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Efficacy of antibiotic prophylaxis among intermittent catheter users with different neurologic diseases: A secondary analysis of the AnTIC Trial

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ABSTRACT

Objective: To use existing clinical trial data to assess the impact of prophylactic antibiotics on the 1-year UTI rate among people with different neurologic diseases, and to determine if UTIs impact renal function.
Methods: We conducted a secondary analysis of community dwelling participants with a neurologic disease and intermittent catheter use who participated in a 12-month randomized trial (AnTIC) of low dose antibiotic prophylaxis. We calculated incident rate ratios (IRR) of symptomatic UTIs that required antibiotics. Renal function was assessed using the estimated glomerular filtration rate.
Results: We identified 138 patients who had a neurologic disease (multiple sclerosis (25%), spinal cord injury (21%), spina bifida (18%), and other disorders (36%)). The incidence of symptomatic, antibiotic treated urinary infections was 1.48 per person–year in the prophylaxis group, and 2.51 per person–year in the usual care group; the IRR was 0.59 (95% CI 0.46, 0.76) in favor of continuous antibiotic prophylaxis. The IRR was lowest (most protective) among those with spinal cord injury (IRR 0.23, $p < 0.01$) and highest (least protective) in those with spina bifida (IRR 0.85, $p = 0.57$). There were small, non-significant decreases in renal function that did not differ by randomization. There were no significant differences in pre- and post-study renal function based on the number of UTIs participants experienced.
Conclusion: Continuous antibiotic prophylaxis may be more effective for certain patient populations with neurologic lower urinary tract dysfunction. Renal function is not significantly impacted by a higher number of UTIs over the course of one year.

1. Introduction

In adults, neurogenic lower urinary tract dysfunction (NLUTD) is defined by the International Continence Society as the abnormal function of either the bladder, bladder neck, and/or its sphincters due to a neurologic disorder [1]. Patients with spinal cord injury (SCI) and multiple sclerosis (MS) often have lesions of the central nervous system that result in neurogenic detrusor overactivity (leading to incontinence), and detrusor sphincter dyssynergia or detrusor underactivity (leading to incomplete bladder emptying) [2]. Patients with NLUTD from SCI or MS can experience significant morbidity from urinary tract infections [2]. After SCI, urinary infections are a high priority secondary health complication, and may be associated with significant morbidity such as urosepsis [3,4]. In patients with MS, urinary infections are one of the most common reasons for hospitalization, and a potential trigger for MS relapse, which can have significant neurologic and quality of life consequences for patients [5]. Urinary infections are a common potential complication of intermittent catheter (IC) usage, which is often necessary in neuro-urologic patients who cannot effectively empty their bladder [6]. The reported rates of UTIs in neurologic patients is quite variable, however most studies suggest that IC users have a mean frequency of 2–3/year [7,8].

Unfortunately, there are few interventions available to help patients who use IC and have frequent, bothersome urinary infections [9]. The evidence does not support the use of supplements such as cranberry or medications such as methenamine [9,10], and there are financial barriers and a relatively small effect size with the use of hydrophilic intermittent catheters (which may reduce the risk of UTI by 19%) [11]. Intravesical bladder irrigations are a potentially effective option, but they are not always easy to implement in clinical practice [12]. The use of continuous antibiotic prophylaxis in the neuro-urologic population is

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limited by a lack of published evidence in this patient population [13, 14] The AnTIC trial provided the highest level of evidence to weight the risk and benefits of continuous antibiotic prophylaxis among IC users, however the population was not specific to patients with NLUTD [15]. Different neuro-urologic conditions have specific functional limitations, unique comorbidities, and immunologic differences that may limit the generalizability of the AnTIC trial to all people with neurological lower urinary tract dysfunction. In addition, the neuro-urological population is at risk of renal deterioration [16]; it has been hypothesized that urinary tract infections could contribute to renal dysfunction [17], although to our knowledge a causative association has not been proven. Our objective was to conduct a secondary analysis of the AnTIC trial participants who had a neuro-urologic disease to better understand the efficacy and risks of continuous antibiotic prophylaxis in this patient population.

