Continuous low-dose antibiotic prophylaxis to prevent urinary tract infection in adults who perform clean intermittent self-catheterisation: the AnTIC RCT

Robert Pickard,1*† Thomas Chadwick,2 Yemi Oluboyede,2 Catherine Brennand,3 Alexander von Wilamowitz-Moellendorff,3 Doreen McClurg,4 Jennifer Wilkinson,3 Laura Ternent,2 Holly Fisher,2 Katherine Walton,5 Elaine McColl,2 Luke Vale,2 Ruth Wood,3 Mohamed Abdel-Fattah,6 Paul Hilton,7 Mandy Fader,8 Simon Harrison,9 James Larcombe,10 Paul Little,11 Anthony Timoney,12 James N’Dow,6 Heather Armstrong,13 Nicola Morris,12 Kerry Walker4 and Nikesh Thiruchelvam14

1Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK
2Institute of Health and Society, Newcastle University, Newcastle upon Tyne, UK
3Newcastle Clinical Trials Unit, Newcastle University, Newcastle upon Tyne, UK
4Nursing, Midwifery and Allied Health Professions Research Unit, Glasgow Caledonian University, Glasgow, UK
5Department of Microbiology, Newcastle upon Tyne Hospitals NHS Foundation Trust, Freeman Hospital, Newcastle upon Tyne, UK
6Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, UK
7Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK
8Health Sciences, University of Southampton, Southampton, UK
9Department of Urology, Mid-Yorkshire Hospitals NHS Trust, Pinderfields Hospital, Wakefield, UK
10Skerne Medical Centre, Sedgefield, UK
11Primary Care and Population Sciences, University of Southampton, Southampton, UK
12Bristol Urological Institute, North Bristol NHS Trust, Bristol, UK
13Patient representative, no affiliation
14Department of Urology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

*Corresponding author robert.pickard@newcastle.ac.uk
†Chief investigator
Declared competing interests of authors: Robert Pickard reports grants from the National Institute for Health Research (NIHR) during the conduct of the study. Thomas Chadwick reports grants from the NIHR Health Technology Assessment (HTA) programme during the conduct of the study and outside the submitted work. Katherine Walton reports grants from NIHR during the conduct of the study. Elaine McColl reports grants from the NIHR HTA programme during the conduct of the study and from the NIHR Journals Library outside the submitted work. From 2013 to 2016 she was an editor for the NIHR Programme Grants for Applied Research (PGfAR) series, with a fee paid to her employing organisation. Luke Vale reports that he is a member of the NIHR HTA Clinical Evaluation and Trials panel and is co-director of NIHR Research Design Service North East. Mohamed Abdel-Fattah reports grants from Bard Medical UK (Crawley, UK), Astellas Pharma Inc. (Tokyo, Japan), Coloplast (Humlebæk, Denmark), Pfizer Inc. (New York, NY, USA), Advanced Medical Solutions [(AMS) Winsford, UK] and Ethicon Inc. (Somerville, NJ, USA) outside the submitted work and is a member of the HTA Interventional Procedures panel. Paul Hilton reports a grant from the NIHR HTA programme during the conduct of the study and grants from the William Harker Foundation and Wellbeing of Women outside the submitted work. He was a member of the National Institute for Health and Care Excellence (NICE) Interventional Procedures Advisory Committee (2002–7), NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC)-HTA Therapeutic Procedures Panel (2007–8) and NETSCC-HTA Clinical Evaluations and Trials Prioritisation Group (2008–10). He chaired the NICE development group for clinical guideline on urinary incontinence in women (2004–7). Mandy Fader reports grants from NIHR (reference number RP-PG-0610-10078) and from the Small Business Research Initiative grant outside the submitted work. Simon Harrison reports grants from the NIHR HTA programme (reference number 11/72/01) during the conduct of the study. James Larcombe reports grants from the NIHR HTA programme during the conduct of the study and is a member of the HTA Elective and Emergency Specialist Care panel. Paul Little reports that he is director of PGfAR and editor-in-chief of the PGfAR publication in the NIHR Journals Library. James N’Dow is a member of the HTA General Board. Nikesh Thiruchelvam reports grants from Astellas, non-financial support from Astellas and personal fees from Coloplast outside the submitted work.

