Title: Pragmatic randomised, controlled trial of impregnated central venous catheters for preventing bloodstream infection in children

Authors: Gilbert RE, Mok Q, Dwan K, Harron K, Moitt T, Millar M, Ramnarayan P, Tibby S, Hughes D, Gamble C, on behalf of the CATCH trial*

Ruth Gilbert MD	Professor of Clinical Epidemiology, UCL Institute of Child Health, 30 Guilford St, London, WC1N 1EH. R.gilbert@ucl.ac.uk, Tel: +442079052101 Fax:+442079052793
Quen Mok FRCP	Consultant in Paediatric Intensive Care, Great Ormond Street Hospital for Children. Quen.Mok@gosh.nhs.uk
Kerry Dwan PhD	Research Associate, Department of Biostatistics, University of Liverpool. Kerry.Dwan@liverpool.ac.uk
Katie Harron PhD	Research Fellow, UCL Institute of Child Health, London. k.harron@ucl.ac.uk
Tracy Moitt	Senior Trials Manager, Medicines for Children Clinical Trials Unit, University of Liverpool. tracyb@liverpool.ac.uk
Mike Millar PhD, FRCPath	Consultant in Infection, Barts Health NHS Trust (Honorary Professor, Queen Mary, University of London. Michael.Millar@bartshealth.nhs.uk,
Padmanabhan Ramnarayan MD	Consultant in Paediatric Intensive Care and Retrieval, Children's Acute Transport Service, Great Ormond Street Hospital for Children, London. ramnap@gosh.nhs.uk,
Shane M Tibby MB ChB	Consultant in Paediatric Intensive Care, Evelina Children's Hospital, London. Shane.Tibby@gstt.nhs.uk
Dyfrig Hughes PhD	Professor of Pharmacoeconomics, Centre for Health Economics & Medicines Evaluation, Bangor University. D.a.hughes@bangor.ac.uk,

Carrol Gamble PhD	Professor of Medical Statistics, Department of Biostatistics, University of Liverpool. C.Gamble@liverpool.ac.uk

*Names and contributions given in acknowledgements

Word count 3721

Key words: randomised controlled trial, bloodstream, infection, central venous catheter, pediatric intensive care, antibiotic, heparin

Abstract

Background: Impregnated central venous catheters (CVCs) are recommended for adults to reduce bloodstream infection (BSI) but not for children due to a lack of evidence for their effectiveness.

Methods: Randomised trial of children admitted to 14 English paediatric intensive care units (PICUs). The primary outcome, time to first BSI between 48 hours after randomisation and 48 hours after CVC removal, was compared for any impregnation (antibiotic or heparin) versus standard CVCs (primary analyses) and in pair-wise comparisons of all three CVC types (secondary analyses).

Findings: BSI occurred in 3.59% (18/502) randomised to standard CVC, 1.44% (7/486) to antibiotic and 3.42% (17/497) to heparin CVC. Primary analyses showed no effect of impregnated (antibiotic or heparin) compared with standard CVCs (hazard ratio for time to first BSI 0.71; 95%CI 0.37-1.34) Secondary analyses showed antibiotic CVCs were superior to standard (HR 0.43; 0.20-0.96) and to heparin CVCs (HR 0.42; 0.19-0.93), but heparin did not differ from standard (HR 1.04; 0.53-2.03). Clinically important and statistically significant absolute risk differences were found only for antibiotic vs standard (-2.15%; 95%CI: -4.09, -0.20; number needed to treat=47; 95%CI: 25, 500) and antibiotic vs heparin CVCs (-1.98%; -3.90, -0.06; NNT=51; 26, 1667). Time to thrombosis, mortality by 30 days, and minocycline or rifampicin resistance, did not differ by CVC allocation.

Interpretation: Antibiotic-impregnated CVCs significantly reduced the risk of BSI compared with standard and heparin CVCs. Widespread adoption of antibiotic-impregnated CVCs could help prevent BSI in PICU.

(ClinicalTrials.gov Identifier:NCT01029717)

Funding: UK National Institute for Health Research.

Introduction

Bloodstream infections (BSI) are important causes of adverse clinical outcomes and costs to health services. Paediatric intensive care units (PICUs) have one of the highest reported rates of hospital-acquired BSI of any clinical specialty with central venous catheters (CVCs) being a frequent cause of BSI in PICU.[1, 2] US studies report the success of improved aseptic practices during insertion and maintenance of CVCs for reducing rates of catheter-related BSI (CR-BSI).[3-5] The UK Department of Health invested in similar infection reduction initiatives, including the *Saving Lives* CVC care bundle and the *Matching Michigan* scheme.[6-8]

Use of CVCs that are impregnated, for example with antibiotics, chlorhexidine or heparin, has been recommended as part of these infection reduction initiatives in the US and UK, but only for adults at high risk of BSI.[7, 9] Impregnated CVCs have not been recommended for children.[10] The evidence for reduced rates of CR-BSI with impregnated compared with standard CVCs derives from trials predominantly of adults. Recent systematic reviews draw on evidence from 56 randomised controlled trials (RCT).[11-14] A network meta-analysis of direct and indirect comparisons of impregnated and standard CVCs found that heparin-bonded or antibiotic-impregnated CVCs were the most effective options, with an associated 70%-80% reduction in the risk of CR-BSI.[14]