2. Methods

We performed a secondary analysis of a multicentered, randomized, clinical trial that was carried out in the United Kingdom [15]. Briefly, community dwelling adults that were using IC were invited to participate. They had to have two urinary infections related to IC, or a hospital admission for a urinary infection, in the year prior to randomization. They were randomized to either low dose continuous antibiotic prophylaxis (nitrofurantoin 50 mg, trimethoprim 100 mg, or cefalexin 250 mg), or no antibiotic prophylaxis (usual care), and randomization was stratified by ≥4 urinary infections in the past year, neurologic diagnosis, and gender. Outcome assessors, but not participants, were blinded to treatment allocation. Participants were assessed periodically over the 12-month trial period, and submitted asymptomatic urine samples at 3, 6, 9 and 12 months, and perineal swabs at 6 and 12 months. The primary outcome was symptomatic urinary infections that were treated with antibiotics (based on quarterly reviews and participant reports). Secondary outcomes of interest in this analysis were culture positive symptomatic urinary infections, kidney function, antibiotic related adverse events, and the change in frequency of antimicrobial resistance. The measure of kidney function was estimated glomerular filtration rate (eGFR) based on serum creatinine; eGFR was calculated using the CKD-EPI formula which takes into account gender, and race [18]. At baseline, creatinine clearance was calculated using serum creatinine to ensure all participants had a creatinine clearance >45 mL/min. This trial was registered at ISRCTN (67145101) and EudraCT (2013-002556-32), and appropriate institutional ethics approvals are detailed in the original paper [15].

For this analysis, we only considered the patients who self-identified as having a neurologic disease affecting the lower urinary tract. This group was further categorized into four *a priori* diagnostic groups: multiple sclerosis, spinal cord injury, spina bifida, and other.

3. Statistical methods

The primary analysis was the relative difference in symptomatic urinary infections that required antibiotics between the continuous prophylactic antibiotic group and the usual care group. An exploratory analysis was carried out within each of the four neuro-urologic diagnostic groups. Means and standard deviations (SD) or medians and interquartile range (IQR) are reported depending on the normality of the data. Like the original analysis, all participations who had at least 6 months of continuous follow-up were included in the modified intention to treat analysis, and incidence rate ratios (IRR) were calculated to account for variable follow-up periods. This same analytic approach was used for the secondary outcome of culture-positive symptomatic urinary infections.

The incidence of antibiotic resistance was compared using a chi-squared test to determine if rates of resistance were significantly different between the continuous antibiotic group and the non-continuous antibiotic group using the 9–12 month surveillance urine samples. Univariate analysis of change in kidney function was done using a two-sample t-test. All analyses were done in STATA version 16. We reported IRR and 95% confidence intervals; a *p*-value is reported for the comparisons between the control group and the continuous antibiotic group, with a $p<0.05$ considered significant.

4. Results

The original AnTIC trial screened 1743 participants between November 25 2013 and January 29 2016. Of the 404 participants, 361 had at least 6 months of continuous follow-up and were included in the original published analysis [15]. Of these, 38% (138/361) had a neurologic disease, including MS (25%, n = 35), SCI (21%, n = 29), spina bifida (18%, n = 25), and other disorders (36%, n = 49), and were included for this analysis. The "other" neurologic disease group included most commonly: neurodegenerative diseases, other congenital lesions, lumbar disc disease, and prior pelvic surgery. Among the 138 participants with a neurologic disease, 11 participants in the prophylaxis group stopped prophylaxis during the 12-month study period, and 12 participants in the non-prophylaxis group started prophylaxis during the 12-month study period. The baseline characteristics of the neuro-urologic cohort are shown in Table 1 (and further detailed in Appendix A). Prior to enrollment in the trial, approximately 2/3 people in each trial arm had a self-reported frequency of ≥4 UTIs in the past year, and most did IC approximately 5x/day (with single use catheters). Approximately 40% of participants in each group had baseline bacteriuria.