Published May 2018
DOI: 10.3310/hta22240

Scientific summary

The AnTIC RCT
Health Technology Assessment 2018; Vol. 22: No. 24
DOI: 10.3310/hta22240

NIHR Journals Library www.journalslibrary.nihr.ac.uk
Scientific summary

Background

Clean intermittent self-catheterisation (CISC) is an important management option for people who cannot empty their bladder naturally due to bladder outlet obstruction or the failure of bladder muscle contraction, often associated with neurological disease. Recurrent urinary tract infection (UTI) is common among CISC users, affecting 12–88% of patients.

This trial was motivated by the need to determine whether or not the possible benefit of continuous, once-daily low-dose antibiotic (prophylaxis) for recurrent UTI seen in small trials in specific groups could be applied to the wider population of adult CISC users. Any benefit must be worthwhile to patients and society in terms of financial costs and harms, including the emergence of antimicrobial resistance.

Objectives

The hypothesis addressed is that an experimental strategy of once-daily low-dose antibiotic prophylaxis will reduce the rate of symptomatic antibiotic-treated UTI by ≥ 20% compared with a control strategy of no prophylaxis over a 12-month trial period. To investigate this hypothesis, the following objectives were set.

Primary objectives

- Determine the impact of prophylaxis on incidence of symptomatic antibiotic-treated UTI.
- Determine the incremental cost per symptomatic UTI avoided.

Secondary objectives

- Determine the effect of prophylaxis on incidence of microbiologically confirmed UTI.
- Determine the rates of fever and hospitalisation because of UTI.
- Determine the rates of asymptomatic bacteriuria.
- Record adverse events (AEs) related to use of prophylactic and treatment antibiotics.
- Assess change in resistance of pathogens isolated from urine and from perianal swabs.
- Measure overall satisfaction with prophylactic antibiotic treatment.
- Determine the relative effect on health status.
- Measure the incremental cost per quality-adjusted life-year (QALY) gained.
- Assess participants’ willingness to pay (WTP) to avoid a UTI.
- Qualitatively assess the experience and impact of using CISC and suffering recurrent UTI, exploring health beliefs concerning trial interventions, antibiotic use and antimicrobial resistance.

Methods

Design

An open-label, patient-randomised, parallel-group superiority trial comparing an experimental strategy of once-daily low-dose antibiotic prophylaxis using 50 mg of nitrofurantoin, 100 mg of trimethoprim (Kent Pharmaceuticals, Ashford, UK) or 250 mg of cefalexin (Sandoz Ltd, Holzkirchen, Germany) with a control strategy of no prophylaxis in adults using CISC who suffer recurrent UTI over 12 months. A centralised randomisation system using random block allocation set by an independent statistician allocated...
participants to each group. Central trials office and laboratory staff assessed outcomes without knowledge of participants’ allocated group.

Setting and participants
The trial was set in the UK, recruiting participants from primary, community and secondary care NHS organisations.

Inclusion criteria
- Adult aged ≥ 18 years.
- Established user of CISC who was predicted to continue using it for ≥ 12 months.
- Able to give informed consent for participation in the trial.
- Able and willing to adhere to a 12-month follow-up period.
- Had suffered either at least two episodes of UTI related to CISC in the previous 12 months or at least one episode of UTI requiring hospitalisation. Or, for those already using prophylaxis, the completion of a 3-month washout period without prophylaxis.
- Able to take a once-daily oral dose of at least one of 50 mg of nitrofurantoin, 100 mg of trimethoprim or 250 mg of cefalexin.

Patients were excluded if they were taking prophylactic antibiotic against UTI and declining the 3-month washout period. Women who were pregnant or breastfeeding, or who intended to become pregnant during the trial period, and people unable to give informed consent were excluded.

Measurement of clinical outcomes

Primary
Occurrence of clinical UTI was defined as the presence of symptoms together with taking a treatment course of antibiotic for UTI. This was measured by participant return of a UTI record for each event, as well as a 3-monthly participant questionnaire and a 3-monthly trial visit case report form (CRF) completed by the local research team. At the end of the trial, these records were reviewed by two members of the central trial team and the primary outcome adjudicated in accordance with a written protocol to avoid double-counting of episodes. Any disagreement or uncertainty was arbitrated by a third member of the central trial team, who also checked 10% of episodes. All outcome assessors were unaware of allocated group.