Despite the large number of randomised controlled trials, there is relatively weak evidence to guide policy about adoption of impregnated CVCs for all who need them, particularly children. Firstly, there are inherent biases in the use of CR-BSI - the primary outcome used in all previous trials - as this could overestimate benefits of antibiotic impregnation.[11, 15] CR-BSI requires positive cultures of the same organism from the CVC tip and from blood, which excludes many patients with BSI and may favour antibiotic impregnated CVC tips through inhibition of bacterial growth in culture media.[16] Secondly, few studies have been conducted in the context of the low infection rates associated with improved asepsis programmes.[6, 7, 17] Thirdly, very few trials involve children (see box on research in

58 context).[18-20] Compared with adults, children require narrower CVCs, which thrombose more readily.
59 Standard, non-impregnated CVCs are still used for the majority of children in UK PICUs.[10] However,
60 there could be significant gains for children's health and healthcare costs if impregnated CVCs could
61 be confirmed to reduce rates of BSI.
62
63 We conducted a pragmatic, three-arm randomised controlled trial to determine the effectiveness of
64 any type of impregnation (antibiotic or heparin) compared with standard CVCs for preventing BSI in
65 children requiring intensive care. A secondary aim was to determine which of the three types of CVC
66 was most effective. We also determined the effectiveness of type of CVC on CR-BSI, duration of
67 care, and safety, including mortality and adverse events such as antibiotic resistance.
68

Methods

Design, study population and intervention

Children admitted to 14 PICUs in England between December 2010 and November 2012 were randomised to CVCs impregnated with antibiotics or heparin or to standard CVCs. Both types of impregnation involve internal and external surfaces. We used polyurethane CVCs manufactured by Cook Medical Incorporated (IN 47404 USA). Sizes used were French gauge 4 (double lumen), 5 or 7 (triple lumen). Cook reports a concentration of 503 µg/cm minocycline and 480 µg/cm rifampicin for their antibiotic impregnated CVC, which reduces biofilm formation.[21] Heparin bonding reduces thrombus and thereby biofilm formation and uses benzalkonium chloride as an anti-infective bonding agent.[16 22]

Children <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 or more days. For children admitted to PICU following elective surgery, we sought prospective parental consent during pre-operative assessment. For children who required a CVC as an emergency, we sought parental consent after randomisation and stabilisation (deferred consent) to avoid delaying treatment. Parents consented to the use of their child's data for the trial, to follow-up using routinely recorded clinical data, and to an additional 0.5ml of blood being collected for PCR testing whenever a blood culture was clinically required. Further details are given in the protocol (see supplementary material).

Randomisation and masking

Children were randomised at the bedside or in theatre (operating room) immediately prior to CVC insertion. The clinician or research nurse opened a pressure sealed, sequentially numbered, opaque envelope containing the CVC allocation. Randomisation sequences were computer generated in a 1:1:1 ratio by an independent statistician in random blocks of three and six, stratified by method of

consent, site and envelope storage location within the site to facilitate easy access to envelopes (e.g. for insertion in theatre and in PICU).

CVC allocation was not blinded to the clinician responsible for inserting the CVC (due to different colour strips for antibiotic and heparin CVCs) but since CVCs looked identical whilst in situ, allocation was concealed from patients, their parents and PICU personnel responsible for their care. Labels identifying the type of CVC were held securely in a locked drawer in case unblinding was required. Participant inclusion in analyses and occurrence of outcome events were established prior to release of the randomisation sequence for analysis and for the data monitoring committee.

Comparisons and end points

The primary analysis for the trial compared any impregnated CVCs (antibiotic or heparin) with standard CVCs. Secondary analyses involved pair-wise comparisons for the three types of CVC.

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 included in the primary outcome 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 due to suspected infection. Blood cultures were recorded as positive for the primary outcome if any organism was isolated that was not a skin commensal or if coagulase-negative staphylococci (or other skin commensals) were isolated and there were two or more positive cultures of the same organism within 48 hours of each other. A clinical committee reviewed all primary outcomes involving positive cultures without knowledge of CVC allocation status. A sensitivity analysis assumed that the primary outcome occurred for those with a record of clinical indication but no blood culture taken in the primary outcome time window.

Secondary BSI-related outcomes were: (1) CR-BSI: based on same organisms cultured from blood and CVC tip between 48 hours after randomization and 48 hours after CVC removal; or differential positivity of cultures from multiple CVC lumens on two or more occasions; or exit site infection or CVC removed for infection; (2) rate of BSI per 1000 CVC-days: based on one or more BSI between randomisation and CVC removal; and (3) time to a composite measure of BSI comprising the primary outcome or a negative blood culture combined with a positive 16S PCR result for bacterial DNA, 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.

