performed by a home-care nurse. Patients were instructed to self-administer the gentamicin solution (80 mg of gentamicin dissolved in 20 mL 0.9% sodium chloride) following self-catheterisation at bedtime, and to retain the solution in the bladder overnight until the next micturition or catheterisation.

The standard frequency of instillations was daily for 2 weeks, every other day for 10 weeks, and twice weekly for 12 weeks (total of 24 weeks).

Patients with symptomatic UTI were instructed to collect midstream urine for microscopy and culture. In patients receiving intravesical gentamicin twice weekly, the instillation frequency was intensified to once daily. After 1 week of daily instillations, the frequency, according to the regular schedule, was continued. In other cases, empirical treatment based on prior sensitivity patterns was started. Patients with febrile UTI were admitted to receive intravenous antibiotics.

UTI was defined as an episode of ≥1 urinary symptom (dysuria, frequency, urgency, suprapubic or perineal pain) and isolation of ≥10^3 CFU of uropathogens/mL in a urine culture with leukocyturia. Chronic bacterial prostatitis was presumptively diagnosed in men with rUTI with the same uropathogen and susceptibility patterns.

Assessments

Baseline data on demographic variables and clinical characteristics, and serum creatinine samples were collected, cultures of urine and rectal swabs were performed, and audiometric testing was conducted to document pre-existing hearing impairments.

Follow-up visits were scheduled at 2, 12 and 24 weeks after the start of treatment, and at 3 and 6 months after the discontinuation of the instillations. The systemic uptake of gentamicin was evaluated by measurement of serum gentamicin concentration immediately after the bladder was emptied of the instillation solution.

Serum creatinine levels, urine cultures and rectal swabs were repeated during and after treatment. The occurrence of UTIs and adverse events was documented at follow-up visits. Audiograms and ear-nose-throat consultations were ordered for patients with complaints of hearing loss or tinnitus. Follow-up cystoscopy was planned one year after the start of gentamicin instillation.

Cultures were analysed according to standard microbiological methods, as described previously [11]. Susceptibility testing was performed using the VITEK-2 system (bioMérieux, The Netherlands), and the detected gentamicin resistance was confirmed by the Etest (bioMérieux) in the available isolates. Rectal swabs were cultured on selective plates for the detection of Gram-negative bacteria and (multi)drug resistance. Resistance was defined according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines.[12]

Statistical analysis

Descriptive statistics were expressed as counts (percentages), means (standard deviation [SD]) or medians (interquartile range or range), as appropriate. Univariate analysis was performed using the Student's t-test or Mann-Whitney U test for continuous variables and chi-square tests for categorical variables. We modelled the probability of the participants being UTI-free at each time-point during the 6 months of treatment using Kaplan-Meier estimates. P-values <0.05 were considered statistically significant. SPSS software version 24.0 (SPSS Inc. Chicago, IL) was used for the statistical analysis.

RESULTS

Baseline patient characteristics

A total of 90 patients with rUTI were analysed; 63 and 27 patients participated in the prospective and retrospective studies, respectively. The patients' characteristics are outlined in Table 1. In most patients (91%), oral prophylactic antibiotics had previously failed.

A majority of the UTIs before enrolment was caused by MDR bacteria (78%) and the resistance rates for the antibiotics commonly used for UTI–nitrofurantoin (41%), ciprofloxacin (64%) and trimethoprim-sulfamethoxazole (65%)–were much higher than those in the general population (Table S1).[13] Gentamicin resistance was detected in 16% of the 80 available isolates before enrolment (available MICs are provided below Table 1).