During the 12-month study period, the incidence of symptomatic, antibiotic treated urinary infections was 1.48 per person–year (95% CI 1.12, 1.96) in the prophylaxis group, and 2.51 per person–year (95% CI 2.05, 3.07) in the usual care group. The IRR was 0.59 (95% CI 0.46, 0.76) in favor of continuous low-dose antibiotic prophylaxis. In the continuous prophylaxis group, 42% (29/69) had no urinary infections during the study, compared to 17% (12/69) in the non-prophylaxis group. The IRR for each of the neuro-urologic diagnostic groups are shown in Table 2; There was a statistically significant IRR among those with SCI, and the other neurologic disorders group. People with SCI had the largest magnitude of UTI reduction with antibiotic prophylaxis (IRR 0.23, 95% CI 0.11–0.50) compared with spina bifida which had the least magnitude of UTI reduction (IRR 0.85, 95% CI 0.49–1.48). The secondary outcome of culture positive symptomatic urinary infections had similar results to the primary outcome of all self-reported UTIs requiring an antibiotic (Table 2). It was not possible to further restrict the analysis to febrile urinary infections, or to urinary infections associated with a hospital admission due to low numbers of events. Of those expressing a preference at the end of the 12 months, 30/38 (79%) of the prophylaxis group, and 33/43 (77%) of the non-prophylaxis group wished to continue with their randomized management strategy.

At baseline, the two groups did not differ significantly in antimicrobial resistance to nitrofurantoin, trimethoprim, or cephalexin. In the asymptomatic urine samples submitted at 9–12 months, there was insufficient evidence to confirm there was a significant difference between groups in resistance to nitrofurantoin (4/18 [22%] participants with at least one isolate from the prophylaxis group vs 2/24 [8.3%] participants with at least one isolate from the control group; p = 0.20), trimethoprim (8/18 [44%] participants vs 6/24 [25%] participants; p = 0.19), or cefalexin (4/18 [22%] participants vs 2/24 [8.3%] participants; p = 0.20). Treatment related adverse events were lower in the prophylaxis group (Appendix B).

The mean difference in the eGFR of participants who were randomized to receive low dose prophylaxis compared to those who were not was similar (Table 3). Among people who had 0, 1, 2, or ≥3 UTIs during the 12-month period (irrespective of randomization status), an end of study eGFR was available for 71% (98/138); the change in eGFR was minimal, and did not follow an exposure-response gradient (Table 4).

Table 1
Baseline characteristics. Data are n (%), median (IQR) or mean (SD).

	Prophylaxis group n = 69	Usual care group n = 69
Age	47.9 (14.1)	52.3 (13.8)
Male	34 (49%)	36 (52%)
Number of UTIs in year prior to randomization		
<4	25 (36%)	27 (39%)
≥4	44 (64%)	42 (61%)
Route of catheter		
Urethral	67 (97%)	68 (99%)
Catheterisable channel	2 (3%)	1 (1%)
Creatinine clearance, mL/min (median, IQR)	114.5 (92.0, 135.2)	116.4 (96.1, 142.4)
Frequency of IC	4.7 (1.9)	4.8 (2.1)
Baseline urine culture results		
Positive	30 (43%)	27 (39%)
Negative	29 (42%)	25 (36%)
Missing data	10 (14%)	17 (25%)

Table 2
Incidence rates (IR) and incidence rate ratios (IRR) of the primary outcome, compared between the prophylaxis and the usual care groups.

	Prophylaxis n = 69	Usual care group n = 69		
	IR (95% CI)	IR (95% CI)	IRR (95% CI)	p value
Self-report UTIs requiring antibiotics				
Neurogenic disease overall	**1.48 (1.12, 1.96)**	**2.51 (2.05, 3.07)**	**0.59 (0.46, 0.76)**	<0.001
MS (n = 35)	1.76 (0.98, 3.15), n = 16	2.54 (1.90, 3.38), n = 19	0.69 (0.43, 1.12)	0.133
SCI (n = 29)	0.54 (0.21, 1.38), n = 15	2.37 (1.36, 4.12), n = 14	0.23 (0.11, 0.50)	<0.001
Spina bifida (n = 25)	1.86 (1.09, 3.16), n = 14	2.18 (1.20, 3.97), n = 11	0.85 (0.49, 1.48)	0.569
Other neurologic disorders (n = 49)	1.67 (1.11, 2.50), n = 24	2.70 (1.95, 3.76), n = 25	0.62 (0.42, 0.91)	0.016
Culture positive symptomatic urinary infection				
Neurogenic disease overall	**0.73 (0.49, 1.07)**	**1.42 (1.08, 1.88)**	**0.51 (0.36, 0.72)**	<0.001
MS (n = 35)	0.61 (0.24, 1.53), n = 16	1.84 (1.28, 2.64), n = 19	0.33 (0.16, 0.69)	0.003
SCI (n = 29)	0.27 (0.11, 0.64), n = 15	1.26 (0.62, 2.58), n = 14	0.21 (0.07, 0.64)	0.006
Spina bifida (n = 25)	1.14 (0.57, 2.31), n = 14	1.09 (0.49, 2.42), n = 11	1.05 (0.50, 2.21)	0.903
Other neurologic disorders (n = 49)	0.83 (0.46, 1.50), n = 24	1.35 (0.80, 2.28), n = 25	0.62 (0.35, 1.07)	0.088