Secondary
Microbiologically proven UTI was defined as the confirmed report of symptomatic antibiotic-treated UTI (primary outcome) together with a positive urine culture. In addition, a fever of > 38 °C and hospitalisation for UTI were recorded. We defined a positive culture as the presence of one or two isolates at ≥ 10^4 colony-forming units/ml. Asymptomatic bacteriuria was defined as a positive culture from urine specimens submitted at baseline and 3, 6, 9 and 12 months in the absence of clinical UTI.

Adverse reactions related to prophylaxis and the treatment antibiotic were recorded by a participant-completed UTI record and a 3-monthly participant questionnaire, in addition to a 3-monthly visit CRF and health record review completed by local research staff. AEs were collected by 3-monthly health record review and those deemed serious (serious adverse events) were sent urgently to the central trial office by fax transmission.

Bacterial ecological change was assessed by comparing resistance patterns of pathogens isolated from urine specimens sent to the central laboratory by participants at the time of UTI with pathogens isolated during asymptomatic periods at the time of 3-monthly review visits. Changes to *Escherichia coli* colonising the faecal microbiome were assessed by culture of perianal swabs taken at baseline and 6- and 12-month trial visits.
Satisfaction with prophylactic antibiotic treatment was measured by participant completion of the Treatment Satisfaction Questionnaire for Medication (TSQM) at 12 months encompassing domains for effectiveness, side effects and convenience.

Health status over 12 months was assessed by participant completion of the Short Form questionnaire-36 items version 2 (SF-36v2) at baseline and 6 and 12 months. The analysis focused on the mental component summary (MCS) score and the physical component summary (PCS) score. Participants were also asked to complete and return the SF-36v2 at the time of symptomatic UTI as part of the UTI questionnaire. Data from complete SF-36v2 were also used to generate utility values and QALYs for the cost-utility analysis.

Participant attitudes towards use of antibiotic prophylaxis were assessed by an exploratory case-based study with thematic analysis of semistructured interviews.

Measurement of health economic outcomes

Primary
Incremental cost per symptomatic UTI avoided was calculated from collected costs associated with prophylaxis and no prophylaxis strategies. Health-care costs were assessed by a participant-completed health resource utilisation questionnaire at 6 and 12 months and 3-monthly record review. Monetary costs of these events were derived from standard UK sources. For patient costs, participants completed a time and travel questionnaire at 12 months.

Secondary
Cost-utility analysis was based on estimated QALYs from responses to the SF-36v2, including at the time of symptomatic UTI. Participants’ WTP to avoid a UTI was assessed by a completion of a bespoke contingent valuation questionnaire after the 12-month trial period.

Statistical analysis
It was assumed that an overall 20% reduction in symptomatic UTI rate from an average of three episodes to 2.4 episodes over 12 months was the minimum clinically important difference. Using the Poisson rate test, completion of the trial by 158 participants in each group, 316 participants in total, would give 90% power to detect this difference at the 5% level. A total of 372 participants would allow for a 15% attrition rate. This gave 92% power to detect a 25% difference in the high-frequency subgroup (from four to three episodes per year) and 99% power for a 50% reduction in the low-frequency subgroup (from two to one episodes per year). All statistical analyses were carried out on a modified intention-to-treat basis, retaining participants in their allocated groups and including all participants in the primary outcome analysis for whom ≥ 6 months of continuous follow-up data had been collected.

The relative rate of symptomatic antibiotic-treated UTI was defined as the incident rate ratio (IRR), calculated by dividing the UTI rate in the prophylaxis group by that found in the no-prophylaxis group, allowing for different durations of follow-up. Analysis of the primary outcome measure was performed as a univariate approach using the Poisson rate test and a Poisson regression modelling approach allowing for days not at risk while taking treatment courses of antibiotics. Regression modelling was used to detect effects of covariates including stratification factors and other baseline variables suggested to increase risk of UTI. The univariate analysis was considered to be the primary analysis for reporting.

For TSQM scores, the two-sample t-test was used as a simple univariate analysis. Chi-squared test and tests for trend were used for analysis of resistance patterns. For univariate analysis of the MCS and PCS components of the SF-36v2, the simple ‘t’-test was used. For adjusted analyses of the TSQM scores and the components of the SF-36v2, a linear regression/analysis of covariance was performed with the same covariates used in the primary outcome analysis.
Health economic analysis
Cost-effectiveness was measured by summing treatment and participant costs and taking an average across participants in each trial group. The number of UTIs was derived from primary outcome data. The incremental cost-effectiveness ratio was then calculated by dividing the difference in costs by the difference in the number of UTIs for each group.