Table 1. Patient characteristics

Patient characteristics	Prospective study n = 63	Retrospective cohort n = 27	Total n = 90
Age in years, median (IQR)	61 (53–72)	67 (56–74)	64 (53–72)
Sex – female	51 (81)	16 (59)	67 (74)
Post-menopausal	40/51 (78)	13/16 (81)	53/67 (79)
Allergy for antibiotics	32 (51)	14 (52)	46 (51)
Diabetes mellitus	14 (22)	7 (26)	21 (23)
Immunocompromised	9 (14)	6 (22)	15 (17)
eGFR (CKD-EPI), median (IQR)	81 (69–92)	82 (56–96)	82 (63–92)
Urologic history			
Intermittent catheterisation	33 (52)	20 (74)	53 (59)
Urolithiasis	5 (8)	2 (7)	7 (8)
Malignancy of urinary tract	1 (2)[§]	1 (4)[§§]	2 (2)
History of urologic surgery:			
- Kidney transplant	7 (11)	5 (18)	12 (13)
- Transurethral resection of the prostate	3 (5)	1 (4)	4 (4)
- Tension-free vaginal tape-obturator	5 (8)	0	5 (6)
- Bladder surgery	4 (6)	2 (7)	6 (7)
- Urethrotomy / meatus dilatation	5 (8)	0	5 (6)
- Neobladder	0	7 (26)	7 (8)
- Other	1 (2)[#]	3 (5)[##]	4 (4)
Cause of recurrent UTI			
Dysfunctional voiding / neurogenic bladder	31 (49)	12 (44)	43 (48)
Urethral strictures	0	1 (4)	1 (1)
Vesicoureteral reflux	0	2 (7)	2 (2)
Neobladder	0	4 (15)	4 (4)
Kidney transplant only	3 (5)	1 (4)	4 (4)
Kidney transplant + dysfunctional voiding / neurogenic bladder	3 (5)	0	3 (3)
Kidney transplant + urethral strictures	1 (2)	1 (4)	2 (2)
Kidney transplant + neobladder	0	3 (11)	3 (3)
No anatomical or structural urinary tract abnormalities	25 (40)	3 (11)	28 (31)
Suspected underlying chronic bacterial prostatitis	9/12 (75)*	4/11 (36)**	14/23 (61)
Previous antibiotic treatment			
Urinary tract infections in preceding year, mean (SD)	8.7 (3.0)	unknown	-
Urinary tract infections in preceding 6 months, mean (SD)	4.8 (1.5)	unknown	-
Patients treated with IV antibiotics for UTI in preceding year; courses mean (SD)	23 (36); 2.0 (1.5)	unknown	-
Previous oral antibiotic prophylaxis	55 (87)	27 (100)	82 (91)
Microbiology			
Causative pathogen in preceding UTI:			
- Escherichia coli	38 (60)	17 (63)	55 (61)
- Klebsiella spp.	16 (25)	5 (18)	21 (23)
- Proteus mirabilis	4 (6)	1 (4)	5 (6)
- Other bacteria	5 (8)[$]	4 (15)[$$]	9 (10)
Gentamicin-resistant pathogen in preceding UTI	8/57 (14)^	5/23 (22)^^	13/80 (16)
Multidrug-resistant pathogen in preceding UTI	49 (78)	21 (78)	70 (78)
ESBL-positive pathogen in preceding UTI	15 (24)	8 (30)	23 (26)
NDM-1-positive pathogen in preceding UTI	1 (2)	0	1 (1)
Multidrug-resistant bacteria in rectal swab	9/58 (15)	-	-

Data are presented as n (%) unless stated otherwise.
SD, standard deviation; IQR, interquartile range; UTI, urinary tract infection; eGFR, epidermal growth factor receptor; CKD-EPI, The Chronic Kidney Disease Epidemiology Collaboration; IV, intravenous; EBSL, Extended-spectrum β-lactamases; NDM-1, New Delhi metallo-β-lactamase; MIC, minimum inhibitory concentration.
[§]non-muscle invasive bladder cancer (n=1). [§§]prostate cancer (n=1).
[#]orchiectomy (n=1). [##]nephrectomy (n=1); prostatectomy + pelvic lymph node dissection (n=1); ureteral reimplantation (n=1). *participants with dysfunctional voiding/neurogenic bladder (n=6); urethral strictures (n=1); benign prostatic hyperplasia (n=2). **participants with dysfunctional voiding / neurogenic bladder (n=3); kidney transplant + urethral strictures (n=1). [$]*Enterobacter asburiae* (n=1), *Morganella morganii* (n=1), *Providencia rettgeri* (n=1), *Stenotrophomonas maltophilia* (n=1), *Aerococcus* sp. (n=1). [$$]*Pseudomonas aeruginosa* (n=2), *Enterococcus faecalis* (n=1), *Citrobacter freundii* (n=1). ^MIC 16 mg/L (n=1); MIC 32 mg/L (n=2); MIC 256 mg/L (n=1); resistant: MIC >4 mg/L (n=4). ^^Intermediate: MIC 2-4 mg/L (n=2); resistant: MIC >4 mg/L (n=3).

