CATheter Infections in CHildren (CATCH): a randomised controlled trial and economic evaluation comparing impregnated and standard central venous catheters in children

Katie Harron,1 Quen Mok,2 Kerry Dwan,3 Colin H Ridyard,4 Tracy Moitt,3 Michael Millar,5 Padmanabhan Ramnarayan,2 Shane M Tibby,6 Berit Muller-Pebody,7 Dyfrig A Hughes,4 Carrol Gamble3 and Ruth E Gilbert1*

1Institute of Child Health, University College London, London, UK
2Great Ormond Street Hospital, London, UK
3Medicines for Children Clinical Trials Unit, University of Liverpool, Liverpool, UK
4Centre for Health Economics and Medicines Evaluation, Bangor University, Bangor, UK
5Barts Health NHS Trust, London, UK
6Evelina London Children’s Hospital, London, UK

*Corresponding author

Declared competing interests of authors: Michael Millar was a member of the National Institute for Health Research Health Technology Assessment Diagnostic Technologies and Screening Panel for the duration of the CATCH study.
Scientific summary

CATheter Infections in CHildren (CATCH)
Health Technology Assessment 2016; Vol. 20: No. 18
DOI: 10.3310/hta20180

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

Background

Bloodstream infection (BSI) is an important cause of adverse clinical outcomes and costs to the NHS in the UK. Paediatric intensive care units (PICUs) have one of the highest reported rates of hospital-acquired BSI of any clinical specialty.

Nine systematic reviews, two cost-effectiveness analyses and at least 48 randomised controlled trials (RCTs; 11,586 patients) have demonstrated substantial benefits of impregnated central venous catheters (CVCs) for reducing catheter-related BSI (CR-BSI) in adults. The best evidence to date shows that antibiotic-impregnated or heparin-bonded CVCs are most effective, producing similar reductions in risk of CR-BSI (70–80%). However, there is a lack of child-specific evidence for impregnated CVCs and they are not recommended for children in UK or US guidance. We compared both types of impregnated CVC (antibiotic and heparin) with standard CVCs to determine their effectiveness in children. Secondary analyses were conducted to investigate the effectiveness of each type of impregnation.

Objectives

1. To determine the clinical effectiveness of impregnated compared with standard CVCs for reducing BSI in children admitted for intensive care.
2. To determine the cost-effectiveness of impregnated CVCs from a NHS perspective.
3. To inform purchasing by assessing the generalisability and the cost impact of adopting impregnated CVCs for all children who need them.

Randomised controlled trial: clinical effectiveness

Methods

We conducted a three-arm RCT to compare the effect of heparin-bonded, antibiotic-impregnated and standard polyurethane CVCs on BSI in children requiring intensive care. The RCT is registered at ClinicalTrials.gov (reference number NCT01029717).

Design, study population and intervention

Children admitted to 14 PICUs in England between December 2010 and November 2012 were randomised to heparin-bonded, antibiotic-impregnated or standard CVCs manufactured by Cook Medical Incorporated (Bloomington, IN, USA).

Children aged <16 years were eligible if they were admitted or being prepared for admission to a participating PICU and were expected to require a CVC for ≥3 days. For children admitted to a PICU following elective surgery, we sought prospective parental consent during preoperative assessment. For children who required a CVC as an emergency, we sought parental consent after randomisation and stabilisation (deferred consent) to avoid delaying treatment.

Randomisation and masking

Children were randomised at the bedside or in theatre immediately before CVC insertion. Randomisation sequences were computer generated in a 1:1:1 ratio, stratified by method of consent, site and envelope storage location within the site.
The clinician responsible for inserting the CVC was not blinded to CVC allocation (because of different colour strips for impregnated CVCs) but, as the CVCs looked identical whilst in situ, allocation was concealed from patients, their parents and PICU personnel responsible for their care.

Comparisons and end points
The primary analysis in the trial compared antibiotic or heparin CVCs with standard CVCs. Secondary analyses consisted of three-way comparisons between standard, antibiotic and heparin CVCs.

The primary outcome was time to the first BSI based on blood cultures taken between 48 hours after randomisation and 48 hours after CVC removal (or prior to death). All blood culture samples were clinically indicated, defined by recorded evidence of infection (one or more of temperature instability, change in inotrope requirements, haemodynamic instability or poor perfusion) or removal of the CVC because of suspected infection. Any positive blood culture was accepted for a non-skin organism, but for skin organisms two or more positive cultures within 48 hours of each other were required.