Table 3
Renal function: mean (SD) glomerular filtration rate (GFR) at baseline and 12 months, with comparison between groups of change from baseline. Data are mean (SD).

	Prophylaxis	Usual care group	Mean difference (95% CI), p-value
All neurogenic disease	n = 69	n = 69	
eGFR (baseline)	99.2 (34.3) (n = 69)	101.5 (28.8) (n = 69)	
eGFR (12 months)	98.4 (32.4) (n = 46)	94.9 (31.5) (n = 52)	
eGFR (change)	−0.6 (15.2) (n = 46)	−5.5 (17.0) (n = 52)	4.89 (−1.62, 11.4), 0.14

Table 4
Renal function based on number of UTIs during the 12 month study period (including patients from both trial arms). Mean (SD) of the estimated glomerular filtration rate (eGFR) at baseline and 12 months, with comparison between groups of change from baseline. Data are mean (SD).

	eGFR Baseline[a]	**eGFR Baseline**[b]	**eGFR 12 months**	Mean difference, p-value
UTI frequency: 0	93.5 (26.1), n = 41	91.8 (24.7), n = 24	93.9 (28.1), n = 24	2.0, p = 0.58
UTI frequency: 1	97.5 (27.1), n = 25	95.1 (22.1), n = 20	89.9 (24.5), n = 20	−5.2, p = 0.12
UTI frequency: 2	102.9 (26.7), n = 31	100.2 (27.3), n = 21	96.8 (26.1), n = 21	−3.4, p = 0.29
UTI frequency: 3+	107.0 (40.7), n = 41	108.0 (44.7), n = 33	102.3 (40.6), n = 33	−5.7, p = 0.07

[a]For all participants.
[b]Restricted to participants with GFR collected at 12 months (included in paired t-test).

5. Discussion

Intermittent catheter users with neurologic disease often have numerous risk factors for urinary infections [8]. While there are several important interventions that can be recommended by physicians, there is often not a non-antibiotic method to substantially decrease these infections. This secondary analysis of the AnTIC trial offers some additional important results for patients that are commonly seen by neuro-urologists (such as SCI, MS or spina bifida). First, despite the added potential risk factors for UTIs, the neurologic patient population

experienced a very similar incidence rate of UTIs compared to the full AnTIC population: 1.5 versus 1.3 (full AnTIC population [15]) in prophylaxis group and 2.5 versus 2.6 (full AnTIC population) in the non-prophylaxis group. This suggests that in this clinical trial patient population, neurologic disease is not an additive risk factor for urinary infections. Second, the use of continuous low-dose prophylactic antibiotics resulted in approximately 1 less self-reported UTI/year, and on average 0.7 less febrile UTIs/year. Interestingly, there was some heterogeneity in the effect of prophylactic antibiotics based on type of neurologic disease, with patients with spina bifida potentially deriving less benefit compared to patients with SCI. Despite this, satisfaction within the two trial arms was quite similar; this suggests that the extra UTI/year may not have been overly meaningful to participants. Third, similar to the general population [15], continuous low dose antibiotic prophylaxis does result in a consistent pattern of greater numbers of patients with antibiotic resistance, however the sample size in this secondary analysis was small and this did not show statistical significance. Fourth, among those with neurologic disease, antibiotic-related adverse events were uncommon and mild with continuous low dose antibiotic prophylaxis. The non-prophylaxis arm experienced more adverse events, likely due to the increased need for treatment dose antibiotics during the study period. Fifth, there was not a significant change in renal function, as measured by eGFR, among patients with NLUTD based on the use of continuous low dose prophylactic antibiotics; when stratified by the number of UTI's experienced during the 12 months, there was no apparent step-wise or statistically significant change in eGFR.