Details on intravesical treatment

In the prospective study, 57% (n=36) of the patients were treated exactly according to the treatment protocol. In the other patients, circumstances such as the persistence of urinary complaints, treatment success (patients unwilling to stop instillations) and other patient-related factors led to an alternative duration or frequency of administration. In four patients, other aminoglycosides were used due to gentamicin resistance in the baseline cultures. The median duration of the aminoglycoside instillations was 26 weeks in both the prospective study (range 6–65) and retrospective cohort (range 6–280). Details on the treatment are provided in Table 2.

Table 2. Treatment details

Treatment details	Prospective study n = 63	Retrospective cohort n = 27	Total n=90
Self-instillation of aminoglycoside	58 (92)	22 (81)	80 (89)
Aminoglycoside used			
- Gentamicin	60 (95)	26 (96)	86 (96)
- Tobramycin	2 (3)	1 (4)	3 (3)
- Amikacin	1 (2)	0	1 (1)
Duration of aminoglycoside instillation in weeks, median (IQR)	26 (23–29)	36 (15–80)	26 (23–36)
Frequency of aminoglycoside instillations			
- Standard frequency (tapering according to protocol)	55 (87)	7 (26)	62 (69)
- Daily	4 (6)	10 (37)	14 (16)
- 2 or 3 times a week	0	10 (30)	8 (9)
Early termination			
- Due to treatment failure	7 (17)	1 (4)	8 (9)
- Other reasons (surgery, diagnostics, planned pregnancy, wrist fracture)	4 (6)	1 (4)	5 (6)
Prolonged treatment (>28 weeks)	16 (25)	16 (59)	32 (36)
Restart of aminoglycoside instillations during follow-up	20 (32)	2 (7)	22 (24)

Data are presented as n (%) unless stated otherwise. IQR, interquartile range.

Outcome

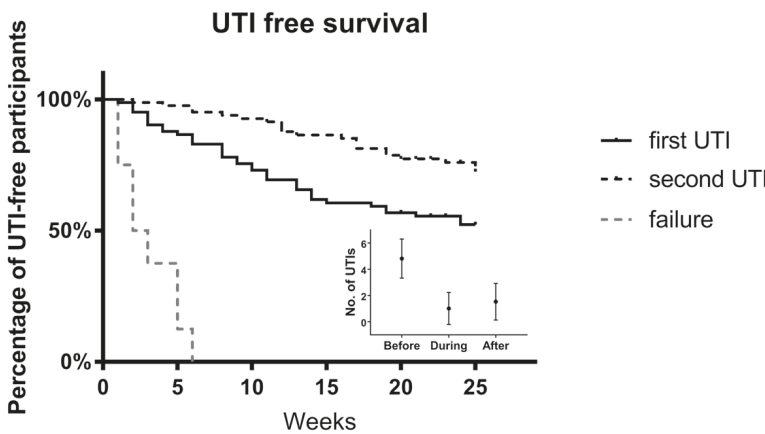
The mean number of UTIs in the prospective trial was significantly reduced to 1.2 (SD 1.3), compared to the 4.8 (SD 1.5) in the 6 months before treatment (Table 3). The mean number of culture-proven UTIs was 1.0 (SD 1.2). Twenty-six (41%) patients in the prospective trial were completely UTI-free during intravesical gentamicin treatment (Table 3). In the remaining patients, breakthrough infections (n=73 in 37 patients) during gentamicin treatment were managed by extra gentamicin instillations in 23% of the UTI episodes, oral antibiotics in 68% and intravenous treatment in 8%.