From participant responses to the SF-36v2 completed at 6 and 12 months and at the time of symptomatic UTI, health state utilities were estimated using an established algorithm applied to the Short Form questionnaire-6 Dimensions. QALYs were then derived using an area-under-the-curve approach. The difference in mean QALYs between groups was calculated. Costs were summed from trial and NHS sources and means calculated for each group. Cost utility was expressed as the incremental cost per QALY gained.

Data from the contingent valuation questionnaire were incorporated into the economic evaluation using a cost–benefit analysis framework.

Qualitative analysis
Those participants who consented to being approached by a qualitative researcher were purposively sampled to ensure that interviews were conducted with both men and women of various ages in each trial group, geographically spread across seven sites. Semi-structured interviews were conducted using a topic guide for consistency, while also allowing participants to raise any other relevant issues. The researcher carried out all interviews by telephone from a private room with audio-recording. Interviews were transcribed, checked for accuracy and manually coded. Data were then subjected to thematic analysis to generate categories and themes appropriate to the quantitative research questions.

Results
We identified 1743 patients, of whom 404 were randomised. Trial participants were recruited from clinics in secondary care (n = 340; 84%), primary care (n = 50; 12%) and community NHS services (n = 14; 4%) over a 26-month period (25 November 2013 to 29 January 2016). A total of 332 (82%) participants completed the 12-month trial of allocated intervention and follow-up, with an additional 29 participants having ≥ 6 months of follow-up data, which were required for inclusion in the primary analysis. Thus, 361 (89%) of the randomised participants were included in the primary analysis.

Participants allocated to prophylaxis (n = 203) were well matched at baseline to those in the no-prophylaxis group (n = 201) with regard to demographics, cause of bladder dysfunction, regimen of CISC use, previous frequency of UTI and presence of risk factors for UTI. The number of participants with asymptomatic bacteriuria in each group at baseline was comparable [prophylaxis, n = 76 (37%); no prophylaxis, n = 77 (38%)].

In univariate analysis, the IRR for symptomatic antibiotic-treated UTI over 12 months in the prophylaxis group relative to no prophylaxis was 0.52 [95% confidence interval (CI) 0.44 to 0.61]. Reduction in frequency of microbiologically proven UTI was similar (IRR 0.49, 95% CI 0.39 to 0.60). The absolute reduction in UTI episodes over 12 months was 50% from a median (interquartile range) of 2 (1–4) in the no-prophylaxis group to 1 (0–2) in the prophylaxis group. These results were unchanged in the Poisson regression model including days at risk of UTI, prior frequency of UTI and other possible confounders.

There was no clinically significant difference in measured health status between the two groups over 12 months and no difference in utility value at the time of UTI. Pathogens, predominantly E. coli (58%), isolated from 3-monthly urine specimens submitted by the prophylaxis group were more likely to have a higher frequency of resistance to trimethoprim (p < 0.001), co-trimoxazole (p = 0.002) and nitrofurantoin (p = 0.038) at 12 months than isolates from the no-prophylaxis group. We found significant trends over 12 months in increased resistance of pathogens isolated from urine specimens provided by the prophylaxis
group to amoxicillin ($p = 0.004$), cefalexin ($p = 0.005$), trimethoprim ($p = 0.016$) and co-trimoxazole ($p = 0.006$). No such trends were seen in the no-prophylaxis group.

The incremental cost of use of prophylaxis to avoid UTI over 12 months was £99 per UTI. The incremental cost per QALY over 12 months was £12,452. Participants in the prophylaxis group were willing to pay approximately £50 more than those in the no-prophylaxis group to avoid one episode of UTI over 12 months in the contingent valuation exercise.

Qualitative findings were that the emotional and practical burden of CISC and UTI in participants’ lives was considerable and influenced their perception of well-being. Psychological adjustment to CISC and UTI was complex, characterised by cognitive, attitudinal and situational factors. Generally, participants had an unconcerned attitude about using antibiotics for UTI. A minority felt concerned that prophylaxis would reduce future effectiveness by inducing antimicrobial resistance. These attitudes affected behaviour towards using prophylaxis, which was also influenced by clinician recommendation. Finally, adhering to the trial schedule was deemed straightforward, and those allocated to the prophylaxis group exploited habitual tendencies to incorporate it into their lives.