Other secondary outcomes included time to CVC removal and time to CVC thrombosis (defined by two episodes within five days of each other of difficulty flushing the CVC or drawing back blood from the CVC, one episode of swollen limb, CVC removal due to thrombosis, or a positive ultrasound indicating thrombosis). We also compared the time to PICU discharge, hospital discharge, and death within 30 days of randomisation. Deaths were recorded by the research team and/or by linkage to death certification data from the Office of National Statistics. Cost-effectiveness analyses based on linked hospital resource data for six-months follow-up will be reported elsewhere.

Safety analyses compared CVC-related adverse events (including unexplained thrombocytopenia after insertion of CVC), mortality, and antibiotic resistance to minocycline (>0.5 μg/ml) or rifampicin (>1.0 μg/ml) based on etest strips applied to organisms isolated from BSI (www.biomerieux-diagnostics.com/etest). Incomplete laboratory testing and reporting limited analyses of resistance in positive blood cultures and prevented analysis of resistance in cultures from the CVC tip (as specified in the protocol).

Study procedures

Participation in the trial did not involve any changes to standard clinical care or data collection apart from collecting an additional 0.5ml of blood whenever a blood culture sample was taken. The sample was sent for PCR testing for 16S rRNA of bacterial ribosome protein to detect bacterial infection. We sought consent to link data from hospital administrative records for six months after randomisation and from the national Paediatric Intensive Care Audit Network (PICANet [23]) to the child's study data to categorise the primary reason for admission and the Paediatric Index of Mortality score on admission (PIM2 [24]).

Sample size

We based the sample size calculation for the primary analysis on a relative risk (RR). We assumed detection of a RR of 0.5 in patients with a baseline risk of 10% would change policy. We assumed the RR would remain relatively constant across baseline risks while the absolute risk difference would be more variable. 1200 children in a 2:1 ratio (impregnated:standard) were required to achieve 80% power to detect a RR 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. A lower than expected BSI rate of 5% would have 62% power to detect a RR of 0.5 or 80% power for a RR of 0.32.

The Independent Data Monitoring Committee recommended continuation of the study until 30 November 2012 after: reviewing the first 209 children; an interim analysis of 650 children using the Peto-Haybittle stopping rule for the primary outcome; recruitment had reached the original target of 1200 pre-schedule in June 2012 and there were no safety concerns. The recommendation for continuation aimed to exhaust available funding.

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.

The statistical analysis plan was developed prior to analysis and is available in the supplementary material. The full statistical report is available from the authors. A 5% level of statistical significance and 95% confidence intervals were used throughout. Absolute risk differences were calculated for proportions. Time to event outcomes were analysed using Kaplan-Meier curves and the log-rank test. Cox regression was used to adjust primary and secondary analyses of time to first BSI for prospective or deferred consent type and suspected infection at baseline. In a post-hoc, sensitivity analysis, we used cumulative incidence curves to evaluate competing risks from death for time to first bloodstream infection. We applied Gray's test to detect whether there was a difference between impregnated and standard CVCs for the primary outcome.[25] For secondary outcomes, binary outcomes were analysed using the chi squared test and continuous outcomes analysed using the Mann Whitney U test. The rate of BSI (defined as the total number of BSI per 1000 CVC-days occurring between randomisation and CVC removal) was analysed using Poisson regression. All analyses were conducted using SAS software version 9.2.

Study oversight and role of funders

The Research Ethics Committee for South West England approved the study protocol (reference number 09/H0206/69). The manufacturer Cook supplied CVCs to participating units at a 20% discounted price. Neither the manufacturer nor the funder (the National Institute of Health Research) had any role in the design of the study, collection or interpretation of data or reporting of results. The CATCH trial is registered with ClinicalTrials.gov (Identifier:NCT01029717). The protocol and Statistical Analysis Plan are available as supplementary files and at http://www.nets.nihr.ac.uk/projects/hta/081347. The full statistical analysis report is available on request from the authors.

Results

Study population

Overall, 1859 children were randomised (501 prospective, 1358 emergency). However, 984/1358 (72%) emergency patients subsequently provided deferred consent, leaving 1485 participants for final analysis (Figure 1). Reasons for non-consent are reported in Figure 1. Of the 1485 randomised participants, 75 (5%) did not receive a CVC: in 53 insertion was attempted but unsuccessful and in 22 CVC insertion was not attempted (16 no longer required, 5 reason not known and 1 patient died). Of those receiving a CVC, more of those randomised to standard CVC received the allocated type of CVC (93%; 468/502 allocated to standard; 90%; 437/486 to antibiotic, and 89%; 440/497 to heparin; Figure 1). The majority of CVCs received but not allocated CVCs were standard CVCs (69%; 45/65; Figure 1). All randomised and consented participants were followed up until 48 hours after CVC removal or attempted CVC insertion.