A previous Cochrane review identified only four clinical trials which assessed continuous low dose antibiotic prophylaxis in adult IC users with neurologic disease [14]. These studies were published between 1980–1993, represented only 240 patients, and often included symptomatic and asymptomatic bacteriuria in their primary outcome definition. Current evidence suggests that the risk of symptomatic infection in patients with NLUTD with asymptomatic bacteriuria is low, and probably should not be treated in most situations, making these results difficult to interpret [19]. This study adds to the previous limited literature on patients with NLUTD. Shared decision-making should be carried out in patients with NLUTD who use intermittent catheters, and the benefits of on average one fewer urinary infection/year should be balanced against the likely development of antibiotic resistance. However, the context of this shared decision-making is important to understand that patients place substantial importance on urinary infection prevention [20,21], and may be ambivalent to the risks of antibiotic resistance [22]; therefore the physician must still act as a gatekeeper and consider the broader risks of antibiotic resistance.

We did identify variability in the efficacy of prophylactic antibiotics based on the type of neurologic disease. This suggests that not all patients with neurologic lower urinary tract dysfunction may be able to expect the same efficacy with continuous low dose prophylactic antibiotics. This may be driven by the epidemiologic specifics of the different diseases; for example, patients with spina bifida are often treated with prophylactic antibiotics as children, and most have received numerous treatment courses of antibiotics by the time they reach adulthood. This may have altered their microbiome, or otherwise negatively impacted the efficacy of low dose antibiotics [23]. This contrasts with those with SCI, who had an otherwise normal bladder and low risk of antibiotic exposure prior to the injury. The neurologic disease states themselves may also respond differently to urinary infection, meaning that antibiotics may play a more or less important role in the prevention of urinary infections [24]. Ultimately this is a hypothesis generating result, which requires prospective study to determine if there really is a difference in the efficacy of continuous low-dose antibiotic prophylaxis across different disease states.

The impact of urinary infections on renal dysfunction in adults is not well understood. While it is well known that urinary infection in childhood when the kidneys are still developing can result in kidney damage, this is less likely in fully developed adult kidneys. In healthy women, acute pyelonephritis may lead to renal scars in after 10–20 years, however this is rarely associated with renal dysfunction [25]. A cohort study of Korean patients with traumatic spinal cord injury found that those with chronic kidney disease had a 5-fold increased risk of previous recurrent urinary infections (defined as >3 hospitalizations/year) [17]. However it is likely that many of these admissions were for sepsis, or pyelonephritis, which do have a risk of kidney injury [26]. It is also impossible to determine if this is an association or a causative relationship. Most of the participants in this study likely experienced bacterial cystitis, which should not directly impact long-term renal function. However, several economic analyses of different intermittent catheters include progressive renal dysfunction as a complication of urinary infection [27], and this often weights the analysis of quality-adjusted years towards any catheter with a slightly lower risk of urinary infections. Our results suggest that there is no statistically significant impact on renal function when considered self-reported UTIs that require antibiotics; the impact of more serious infections, and the long-term impact of these infections still needs to be assessed.

While we feel that these results are unique and important (especially given the general lack of high-quality randomized clinical trials in neurourology), there are limitations that are necessary to acknowledge to put our results in context. We conducted a post-hoc analysis of a randomized trial with the intention of providing neurogenic-specific results; however, the study was not specifically designed for this purpose, therefore the details around the neurologic diseases were limited, and patients were only stratified in the randomization by neurologic disease as a binary variable. The sample sizes for the individual neurologic diseases were small, therefore our confidence intervals for many of the IRR estimates are wide and our statistical power was limited; because of this we could not use multivariable models. As such, our results around the individual neurologic diseases should be further assessed in future prospective studies. Finally, serum creatinine was the only measure of renal function that was collected in this study, and it has limited sensitivity in some patients with neurologic disease due to reduced muscle mass; [17] longer periods of follow-up are necessary to understand if UTIs influence renal function over a person's lifetime.