Secondary BSI-related outcomes were:
1. CR-BSI: the same organisms cultured from blood and the CVC tip between 48 hours after randomisation and 48 hours after CVC removal; or differential positivity of cultures from multiple CVC lumens on two or more occasions; or BSI and exit site infection or BSI and CVC removed for suspected infection
2. rate of BSI per 1000 CVC-days: number of BSIs between randomisation and CVC removal
3. time to a composite measure of BSI consisting of the primary outcome or a negative blood culture combined with a positive 16S polymerase chain reaction result for bacterial ribosomal ribonucleic acid, removal of the CVC because of suspected infection or a start of antibiotics or change in type of antibiotics on the same or next day.

We also compared time to CVC removal, CVC thrombosis, PICU discharge, hospital discharge and mortality within 30 days. Safety analyses compared CVC-related adverse events, mortality and antibiotic resistance to minocycline (> 0.5 µg/ml) or rifampicin (> 1.0 µg/ml).

Sample size
In total, 1200 children were required to achieve 80% power to detect a relative risk of 0.5 at a 5% level of significance, based on an estimated BSI rate of 10% and allowing for 5% loss to follow-up.

Statistical analysis
Outcome data were analysed according to the intention-to-treat principle. Safety analyses included the subset of children for whom CVC insertion was attempted, grouped by CVC actually received or, if insertion was not successful, the type used in the attempt.

The statistical analysis plan was developed prior to analysis and is available in Appendix 1. Time-to-event outcomes were analysed using Kaplan–Meier curves and the log-rank test. Cox regression was used to adjust the primary analysis of time to BSI for the use of prospective or deferred consent and suspected infection at baseline. Poisson regression was used to analyse the rate of BSI. All analyses were conducted using SAS software (version 9.2; SAS Institute Inc., Cary, NC, USA).

Results
Study population
In total, 1859 children were randomised, of whom 501 children were randomised prospectively and 1358 were randomised as an emergency; of those randomised as an emergency, 984 subsequently provided deferred consent for follow-up.
Baseline characteristics
In total, 58% of the children were aged < 12 months at admission and 33% were aged < 3 months. One-third had surgery prior to admission to the PICU and half had cardiovascular problems as their primary diagnosis at admission. CVC insertion took place in theatre for 437 out of 493 (89%) in the prospective consent (elective) group but in only 34 out of 917 (4%) of the deferred consent (emergency) group.

End points

Primary outcome
Bloodstream infection was recorded for 42 children [standard group 18/502 (3.59%); antibiotic group 7/486 (1.44%); heparin group 17/497 (3.42%)]. There was no significant difference in the primary outcome of time to first BSI comparing any impregnated CVC with the standard CVC [hazard ratio (HR) 0.71, 95% confidence interval (CI) 0.37 to 1.34; \( p = 0.29 \)]. BSI risk was reduced for antibiotic compared with standard CVCs (HR 0.43, 95% CI 0.20 to 0.96; \( p = 0.04 \)) and for antibiotic compared with heparin CVCs (HR 0.42, 95% CI 0.19 to 0.93; \( p = 0.03 \)) but not for heparin compared with standard CVCs (HR 1.04, 95% CI 0.53 to 2.03; \( p = 0.90 \)). The risk difference in BSI comparing any impregnated CVC with standard CVCs was –1.14 (95% CI –3.04 to 0.75) (heparin vs. standard CVCs –0.17, 95% CI –2.45 to 2.12; antibiotic vs. standard CVCs –2.15, 95% CI –4.09 to –0.20; antibiotic vs. heparin CVCs –1.98, 95% CI –3.90 to –0.06).

Secondary outcomes
For CR-BSI there was no significant difference between any impregnated CVC and standard CVCs (\( p = 0.13 \)) but the risk of CR-BSI was significantly lower for antibiotic CVCs than for standard CVCs (\( p = 0.03 \)). There was no significant difference in the risk of CR-BSI between antibiotic CVCs and heparin CVCs (\( p = 0.09 \)) or between heparin CVCs and standard CVCs (\( p = 0.68 \)). The BSI rate per 1000 CVC-days was lowest in the antibiotic group. The composite measure of BSI or culture-negative infection did not differ by CVC. No other secondary outcomes were associated with type of CVC.

Safety
No CVC-related adverse events (31 events) or mortality (148 events) were attributed to type of CVC. Only 12 out of 42 children with the primary outcome BSI had minocycline and rifampicin resistance reported using Etest® strips [see www.biomerieux-diagnostics.com/etest (accessed 20 November 2015)]; 8 out of 12 were resistant, in each case to both antibiotics (3/5 standard group; 2/2 antibiotic group; 3/5 heparin group).