Baseline characteristics

Table 1 shows that over half (58%) of children were aged under 12 months at admission, with one-third aged less than 3 months. One third of children had surgery prior to admission to PICU and half had cardiovascular problems as their primary diagnosis at admission. CVC insertion took place in the operating room for 437/493 (89%) in the prospective consent (elective) group, but in only 34/917 (4%) of the deferred consent (emergency) group

Endpoints

Primary outcome

Clinical indicators of infection were recorded during the primary outcome time interval from 48 hours after randomisation up to 48 hours after CVC removal for 610/1485 (41%) participants, most of whom (593/610; 97%) had blood cultures taken (Figure 1). Derivation of the primary outcome and the number of BSI excluded from the primary outcome is shown in supplementary Figure 1. The

primary outcome of BSI was recorded for 42 children: standard 18/502 (3.6%); antibiotic 7/486 (1.4%); heparin 17/497 (3.4%). Gram positive organisms accounted for the majority of BSI (23/42; 55%) of which 6 (14%) were positive for coagulase negative staphylococci (Table 2). Details of all organisms isolated in the primary outcomes are given in supplementary Table 1. All outcomes are reported by CVC type in Table 2.

In the primary comparison, time to BSI did not differ between impregnated CVCs (antibiotic or heparin combined) and standard CVCs (Hazard ratio 0.74; 95%CI: 0.37, 1.34; Table 3). In secondary, pair-wise comparisons, antibiotic impregnated CVCs reduced the risk of BSI compared with standard CVCs (HR 0.43; 0.20, 0.96) and compared with heparin CVCs (HR 0.42; 0.19, 0.93). Absolute risks of BSI differed significantly at the 5% level only for antibiotic CVCs compared with standard (-2.15%) and heparin CVCs (-1.98%; Table 3).

Figure 2 shows the Kaplan-Meier curve for time to first BSI. There was no significant difference in time to first BSI comparing any impregnated CVC with standard (p=0.29) or heparin with standard (p=0.90). BSI risk was reduced for antibiotic compared with standard CVCs (p=0.04) and for antibiotic compared with heparin CVCs (p=0.03). The direction of these results was robust to the sensitivity analysis in which the 17 cases with clinical indicators but no blood culture taken were assumed to have a positive BSI (supplementary appendix Table A2). The direction of results did not change in the regression analysis (supplementary appendix Table A3). Competing risks analyses using Gray's test indicated no difference between impregnated compared with standard CVCs for either competing risks (p-values of p=0.29 for bloodstream infection and p=0.89 for death).

Secondary outcomes

There was no significant difference between any impregnated and standard CVCs (p=0.13) in the risk of CR-BSI. The risk of CR-BSI was significantly lower for antibiotic vs standard CVC (p=0.03) and for

antibiotic vs heparin CVCs (p=0.09; Table 3). The BSI rate per 1000 CVC-days was lowest in the antibiotic group (Table 2). No children had more than one BSI whilst the trial CVC was in place. The inter-relationship between outcomes involving BSI is shown by time since randomisation in supplementary appendix Figure 2. The composite measure of BSI or culture negative infection did not differ by CVC (Tables 2 and 3). Supplementary Table A4 shows indicators of infection contributing to the composite measure. No other secondary outcomes were associated with type of CVC (Table 3).

Safety

The cohort for safety (per protocol) analyses were based on children who had a CVC insertion attempted. These analyses comprised more children in the standard group (n=533) than the antibiotic (n=451) or heparin groups (n=479; Table 2; see statistical analysis plan section 11). No CVC-related adverse events (31 events) or mortality (148 events) were attributed to type of CVC received (Table 2). Two children developed thrombocytopenia unrelated to the type of CVC. One was allocated to antibiotic and the other to heparin CVC (full statistical analysis report available from the authors).

Testing for antibiotic resistance varied by centre. Only 12 of the 42 children with the primary outcome BSI had minocycline and rifampicin resistance reported using etest strips; 8/12 were resistant to one or both antibiotics (3/5 standard; 2/2 antibiotic; 3/5 heparin; supplementary Table 5). Most resistance occurred in gram negative organisms (7/9 organisms cultured from 8 BSI episodes; Table A5). Resistance was detected in two BSI that were positive for staphylococcal species: one allocated to antibiotic and the other to heparin CVC (supplementary appendix Table A5).

Discussion

Impregnated CVCs are not recommended for use in children because of the lack of clear evidence of their effectiveness. In this first trial to compare two types of impregnated CVCs with standard CVCs in children our primary analysis showed no evidence of a statistically significant difference between time to first BSI for any impregnated CVCs (antibiotic and heparin combined) compared with standard CVCs. However, antibiotic impregnation reduced the risk of BSI by 57% compared with standard CVCs, and by 58% compared with heparin-bonded CVCs. Antibiotic-impregnated CVCs were associated with an absolute risk reduction of 2.15% compared with standard CVCs, meaning 47 children (95% CI: 25, 500) would need to be treated with an antibiotic-impregnated CVC instead of a standard CVC to prevent one case of BSI.