6. Conclusions

Continuous low dose prophylactic antibiotics significantly reduces urinary infections in patients with neurogenic disease who use intermittent catheters, however, there may be a risk of antibiotic resistance. The efficacy of this approach may vary based on the type of neurologic disease. Renal function was not significantly impacted by continuous low dose prophylactic antibiotic use in this patient population and did not seem to be significantly related to the number of urinary infections during a one year period.

CRediT authorship contribution statement

Blayne Welk: Project conception, study design, and interpretation of the data, Wrote the initial draft of the manuscript, Revised the manuscript and approved the final version. **Holly Fisher:** Project conception, study design, and interpretation of the data, Statistical analysis, Revised the manuscript and approved the final version. **Thomas Chadwick:** Project conception, study design, and interpretation of the data, Revised the manuscript and approved the final version. **Chris Harding:** Project conception, study design, and interpretation of the data, Revised the manuscript and approved the final version.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table A.1
Baseline characteristics by neurologic disease.

Multiple Sclerosis			
Factor	Level	Prophylaxis	No prophylaxis
N		16	19
Age, mean (SD)		49.8 (10.7)	56.1 (12.5)
Sex	Male	3 (19%)	9 (47%)
	Female	13 (81%)	10 (53%)
Baseline UTI episodes	<4	6 (38%)	11 (58%)
	>=4	10 (63%)	8 (42%)
Catheter Route	Urethra	16 (100%)	19 (100%)
Frequency CIC, mean (SD)		3.0 (1.5)	3.7 (1.6)
htCreatClear, mL/min, median (IQR)		118.0 (92.7, 127.4)	111.4 (105.7, 121.4)
Baseline study culture	No Growth	7 (44%)	4 (21%)
	Pure Growth of 1 or 2 isolates	8 (50%)	10 (53%)
	Missing	1 (6%)	5 (26%)
Spinal cord injury			
Factor	Level	Prophylaxis	No prophylaxis
N		15	14
Age, mean (SD)		53.2 (9.6)	54.3 (17.0)
Sex	Male	12 (80%)	9 (64%)
	Female	3 (20%)	5 (36%)
Baseline UTI episodes	<4	7 (47%)	5 (36%)
	>=4	8 (53%)	9 (64%)
Catheter Route	Urethra	15 (100%)	13 (93%)
	Mitrofanoff	0 (0%)	1 (7%)
Frequency CIC, mean (SD)		4.8 (1.8)	6.1 (1.2)
CreatClear, mL/min, median (IQR)		105.4 (87.0, 135.3)	127.4 (101.2, 155.2)
Baseline study culture	No Growth	5 (33%)	3 (21%)
	Pure Growth of 1 or 2 isolates	7 (47%)	6 (43%)
	Missing	3 (20%)	5 (36%)
Spina bifida			
Factor	Level	Prophylaxis	No prophylaxis
N		14	11
Age, mean (SD)		34.5 (10.1)	42.7 (10.9)
Sex	Male	7 (50%)	6 (55%)
	Female	7 (50%)	5 (45%)
Baseline UTI episodes	<4	6 (43%)	3 (27%)
	>=4	8 (57%)	8 (73%)
Catheter Route	Urethra	13 (93%)	11 (100%)
	Mitrofanoff	1 (7%)	0 (0%)
Frequency CIC, mean (SD)		5.6 (1.3)	4.8 (1.5)
CreatClear, mL/min, median (IQR)		124.3 (103.2, 142.6)	133.3 (119.0, 187.5)
Baseline study culture	No Growth	5 (36%)	4 (36%)
	Pure Growth of 1 or 2 isolates	8 (57%)	6 (55%)
	Missing	1 (7%)	1 (9%)
Other neurologic disease			
Factor	Level	Prophylaxis	No prophylaxis
N		24	25
Age, mean (SD)		51.0 (16.0)	52.6 (12.5)
Sex	Male	12 (50%)	12 (48%)
	Female	12 (50%)	13 (52%)
Baseline UTI episodes	<4	6 (25%)	8 (32%)
	>=4	18 (75%)	17 (68%)
Catheter Route	Urethra	23 (96%)	25 (100%)
	Mitrofanoff	1 (4%)	0 (0%)
Frequency CIC, mean (SD)		5.2 (1.9)	5.0 (2.6)
CreatClear, mL/min, median (IQR)		100.4 (91.5, 138.8)	112.2 (90.2, 134.4)
Baseline study culture	No Growth	12 (50%)	14 (56%)
	Pure Growth of 1 or 2 isolates	7 (29%)	5 (20%)
	Missing	5 (21%)	6 (24%)

(*continued on next page*)

Table A.1 (*continued*).