The mean number of all UTIs remained low (1.5 [SD 1.4]) after the cessation of intravesical gentamicin, and 31% of the patients remained UTI-free during the follow-up. Noteworthily, many patients (63%) continued using intravesical gentamicin off-protocol (continued prophylaxis, or restarted after experiencing one or more UTIs).

The mean number of UTIs in the retrospective cohort was 0.6 (SD 1.0) during the 6 months of gentamicin instillation, and 67% of the patients were UTI-free. Breakthrough UTIs were managed with oral antibiotics in 20/22 (91%) episodes, and intravenous treatment in 2/20 (9%) cases.

In the total population, the mean number of UTIs reduced to 1.0 (SD 1.2) during the 6 months of intravesical gentamicin treatment (Figure 1). No differences were observed between subgroups (e.g. sex, cause of rUTI, immunocompromised state). Data on the UTI-free survival during gentamicin treatment are shown in Figure 1.

Figure 1. Urinary tract infection-free survival.



Time in weeks to the first and second UTIs after the start of gentamicin instillation. Failure: early termination of gentamicin instillation because of failure (n=8).
Inset: Mean number of urinary tract infections (with standard deviation) in the 6 months before, during and after the gentamicin instillations (prospective trial and retrospective cohort combined, n=90, $p < 0.01$).
UTI, urinary tract infection

In eight patients, intravesical treatment was stopped because of clinical failure (Table 3). Three patients experienced bacteriologic failure. One man with suspected prostatitis had persistent asymptomatic bacteriuria. Two women in the retrospective cohort had persistent asymptomatic positive cultures under gentamicin instillation and were diagnosed with urolithiasis. In both cases, the cultures yielded negative results after the treatment of urolithiasis.

Details on the microbiology results are shown in Supplementary Table S1. The rate of multidrug resistance of the causative uropathogens dropped from 78% before gentamicin instillation to 24% afterwards. In the 13 patients who had UTIs caused by gentamicin-resistant bacteria, the mean number of UTIs reduced to 0.7 (SD 0.9), and one patient with chronic bacterial prostatitis (MIC 16 mg/L) experienced treatment failure.

Post-treatment, gentamicin resistance was observed in 13 patients; four patients exhibited the asymptomatic colonisation of gentamicin-resistant bacteria and nine experienced UTIs caused by gentamicin-resistant uropathogens. In three of these patients, gentamicin resistance was also observed before the start of the instillations (Table S2).

Table 3. Patient outcomes

Outcome	Prospective study n = 63	Retrospective cohort n = 27	Total n = 90
Urinary tract infections during the 6 months of instillation	n=63	n=27	n=90
All UTIs*, mean (SD)	1.2 (1.3), range 0–4	0.6 (1.0), range 0–4	1.0 (1.2), range 0–4
UTI according to protocol definition**, mean (SD)	1.0 (1.2), range 0–4	0.6 (1.1), range 0–4	0.8 (1.1), range 0–4
Patients without UTI	26 (41)	18 (67)	44 (49)
Patients without systemic antibiotics for UTI during instillations	32 (51)	18 (67)	50 (56)
UTI-free time in weeks, mean (SD)	15.2 (9.0)	18.4 (9.0)	16.1 (9.1)
Episodes of UTI	n=73	n=22	n=95
- Treated with oral antibiotics	50/73 (68)	20/22 (91)	70/95 (74)
- Treated with iv antibiotics	6/73 (8)	2/22 (9)	8/95 (8)
- Treated with extra aminoglycoside instillations only	17/73 (23)	0	17/95 (18)
Days of oral antibiotic use for UTI, mean (SD)	6.0 (8.4)	-	-
Days of IV antibiotic use for UTI, mean (SD)	0.63 (3.6)	-	-
Treatment failures			
Causes of treatment failure (early termination of instillations):	7 (11)	1 (4)	8 (9)
- Exogenous reinfections (no cause found)	2[#]	1[##]	3
- Chronic bacterial prostatitis with persistent symptoms and positive cultures with Escherichia Coli (MIC of gentamicin 16 mg/L)	2	0	2
- Persistent bacteriuria suspected for endogenous focus in the higher urinary tract (selective sampling of urine was positive in both ureters, suspicions of chronic infections of the upper urinary tract, nephrolithiasis or other causes of endogenous infection were ruled out by computed tomography)	1	0	1
- Alternative diagnosis (IC/BPS with resolution of symptoms after coagulation of Hunner's ulcer)	1	0	1
- Alternative diagnosis (female patient who had no improvement on culture-directed antibiotic treatment and reported resolution of symptoms after start of solifenacin; suggestive of overactive bladder syndrome)	1	0	1