Cost-effectiveness
We determined the cost-effectiveness of type of CVC per BSI averted using individual-level data on hospital use captured for study participants.

Methods

Resource use and costs
We assumed that inpatient hospital costs would capture the main cost drivers and the greatest proportion of direct medical costs. The time horizon aimed to include costs associated with managing BSI and was defined as 6 months post randomisation (or death).

Resource use was evaluated using:

i. trial case report forms (CRFs) recording admission and transfer/discharge dates for PICUs, high-dependency units (HDUs) and paediatric wards within participating hospitals

ii. Hospital Episode Statistics (HES) containing Healthcare Resource Groups (HRGs) for admissions to NHS hospitals in England
iii. the Paediatric Intensive Care Audit Network (PICANet), containing length of stay and HRGs for HDU and PICU admissions
iv. Hospital Patient Administration Systems (PASs) of participating hospitals, capturing length of stay and HRGs in PICUs and wards

The primary cost analysis was based on CRFs and PASs, with 6-month costs taken from HES, supplemented with HDU and intensive care unit (ICU) data from PICANet. Total individual patient costs were calculated from the sum of their bundled (ward) HRGs coded from the national tariff and their unbundled (ICU/HDU) codes taken from the national schedule.

Incremental analysis
The cost-effectiveness of each type of CVC was evaluated by (1) ranking type of CVC according to decreasing effectiveness and (2) eliminating ineffective or dominated interventions (those that are less effective but more costly than others). The incremental cost-effectiveness ratio (ICER) for the remaining CVCs was calculated as the difference in adjusted total costs divided by the difference in risk of BSI.

A cost-effectiveness acceptability curve was generated, using bootstrapping to account for the joint uncertainty in costs and outcomes.

Value of health-care resources associated with bloodstream infection
The value of health-care resources associated with BSI was estimated using generalised linear regression to model total post-randomisation costs, adjusting for significant prespecified baseline variables.

All analyses were performed using Stata version 10 (StataCorp LP, College Station, TX, USA).

Results
The average post-randomisation stay in the PICU was 10.5 days (95% CI 9.2 to 11.9 days) for standard CVCs, 10.8 days (95% CI 9.3 to 12.5 days) for antibiotic CVCs and 9.9 days (95% CI 8.6 to 11.4 days) for heparin CVCs. There were no significant differences in length of stay by CVC in PICUs ($p = 0.61$), HDUs ($p = 0.73$) or wards ($p = 0.54$).

The mean 6-month unadjusted costs per patient were £44,503 (95% CI £40,554 to £48,776) for standard CVCs, £45,663 (95% CI £41,600 to £49,994) for antibiotic CVCs and £42,065 (95% CI £38,220 to £46,246) for heparin CVCs. Costs were not significantly different by CVC type ($p = 0.46$). The 6-month incremental costs were positive (£1160, 95% CI £–4743 to £6962) for antibiotic CVCs and negative (£2439, 95% CI £–8164 to £3359) for heparin CVCs compared with standard CVCs.

As heparin CVCs were shown not to be clinically effective compared with standard CVCs, the incremental analysis was limited to antibiotic CVCs compared with standard CVCs. The ICER for the 6-month time frame was £54,057 per BSI averted for antibiotic CVCs compared with standard CVCs, with a probability of 0.35 of antibiotic CVCs being cost saving or dominant.

Costs were very sensitive to the time horizon of analysis. Limiting the analysis to costs associated with the index stay only resulted in antibiotic CVCs dominating standard CVCs with a saving of £97,543 per BSI averted. The costs of antibiotic and standard CVCs became equal when the time horizon of analysis was 122 days.

The value of health-care resources associated with each BSI averted (adjusted cost per BSI estimated from the regression analysis) was £10,975 (95% CI £–2801 to £24,751).
Generalisability and cost impact

The generalisability and cost impact analysis aimed to inform the adoption of antibiotic CVCs for all children who need them during admission to PICUs in England.

Methods

Generalisability analysis
We determined the generalisability of the CATCH findings to the baseline risk of BSI in children with a CVC across PICUs in England. Rates of BSI in all children requiring a CVC in the PICU were estimated from a data linkage study using detailed information from PICANet and national laboratory surveillance data co-ordinated by Public Health England. Rates of BSI per 1000 bed-days were modelled using multilevel Poisson regression, adjusting for significant patient risk factors ($p < 0.05$).