Table B.1
Adverse events associated with a treatment antibiotic from the urinary tract infection record form over the 12 months of trial participation (participant reported).

	Prophylaxis n = 69	Usual care group n = 69
Any adverse event	**10 (14.5%)**	**26 (37.7%)***
Skin rash	0 (0%)	1 (1%)
Nausea	9 (13%)	18 (26%)
Diarrhea	4 (6%)	11 (16%)
Thrush	5 (7%)	10 (14%)
Other antibiotic side effects	2 (3%)	5 (7%)

*p = 0.002.

Data availability

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

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Ethics approval

The ethical approval for the clinical trial was given on Aug 1, 2013, by the NHS Research Ethics Service Committee North East (Sunderland; 13/NE/0196).

Clinical trial registration

This trial was registered at ISRCTN (67145101) and EudraCT (2013-002556-32).

Appendix A

See Table A.1.

Appendix B

See Table B.1.

References

[1] J.B. GaJewski, B. Schurch, R. Hamid, M. Averbeck, R. Sakakibara, E.F. Agrò, et al., An international continence society (ICS) report on the terminology for adult neurogenic lower urinary tract dysfunction (ANLUTD), Neurourol. Urodyn. (2017) Nov 17.

[2] E.A. Gormley, Urologic complications of the neurogenic bladder, Urol. Clin. North Am. 37 (4) (2010) 601–607.

[3] J.J.E. Adriaansen, M.W.M. Post, Groot S. de, Asbeck F.W.A. van, J.M. Stolwijk-Swüste, M. Tepper, et al., Secondary health conditions in persons with spinal cord injury: a longitudinal study from one to five years post-discharge, J. Rehabil. Med. Official J. UEMS Eur. Board Phys. Rehabil. Med. 45 (10) (2013) 1016–1022.