Data are presented as n (%) unless stated otherwise. SD, standard deviation; UTI, urinary tract infection; IC/BPS, interstitial cystitis / bladder pain syndrome; MIC, minimum inhibitory concentration.
*Culture proven and non-culture proven combined. **Culture proven only. [#]Female patients with frequent breakthrough infections with different uropathogens during gentamicin instillation. [##]Male patient with recurrent UTI with different microorganisms (secondary to intermittent self-catheterisation 4–6× daily).

Safety

Systemic uptake of gentamicin did not occur, as evidenced by the undetectable serum titres around the instillations (Table 4). Two patients in the prospective study showed a temporary mild increase in the serum creatinine level, which normalised at the next follow-up visit. Three patients reported experiencing hearing loss; this was unlikely to have been related to gentamicin use, since the concentrations of serum gentamicin were undetectable (Table 4).

Follow-up cystoscopy was performed in 49% of the patients. Ten patients showed signs of cystitis/trigonitis, one patient had papillary urothelial carcinoma, and three patients had alternative diagnoses (Table 4).

Table 4. Side-effects

Side-effects	Prospective study n = 63	Retrospective cohort n = 27
Laboratory results		
Undetectable serum gentamicin levels	62/62 (100)	25/25 (100)
Increase in serum creatinine >25%	2 (3)	0
Reported side-effects		
Abdominal discomfort	3 (5)	1 (4)
Reported hearing loss	2 (3)*	1 (4)**
Reported vaginal discomfort or discharge	10/51 (20)	-
Other[#]	3 (5)	-
Patients' satisfaction with instillations		
Mean (SD) satisfaction grade after 2 weeks between 0 – 10, response rate 90%	7.5 (1.4)	-
Mean (SD) satisfaction grade after 12 weeks between 0 – 10, response rate 76%	7.9 (1.3)	-
Mean (SD) satisfaction grade after 24 weeks between 0 – 10, response rate 76%	8.0 (1.2)	-
Cystoscopy 6 months after instillations		
Cystoscopy performed	30 (48)[##]	14 (52)
Abnormalities at cystoscopy	10/21 (48)	3/14 (21)
- Hunner's ulcer	2	0
- Trigonitis	1	1
- Suspected cystitis (mucosal erythema)	5	0
- Cystitis cystica	2	1
- Low-grade papillary urothelial carcinoma	0	1

Data are presented as n (%) unless stated otherwise. SD, standard deviation.
*Patient with otitis media with effusion (n=1), patient with unchanged audiogram (n=1).
**Patient with repeatedly undetectable tobramycin levels who was also treated with intravenous vancomycin and declined a follow-up audiogram (n=1). [#]painful catheterisation (n=1); cold sensation after instillation (n=1); mild headache during first day of instillation (n=1). [##]Cystoscopy results pending (n=9), refused by patient (n=16), not performed due to the early termination of instillation or loss to follow-up (n=9).

DISCUSSION

Our study demonstrates that intravesical gentamicin is a practical, safe, and feasible prophylactic treatment option in patients with rUTIs refractory to conventional measures. The mean UTI frequency reduced by 79% during the 6 months of treatment and the use of systemic antibiotics was avoided completely in 56% of the patients during gentamicin instillation.