Cost impact analysis
The baseline risk was defined as the number of BSIs per 1000 bed-days in children using standard CVCs in English PICUs during 2012. We estimated the BSI rate using antibiotic CVCs by applying the rate ratio from the trial to the baseline BSI rate, assuming that, irrespective of baseline risk, the relative effect of impregnated CVCs would be the same in all children. The number of BSIs averted using antibiotic CVCs was estimated by applying the respective BSI rates to the total number of bed-days in 2012. We estimated the number of admissions requiring CVCs from responses to a PICU survey on the percentage of emergency and elective admissions receiving CVCs in 2012.

We determined the budget and cost impacts of adopting antibiotic-impregnated CVCs by synthesising the following evidence: (1) the estimated risk of BSI using standard CVCs (derived from the data linkage study); (2) the number of BSIs potentially averted by using antibiotic-impregnated CVCs (based on the relative treatment effect in the trial); (3) the additional £36 associated with purchasing each impregnated CVC for all children expected to require one (numbers of CVCs based on PICU survey data); and (4) the value of the health-care resources associated with each averted BSI (from the trial economic analysis).

Results
The additional cost of purchasing antibiotic CVCs for all children in English PICUs in 2012 corresponded to an estimated budget impact of £317,916 (8831 CVCs). Based on 2012 BSI rates, the cost impact of managing BSIs occuring with standard compared with antibiotic CVCs in all PICUs was £2.5M per year (95% uncertainty interval –£66,544 to £5,557,451). The BSI rate using standard CVCs was 4.58 (95% CI 4.42 to 4.74) per 1000 estimated CVC-days in 2012. Applying the rate ratio gave an estimated 232 BSIs averted using antibiotic CVCs. The additional costs of antibiotic CVCs would be less than the value of resources associated with managing BSIs in PICUs with a standard BSI rate $> 1.2$ per 1000 CVC-days.

Conclusions

Implications for practice
The primary outcome, time to BSI, did not differ between impregnated and standard CVCs. Secondary analyses showed that antibiotic CVCs reduced the risk of BSI compared with standard or heparin CVCs. Therefore, use of impregnated CVCs for children admitted to PICUs could result in clinically important reductions in BSI rates. The benefits of antibiotic-impregnated CVCs apply even for PICUs with low BSI rates, although uncertainty remains whether or not they are cost-effective for the NHS.
Recommendations for research

- Adoption of impregnated CVCs in PICUs should be considered. Implementation strategies could be monitored through linkage of electronic health-care data and clinical data on CVC use with laboratory surveillance data on BSI.
- Further trials comparing antibiotic-impregnated or heparin-bonded CVCs with standard CVCs for children or adults in intensive care are not recommended.
- The NHS should work with industry to evaluate different types of impregnation for specific patient groups (e.g. neonates or patients requiring long-term CVCs).
- Use of linked administrative data should be considered for future trials to determine the generalisability of interventions when the event rate is likely to change substantially over the lifetime of the trial and to monitor implementation of effective interventions.

Trial registration

This trial is registered as ClinicalTrials.gov NCT01029717.

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 08/13/47. The contractual start date was in March 2010. The draft report began editorial review in May 2015 and was accepted for publication in October 2015. 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. 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.

© Queen’s Printer and Controller of HMSO 2016. This work was produced by Harron et al. under the terms of a commissioning contract issued by the Secretary of State for Health. 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).
Health Technology Assessment 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 HTA Programme, UK

NIHR Journals Library Editors

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

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

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

Professor Matthias Beck  Chair in Public Sector Management and Subject Leader (Management Group), Queen’s University Management School, Queen’s University Belfast, UK

Professor Aileen Clarke  Professor of Public Health and Health Services Research, Warwick Medical School, University of Warwick

Dr Tessa Crilly  Director, Crystal Blue Consulting Ltd, UK

Dr Peter Davidson  Director of NETSCC, HTA, UK

Ms Tara Lamont  Scientific Advisor, NETSCC, UK

Professor Elaine McColl  Director, Newcastle Clinical Trials Unit, Institute of Health and Society, Newcastle University, UK

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

Professor Geoffrey Meads  Professor of Health Sciences Research, Health and Wellbeing Research and Development Group, University of Winchester, UK

Professor John Norrie  Health Services Research Unit, University of Aberdeen, 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 Riemsma  Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

Professor Helen Roberts  Professor of Child Health Research, UCL 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

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

Editorial contact: nihredit@southampton.ac.uk