[4] L.E. Nicolle, Urinary tract infections in patients with spinal injuries, Curr. Infect. Dis. Rep. 1 16 (1) (2014) 390.
[5] V. Phé, M. Pakzad, C. Curtis, B. Porter, C. Haslam, J. Chataway, et al., Urinary tract infections in multiple sclerosis. Multiple sclerosis (Houndmills, Basingstoke, England), 2016, Feb 18, 1352458516633903.
[6] D.N. Patel, C.G. Alabastro, J.T. Anger, Prevalence and cost of catheters to manage neurogenic bladder, Curr. Bladder Dysfunct. Rep. 13 (4) (2018) 215–223.
[7] L.Y. Garcia-Arguello, J.C. O'Horo, A. Farrell, R. Blakney, M.R. Sohail, C.T. Evans, et al., Infections in the spinal cord-injured population: a systematic review, Spinal Cord. 55 (6) (2017) 526–534.
[8] M. Kennelly, N. Thiruchelvam, M.A. Averbeck, C. Konstatinidis, E. Chartier-Kastler, P. Trøjgaard, et al., Adult neurogenic lower urinary tract dysfunction and intermittent catheterisation in a community setting: Risk factors model for urinary tract infections, Adv. Urol. 2019 (4) (2019) 2757813–2757862.
[9] A.C. Castle, A. Park, A.J. Mitchell, D.Z. Bliss, J.A. Gelf, E.J.B. De, Neurogenic bladder: Recurrent urinary tract infections—Beyond antibiotics, Curr. Bladder Dysfunct. Rep. 13 (4) (2018) 191–200.
[10] H.R. Vigil, D.R. Hickling, Urinary tract infection in the neurogenic bladder, Transl. Androl. Urol. 5 (1) (2016) 72–87.
[11] K. Christison, M. Walter, J.-J.J.M. Wyndaele, M. Kennelly, T.M. Kessler, V.K. Noonan, et al., Intermittent catheterization: The devil is in the details, J. Neurotrauma (2018) Feb 1.
[12] A. Pietropaolo, P. Jones, M. Moors, B. Birch, B.K. Somani, Use and effectiveness of antimicrobial intravesical treatment for prophylaxis and treatment of recurrent urinary tract infections (UTIs): a systematic review, Curr. Urol. Rep. 19 (10) (2018) 78.
[13] S.C. Morton, P.G. Shekelle, J.L. Adams, C. Bennett, B.H. Dobkin, J. Montgomerie, et al., Antimicrobial prophylaxis for urinary tract infection in persons with spinal cord dysfunction, Arch. Phys. Med. Rehab. 83 (1) (2002) 129–138.
[14] B.S. Niël-Weise, Broek P.J. van den, E.M. da Silva, LA. Silva, Urinary catheter policies for long-term bladder drainage, Cochrane Db Syst. Rev. 8 (8) (2012) CD004201.
[15] H. Fisher, Y. Oluboyede, T. Chadwick, M. Abdel-Fattah, C. Brenn, M. Fader, et al., Continuous low-dose antibiotic prophylaxis for adults with repeated urinary tract infections (AnTIC): a randomised, open-label trial, Lancet Infect. Dis. 18 (9) (2018) 957–968.
[16] B. Welk, K. Liu, J. Winick-Ng, S.Z. Shariff, Urinary tract infections, urologic surgery, and renal dysfunction in a contemporary cohort of traumatic spinal cord injured patients, Neurourol. Urodyn. 36 (3) (2017) 640–647.
[17] B.M. Sung, D. Oh, M.H. Choi, H.M. Choi, Chronic kidney disease in neurogenic bladder, Nephrology 23 (3) (2018) 231–236.
[18] A.S. Levey, L.A. Stevens, Epidemiology Collaboration, Estimating GFR using the CKD (CKD-EPI) creatinine equation: More accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions, Am. J. Kidney Dis. 55 (4) (2010) 622–627.
[19] J. Tornic, J. Wöllner, L. Leitner, U. Mehnert, L.M. Bachmann, T.M. Kessler, The challenge of asymptomatic bacteriuria and symptomatic urinary tract infections in patients with neurogenic lower urinary tract dysfunction, J. Urology. 203 (3) (2020) 579–584.
[20] K.M. Theisen, R. Mann, J.D. Roth, J.J. Pariser, J.T. Stoffel, S.M. Lenherr, et al., Frequency of patient-reported UTIs is associated with poor quality of life after spinal cord injury: a prospective observational study, Spinal Cord. (2020) 1–8.
[21] B. Welk, P. McGarry, M. Kennelly, J. Myers, N.B.R. Group, Bladder management experiences among people living with neurologic disease: A systematic review and meta-synthesis of qualitative research, Neurourol. Urodyn. (2018) Nov 29.
[22] D. McClurg, K. Walker, R. Pickard, P. Hilton, H. Ainsworth, K. Leonard, et al., Participant experiences of clean intermittent self-catheterisation, urinary tract infections and antibiotic use on the ANTIC trial – a qualitative study, Int. J. Nurs. Stud. 81 (2018) 1–7.
[23] J. Josephs-Spaulding, T.J. Krogh, H.C. Rettig, M. Lyng, M. Chkonia, S. Waschina, et al., Recurrent urinary tract infections: Unraveling the complicated environment of uncomplicated rUTIs, Front. Cell. Infect. Microbiol. 11 (2021) 562525.
[24] R. Chaudhry, R.J. Madden-Fuentes, T.K. Ortiz, Z. Balsara, Y. Tang, U. Nseyo, et al., Inflammatory response to escherichia coli urinary tract infection in the neurogenic bladder of the spinal cord injured host, J. Urology. 191 (5) (2014) 1454–1461.
[25] R. Raz, W. Sakran, B. Chazan, R. Colodner, C. Kunin, Long-term follow-up of women hospitalized for acute pyelonephritis, Clin. Infect. Dis. 37 (8) (2003) 1014–1020.
[26] C-Y. Hsiao, H-Y. Yang, M-C. Hsiao, P-H. Hung, M-C. Wang, Risk factors for development of acute kidney injury in patients with urinary tract infection, PLoS One 10 (7) (2015) e0133835.
[27] M. Xi, D.S. Elterman, B. Welk, M. Pakosh, B.C.F. Chan, Cost-effectiveness of hydrophilic-coated urinary catheters for individuals with spinal cord injury: A systematic review, Bjui Compass (2020).