Strengths of the study include the use of any BSI as a clinically important primary outcome thereby avoiding the biases inherent in measuring CR-BSI. A further strength was the restriction to positive blood cultures that were clinically indicated, thereby recording an outcome that clinicians would regard as potentially serious and needing treatment. Restriction to clinically indicated blood cultures increased the clinical relevance of the primary outcome, but, in contrast to routine blood culture sampling for all study participants, diminished the sensitivity of the study to detect bacteraemia. Only 41% of children had clinical indicators of blood stream infection recorded during the primary outcome interval but nearly all of these had a blood culture taken. A third strength is the representativeness of the study population in terms of children admitted to the 14 largest PICUs (out of a total of 24) across the country. We were able to enrol a similar proportion of emergency patients (two-thirds) as seen in practice,[26] enabled by the inclusion of retrieved children and the use of deferred consent.

Limitations include the limited power of the study to detect differences in the primary outcome according to the type of CVC. The trial was based on the best available evidence at the time, which

299 indicated large but equivalent benefits of antibiotic and heparin CVCs compared with standard. The
300 key question, which determined our primary analysis and sample size, was whether these benefits
301 occurred in children. Secondary, pair-wise comparisons addressed which type of impregnated CVC
302 was best, but the trial was not adequately powered to detect the anticipated small differences
303 between antibiotic and heparin CVCs. Power was further eroded by the low baseline rate of BSI.
304
305 Another limitation relates to finding that although antibiotic CVCs reduced BSI, we found no
306 differences in secondary outcomes such as mortality, duration of CVC insertion, or the composite
307 measure of BSI or culture negative infection. One potential reason is the complex and varied
308 conditions and disease processes affecting patients receiving intensive care. Antibiotic CVCs may
309 affect BSI in these patients but not other outcomes. For example, none of the deaths were deemed
310 to be directly attributable to BSI. A second reason is the poor specificity of the secondary
311 outcomes. Mortality and duration of CVC placement are affected by a number of treatments, not
312 just CVC impregnation, thereby biasing in favour of a null effect for these secondary outcomes. The
313 reduction in the hazard ratio for antibiotic vs standard CVC was largest for CRBSI (reduced by 75%),
314 less for BSI (reduced by 59%), and small and not significant for the composite measure of BSI or
315 culture negative infection. Of these outcomes, CRBSI is most specifically affected by antibiotic
316 impregnation, whereas the composite measure of BSI is affected by other disease and treatment
317 factors, thereby biasing towards the null effect.
318
319 Another factor likely to bias towards the null effect for secondary outcomes is the potential for
320 'rescue' treatment in response to signs of BSI. Patients in intensive care units are continuously
321 monitored for changes in their condition and treated promptly. As a result, signs of infection should
322 be less likely to develop into septic shock given good intensive care management. Such responses
323 introduce bias towards the null effect for secondary outcomes such as mortality but are difficult to
324 measure adequately.

Lack of blinding was another limitation, although we found no evidence of differential blood culture sampling by trial arm (Figure 1). The number of children who received their allocated CVC was slightly higher for those in the standard arm, probably reflecting the fact that standard CVCs were the default CVC used in many units.[10] Lastly, antibiotic resistance testing using etest strips was not done for all positive blood cultures. This reflects local laboratory administration and processing, which centralised testing of positive cultures could have mitigated. Where reported, resistance occurred in all trial arms, predominantly in gram negative isolates, as expected. The low rates are consistent with previous lack of evidence for the emergence of resistance.[27]

Implications

The primary outcome, time to BSI, did not differ between impregnated and standard CVCs. However, secondary, pair-wise analyses of the type of CVC, showed that only antibiotic CVC reduced the risk of BSI compared with standard and with heparin CVCs. The low rate of BSI in the standard and heparin groups and the multiple, pair-wise comparisons, reduced the power of our study. However, when combined with evidence from systematic reviews, our findings establish the effectiveness of antibiotic-impregnated CVCs compared with standard CVCs and extend this evidence for paediatric use. For the first time we directly demonstrate effectiveness of antibiotic CVCs compared with heparin-bonded CVCs in this population, even in the context of low rates of BSI. Widespread adoption of antibiotic-impregnated CVCs could help prevent BSI in PICU. Whether these benefits outweigh the additional costs depends on differential pricing of antibiotic and standard CVCs by the manufacturer and the cost benefits of avoiding bloodstream infection.

Research in context

Evidence before this study

We searched PubMed, initially for systematic reviews or meta-analyses, using the clinical queries filter for therapy studies or terms for meta-analysis and (catheter* OR central OR venous OR intravenous) (impregnated OR bonded OR coated OR antibiotic OR heparin) and infection. We found 5 systematic reviews published since 2008. The two most recent reviews were both published in the Cochrane Library. One included any type of CVC impregnation, but excluded children (56 RCTs, 5 antibiotic vs standard; 1 heparin vs standard).[13] The other compared heparin bonded with standard CVCs in children (2 trials).[28] All the trials evaluated in these two reviews were included in an earlier systematic review and network meta-analysis by Wang et al which comprised direct and indirect mixed treatment comparisons of 45 RCTs evaluating CR-BSI (6 antibiotic vs standard none in children; 3 heparin vs standard, 2 in children). For antibiotic (minocycline-rifampicin) compared with standard CVC, Wang et al reported a pooled odds ratio for CR-BSI of 0.18 (95%CI; 0.08, 0.34).[14] We found one subsequent randomised controlled trial which compared antibiotic (minocycline and rifampicin) and standard CVCs for children undergoing heart surgery.[19] The trial of 288 participants was terminated early because of a low event rate (3 catheter associated BSI in each group). The mixed treatment comparison for heparin-bonded vs standard CVCs produced a pooled odds ratio of 0.20 (0.06, 0.44), and for antibiotic compared with heparin CVCs (indirect comparisons only), OR 1.18 (0.28, 3.29).[14] A previous cost-effectiveness analysis based on trials in adults estimated that impregnated CVCs would be cost effective even at baseline risks of BSI as low as 0.2%.[12]