**Conclusions**

This trial, designed and conducted in accordance with best practice, provides robust evidence that taking a once-daily low-dose antibiotic chosen from a restricted range of agents results in a substantial reduction in UTI frequency. The result was unchanged by inclusion of possible confounders in the analysis and use of alternative definitions for UTI. The representative sample of adult CISC users enrolled in the trial and the lack of effect of inclusion of patient subgroups as exploratory covariates in the primary outcome model suggests generalisability to the overall population of CISC users. The intervention was well tolerated, with few participants suffering overt harm. The benefit offered appears affordable to patients and the NHS. The increase in antimicrobial resistance of pathogens causing UTI to commonly used antibiotics may reduce the long-term efficacy of prophylaxis in individuals continuing to perform CISC and is also a major public health concern.

**Recommendations for research**

In priority order:

1. longer-term studies of the emergence of antimicrobial resistance
2. studies of clinical effectiveness and cost-effectiveness of non-antibiotic strategies to prevent UTI
3. patient and bacterial phenotypic and genotypic studies to identify groups that benefit most from prophylaxis and pathogens most likely to develop antimicrobial resistance.

**Trial registration**

This trial is registered as ISRCTN67145101 and EudraCT 2013-002556-32.

**Funding**

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.
Criteria for inclusion in the Health Technology Assessment journal

Reports are published in Health Technology Assessment (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in Health Technology Assessment are termed ‘systematic’ when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 11/72/01. The contractual start date was in September 2013. The draft report began editorial review in August 2017 and was accepted for publication in January 2018. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors’ report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NiHR, NETSCC, the HTA programme or the Department of Health and Social Care.

© Queen’s Printer and Controller of HMSO 2018. This work was produced by Pickard et al. under the terms of a commissioning contract issued by the Secretary of State for Health and Social Care. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).
Editor-in-Chief

Professor Hywel Williams  Director, HTA Programme, UK and Foundation Professor and Co-Director of the Centre of Evidence-Based Dermatology, University of Nottingham, UK

NIHR Journals Library Editor-in-Chief

Professor Tom Walley  Director, NIHR Evaluation, Trials and Studies and Director of the EME Programme, UK

NIHR Journals Library Editors

Professor Ken Stein  Chair of HTA and EME Editorial Board and Professor of Public Health, University of Exeter Medical School, UK

Professor Andrée Le May  Chair of NIHR Journals Library Editorial Group (HS&DR, PGfAR, PHR journals)

Dr Martin Ashton-Key  Consultant in Public Health Medicine/Consultant Advisor, NETSCC, UK

Professor Matthias Beck  Professor of Management, Cork University Business School, Department of Management and Marketing, University College Cork, Ireland

Dr Tessa Crilly  Director, Crystal Blue Consulting Ltd, UK

Dr Eugenia Cronin  Senior Scientific Advisor, Wessex Institute, UK

Dr Peter Davidson  Director of the NIHR Dissemination Centre, University of Southampton, UK

Ms Tara Lamont  Scientific Advisor, NETSCC, UK

Dr Catriona McDaid  Senior Research Fellow, York Trials Unit, Department of Health Sciences, University of York, UK

Professor William McGuire  Professor of Child Health, Hull York Medical School, University of York, UK

Professor Geoffrey Meads  Professor of Wellbeing Research, University of Winchester, UK

Professor John Norrie  Chair in Medical Statistics, University of Edinburgh, UK

Professor John Powell  Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK

Professor James Raftery  Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

Dr Rob Riemmsma  Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

Professor Helen Roberts  Professor of Child Health Research, UCL Great Ormond Street Institute of Child Health, UK

Professor Jonathan Ross  Professor of Sexual Health and HIV, University Hospital Birmingham, UK

Professor Helen Snooks  Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

Professor Jim Thornton  Professor of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, University of Nottingham, UK

Professor Martin Underwood  Director, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, UK

Please visit the website for a list of members of the NIHR Journals Library Board: www.journalslibrary.nihr.ac.uk/about/editors

Editorial contact: journals.library@nihr.ac.uk