Treatment with gentamicin instillations had a positive effect on the antimicrobial susceptibility of the uropathogens causing breakthrough UTIs, since the percentage of MDR pathogens dropped from 78% to 24%. No increase in the number of gentamicin-resistant uropathogens was observed. The observed decrease in the antibiotic resistance in the breakthrough UTIs after the start of gentamicin instillations may be attributed to the decrease in the overall oral antibiotic use. Breakthrough infections were managed by extra gentamicin instillations in nearly a quarter of the UTI episodes, and because of lower antimicrobial resistance, the majority of UTI episodes were successfully managed with oral antibiotics.

Positive effects of intravesical gentamicin were also observed in patients with gentamicin-resistant uropathogens before treatment (16%), possibly because the high concentration of gentamicin instilled directly in the bladder (80 mg gentamicin in 20 mL of saline=4000 mg/L) was well above the MIC of uropathogens with lower susceptibility (MIC breakpoint according to EUCAST >4 mg/L, based on reachable serum concentrations).[14] In the case of high-level resistance, gentamicin is no longer active, irrespective of concentration. This enzymatic degradation was avoided by using an alternative aminoglycoside, such as tobramycin (n=3) or amikacin (n=1).

No systemic absorption was observed and no ototoxicity or other relevant side-effects were noted. Bladder instillations were also well-accepted by patients inexperienced in self-catheterisation (41%). The number of UTIs in the prospective study was higher than in the retrospective cohort. This difference could be attributed to the higher number of patients in the retrospective cohort using daily instillations, compared to those in the prospective study who used a tapering protocol.

Five out of eight patients with clinical failure and all those with microbiological failure had alternative diagnoses of urinary complaints, or cause of persistent bacteriuria (e.g. chronic bacterial prostatitis or infected kidney stones).

Intravesical gentamicin can also be used for diagnostic purposes to localise the site of bacterial persistence. In patients with persistent gentamicin-sensitive bacteriuria between instillations, a source in the upper urinary tract is likely, and further analysis should be performed, including imaging of the urinary tract and urine cultures obtained by selective sampling of both ureters. There are some concerns regarding local toxic effects after the intravesical instillation of gentamicin. One patient was diagnosed with low-grade papillary urothelial carcinoma during the follow-up cystoscopy; a causative relationship with gentamicin instillation is unlikely. Aminoglycosides do not provoke inflammation, and instillation into the pleural space, abdominal cavity or cerebrospinal fluid causes no irritation.[15]

After intravenous administration, gentamicin is excreted by glomerular filtration, almost entirely in the active form. The urine concentration varies inversely with urinary volume and in oliguric patients, high concentrations (500–1000 mg/L) have been observed.[16]

Direct intravesical administration of aminoglycosides has been described before [8]. Most of those previous clinical trials did not differentiate between UTI and asymptomatic bacteriuria. However, three studies performed with intravesical gentamicin showed a significant reduction in the prevalence of bacteriuria and UTIs among selected patients.[17-19] Although systemic absorption was not detected in some studies,[18,19] caution is still warranted as ototoxicity has been reported following bladder irrigation with neomycin through indwelling catheters.[20,21] In patients with end-stage renal disease, serum neomycin levels were not monitored. We excluded patients with end-stage renal failure.

Two recently published retrospective case series on prophylactic gentamicin bladder instillations reported a reduction in the frequency of UTI occurrence, with few side-effects.[9,22] Although Cox et al. used once-daily instillations with a lower gentamicin concentration, their results are comparable to those of our study. Additionally, a reduced rate of drug resistance (58% to 47%) of uropathogens was observed, without an increase in gentamicin resistance in the urine cultures.

Ours is the first prospective study, and the largest cohort of patients treated with gentamicin instillations aimed at preventing rUTIs. A limitation of our study is that, due to the lack of control participants we compared the prevalence of UTI after treatment with the self-reported UTI frequency before; this may have led to overestimation. Another limitation is that not all the UTIs were culture-confirmed.

Before starting gentamicin instillation, the rectal swabs of 15% of the patients showed MDR bacteria at levels that were about 3× higher than those in the general Dutch population, as expected in individuals frequently exposed to antibiotics.[23] The intestinal carriage of MDR Enterobacteriaceae remained the same (16%, Table S2) after the instillations, but as the resistance rate of uropathogens causing breakthrough infections dropped, there might have been a quantitative reduction that remained below the detection level.