Added value of this study

This is the first trial to evaluate antibiotic and heparin CVCs in children and in the context of low BSI rates associated with improved asepsis practices. We add new evidence of effectiveness of antibiotic CVCs for any BSI, showing a 57% reduction compared with standard CVCs in children. We confirmed the effectiveness of antibiotic CVCs found in systematic reviews of trials in adults, with a 75% reduction in the risk of CR-BSI (HR 25; 0.07, 0.90) compared with standard CVCs, for the first time in children. We also report for the first time that antibiotic CVCs are superior to heparin CVCs. These results are based on secondary analyses so need to be interpreted with caution. Our results are consistent with previous studies showing no effect of antibiotic impregnation on mortality or adverse effects.

In contrast to evidence from systematic reviews, we found no significant effect for heparin bonded vs standard CVCs. The lack of effectiveness of heparin CVCs may relate to the low baseline event rate observed in CATCH, which was conducted after implementation of CVC care bundles in PICUs to improve asepsis procedures during CVC insertion and maintenance.[10, 29] Another potential explanation could be emergence of resistance to benzalkonium chloride, the bonding agent used for heparin, which is widely used in hand hygiene products.

Implications of the available evidence

When combined with previous systematic reviews, our findings establish the effectiveness of antibiotic-impregnated CVCs compared with standard CVCs and extend this evidence for paediatric use. Widespread adoption of antibiotic-impregnated CVCs could help prevent BSI in PICUs.

Contributions

All authors contributed to the design and/or conduct of the study. RG (chief investigator), QM and CG conceived and designed the study. Statistical analyses were conducted by Kerry Dwan and Carrol Gamble. End point review for the primary outcome was done by QM, MM and RG. RG, QM, KD, KH and CG wrote the paper and all authors commented on the manuscript and approved the final version.

Acknowledgements

We thank the children and families who participated in the CATCH trial and the principal investigators and research nurses at each study site (in order of number of patients recruited): GOSH (Quen Mok, Twin Yen Lee, Samantha Riordan), Southampton General Hospital (Iain Macintosh, Jenni McCorkell, Katie Stearn, Rosie Mitchell), Evelina Children's Hospital (Shane Tibby, Julia Harris, Paul Wellman), Birmingham Children's Hospital (Oliver Bagshaw, Jenna Spry, Simon Laker, Nikki Holdback), Leeds General Infirmary (John Roche, Sian Cooper, Darren Hewett), Alder Hey Children's Hospital (Steve Kerr, Felicity Haigh), Bristol Royal Hospital for Children (Michelle White, Margrid Schindler, Clare Traub, Nina Worrin), Glenfield Hospital (Raghu Ramaiah, Rekha Patel), Royal Brompton Hospital (Duncan Macrae, Sarah Bacon), St Mary's Hospital, London (Mehrengise Cooper, Amina Abdulla, Amy Brewer), Royal Victoria Infirmary (Rachel Agbeko, Christine Mackerness), Queens Medical Centre (Patrick Davies, Daniel Walsh, Lindsay Crate), Freeman Hospital (Rachel Agbeko, Clare Simmister), Leicester Royal Infirmary (Raghu Ramaiah, Rekha Patel). We thank the Local Research Networks (LRNs) in England for supporting the trial implementation; the Trial Steering Committee (Robert Tasker (chair) and Stephen Playfor (chair), Andy Vail, Derek Roebuck and Jim Gray) and the Independent Data Safety and Monitoring Committee (Paul Ewings (chair), Mike Sharland, Neena Modi) for their oversight of the study. In addition to co-authors, Colin Ridyard, Angie Wade, Liz Draper, Oliver Bagshaw, Julia Harris and Darren Hewett participated in the trial management group. Other contributors were Michaela Blundell (quality assurance checks),

Susan Howlin and Lynsey Finnetty (data management), and Ivana Pribramska (administrative support).

Funding

The trial was funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) programme (project number 08/13/47). The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS or the Department of Health. No funding was provided by the manufacturer (Cook) of the CVCs, although participating units could purchase CVCs at a discount of 20% during recruitment to the study. Neither the funder nor the manufacturer had any involvement in the study design, interpretation of the results or writing of the report.

References

1. Abou Elella R, Najm H, Balkhy H, Bullard L, Kabbani M. Impact of bloodstream infection on the outcome of children undergoing cardiac surgery. Pediatr Cardiol. 2010; 31(4): 483-9.

2. Elward AM, Hollenbeak CS, Warren DK, Fraser VJ. Attributable cost of nosocomial primary bloodstream infection in pediatric intensive care unit patients. Pediatrics. 2005; 115(4): 868-72.

3. Bhutta A, Gilliam C, Honeycutt M, Schexnayder S, Green J, Moss M, et al. Reduction of bloodstream infections associated with catheters in paediatric intensive care unit: stepwise approach. BMJ. 2007; 334(7589): 362-5.

4. Pronovost P, Needham D, Berenholtz S, Sinopoli D, Chu H, Cosgrove S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. New Engl J Med. 2006; 355(26): 2725-32.

5. Miller MR, Griswold M, Harris JM, II, Yenokyan G, Huskins WC, Moss M, et al. Decreasing PICU catheter-associated bloodstream infections: NACHRI's quality transformation efforts. Pediatrics. 2010; 125(2): 206-13.

6. Bion J, Richardson A, Hibbert P, Beer J, Abrusci T, McCutcheon M, et al. 'Matching Michigan': a 2-year stepped interventional programme to minimise central venous catheter-blood stream infections in intensive care units in England. BMJ Qual Saf. 2012; 22(2): 110-23.

7. Department of Health. Saving Lives: reducing infection, delivering clean and safe care: Department of Health, London 2007.

8. HM Treasury. Pre-budget report and comprehensive spending review. London: The Stationary Office; 2007.

9. O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, et al. Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis. 2011; 52(9): e162-e93.

10. Harron K, Ramachandra G, Mok Q, Gilbert R. Consistency between guidelines and reported practice for reducing the risk of catheter-related infection in British paediatric intensive care units. Intens Care Med. 2011; 37(10): 1641-7.

11. Gilbert R, Harden M. Effectiveness of impregnated central venous catheters for catheter related blood stream infection: a systematic review. Curr Opin Infect Dis. 2008; 21(3): 235-45.

12. Hockenhull J, Dwan K, Boland A, Smith G, Bagust A, Dündar Y, et al. The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation. Health Technol Asses. 2008; 12(12): 1-154.

13. Lai NM, Chaiyakunapruk N, Lai NA, O'Riordan E, Pau WSC, Saint S. Catheter impregnation, coating or bonding for reducing central venous catheter-related infections in adults. Cochrane Database Syst Rev. 2013; 6: CD007878.

14. Wang H, Huang T, Jing J, Jin J, Wang P, Yang M, et al. Effectiveness of different central venous catheters for catheter-related infections: a network meta-analysis. J Hosp Infect. 2010; 76(1): 1-11.

15. Geffers C, Zuschneid I, Eckmanns T, Rüden H, Gastmeier P. The relationship between methodological trial quality and the effects of impregnated central venous catheters. Intens Care Med. 2003; 29(3): 403-9.

16. Mermel LA, Stolz SM, Maki DG. Surface antimicrobial activity of heparin-bonded and antiseptic-impregnated vascular catheters. J Infect Dis. 1993; 167(4): 920-4.

17. Harron K, Parslow R, Mok Q, Tibby S, Wade A, Muller-Pebody B, et al. Monitoring quality of care through linkage of administrative data: national trends in bloodstream infection in UK paediatric intensive care units 2003-2012. Crit Care Med. 2015; in press.