CONCLUSIONS

The emergence of antimicrobial resistance and the increase in the number of rUTI patients without oral treatment options underline the urgent need for alternative treatment in daily patient care. In patients with UTIs caused by MDR microorganisms, with limited or no oral treatment options, intravesical gentamicin instillation may be valuable.

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SUPPLEMENTARY MATERIAL

Table S1. Resistance of the causative uropathogen before gentamicin instillation

Causative pathogens in the preceding UTI resistant to	Prospective study n = 63	Retrospective cohort n = 27	Total n = 90	p
Amoxicillin	47/56 (84)	24/26 (92)	71/82 (87)	ns
Amoxicillin-clavulanic acid	30/55 (54)	21/26 (81)	51/81 (63)	0.03
Ciprofloxacin	38/62 (61)	18/26 (69)	56/88 (64)	ns
Trimethoprim-sulfamethoxazole	36/61 (59)	21/26 (81)	57/87 (65)	ns
Nitrofurantoin	24/60 (40)	11/25 (44)	35/85 (41)	ns
Fosfomycin	18/56 (32)	4/15 (27)	22/71 (31)	ns
Cefuroxim	26/61 (42)	15/26 (58)	41/87 (47)	ns
Ceftazidim	15/37 (40)	8/21 (38)	23/58 (40)	ns
Gentamicin	8/57 (14)^	5/23 (22)^^	13/80 (16)	ns
ESBL positive	15 (24)	8 (30)	23 (26)	ns
NDM-1 positive	1 (2)	0	1 (1)	ns

Data are presented as n (%) unless stated otherwise. UTI, urinary tract infection; ESBL, Extended-spectrum beta-lactamase; NDM-1, New Delhi Metallo-beta-lactamase; MIC, minimum inhibitory concentration.
^MIC 16 µg/ml (n=1); MIC 32 µg/ml (n=2); MIC 256 µg/ml (n=1); resistant: MIC >4 mg/L (n=4). ^^Intermediate: MIC 2-4 mg/L (n=2); resistant: MIC >4 mg/L (n=3).

Table S2. Microbiology after the start of gentamicin instillation

Microbiology after the start of instillation	Prospective study n=63	Retrospective cohort n=27	Total n=90
Causative uropathogens during 6 months of instillation	**n=60**	**n=19**	**n=79**
Escherichia coli	38 (63)	13 (68)	51 (65)
Enterococcus faecalis	8 (13)	4 (21)	12 (15)
Klebsiella pneumoniae	7 (12)	1 (5)	8 (10)
Candida albicans	0	1 (5)	1 (1)
Other Gram-negatives	3 (5)*	0	3 (4)*
Other Gram-positives	4 (7)**	0	4 (5)**
Antimicrobial resistance			
Multidrug resistance of uropathogens during instillations	14/60 (23)	5/19 (26)	19 (24)
Patients with gentamicin resistance after start instillations	9 (14)	4 (15)	13 (14)
- symptomatic UTI with gentamicin-resistant uropathogen	6 (9)	3 (11)	9 (10)^
- colonization with gentamicin-resistant bacteria without symptoms	3 (5)	1 (4)	4 (4)
Multidrug-resistant pathogen in rectal swab after 6 months of instillations	7/44 (16)	-	-
Multidrug-resistant pathogen in rectal swab after 6 months of follow-up	5/21 (24)	-	-

Data are presented as n (%) unless stated otherwise. UTI, urinary tract infection; MIC, minimum inhibitory concentration
*Enterobacter aerogenes (n=1); *Pseudomonas aeruginosa* (n=1); *Proteus mirabilis* (n=1). **Staphylococcus saprophyticus* (n=1); B-haemolytic streptococcus (n=2); *Aerococcus urinae* (n=1).
^Three of these patients had a gentamicin-resistant microorganism before the start of treatment in the rectal swab (n=1, MIC >4) or urine (n=2, MIC 16 and 256, this last patient was treated with amikacin).