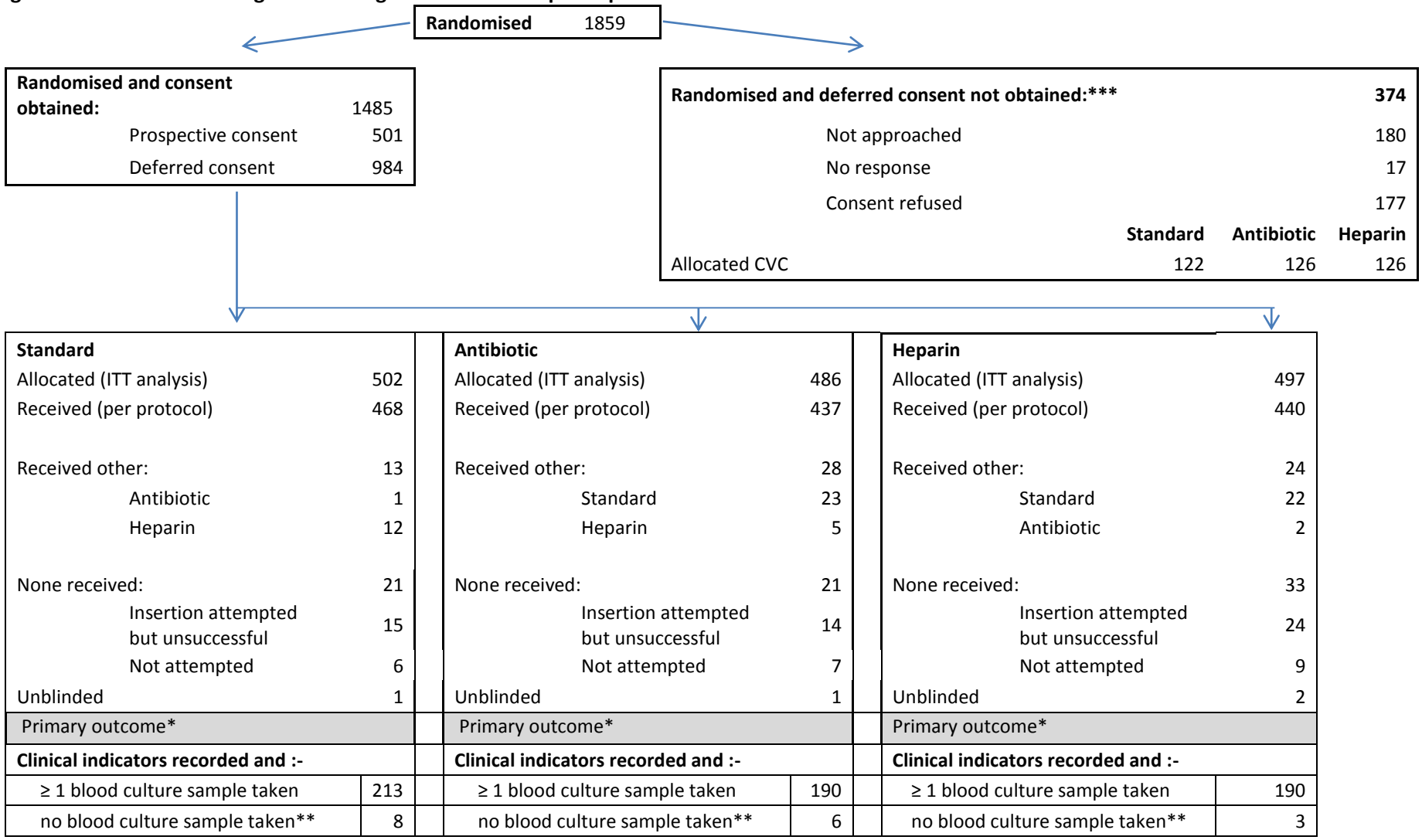
18. Pierce CM, Wade A, Mok Q. Heparin-bonded central venous lines reduce thrombotic and infective complications in critically ill children. Intens Care Med. 2000; 26(7): 967-72.

19. Cox EG, Knoderer CA, Jennings A, Brown JW, Rodefeld MD, Walker SG, et al. A randomized, controlled trial of catheter-related infectious event rates using antibiotic-impregnated catheters versus conventional catheters in pediatric cardiovascular surgery patients. Pediatr Infect Dis J. 2012.

476 20. Abdelkefi A, Achour W, Ben Othman T, Ladeb S, Torjman L, Lakhal A, et al. Use of heparin-
477 coated central venous lines to prevent catheter-related bloodstream infection. J Support Oncol.
478 2007; 5(6): 273-8.
479 21. Cook Incorporated. Cook Spectrum® Central Venous Catheter Minocycline/Rifampin
480 ANtibiotic Impregnated Power Injectable; 2013.
481 22. Raad I, Hanna H, Maki D. Intravascular catheter-related infections: advances in diagnosis,
482 prevention, and management. The Lancet Infectious Diseases. 2007; 7(10): 645-57.
483 23. Universities of Leeds and Leicester. Paediatric Intensive Care Audit Network National Report
484 2011 - 2013; 2013.
485 24. Slater A, Shann F, Pearson G. PIM2: a revised version of the Paediatric Index of Mortality.
486 Intens Care Med. 2003; 29(2): 278-85.
487 25. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing
488 risk. Ann Stat. 1988; 16(3): 1141-54.
489 26. Harron K, Mok Q, Parslow R, Muller-Pebody B, Gilbert R, Ramnarayan P. Risk of bloodstream
490 infection in children admitted to paediatric intensive care units in England and Wales following
491 emergency inter-hospital transfer. Intens Care Med. 2014; 40(12): 1916-23.
492 27. Falagas ME, Fragoulis K, Bliziotis IA, Chatzinikolaou I. Rifampicin-impregnated central venous
493 catheters: a meta-analysis of randomized controlled trials. J Antimicrob Chemoth. 2007; 59(3): 359-
494 69.
495 28. Shah PS, Shah N. Heparin-bonded catheters for prolonging the patency of central venous
496 catheters in children. Cochrane Database Syst Rev. 2014; 17(4): CD005983.
497 29. Harron K, Wade A, Muller-Pebody B, Goldstein H, Parslow R, Gray J, et al. Risk-adjusted
498 monitoring of blood-stream infection in paediatric intensive care: a data linkage study. Intens Care
499 Med. 2013; 39(6): 1080-7.

30. Harron K, Woolfall K, Gamble C, Mok Q, Ramnarayan P, Gilbert R. Deferred consent for randomised controlled trials in emergency paediatric care settings: evidence for trial design and ethics committees. Pediatrics (in press).

Figure 1: CONSORT flow diagram showing numbers of trial participants



* based on a clinically indicated blood culture sample taken ≥ 48 h after randomisation and < 48 hr after CVC removal; ** used in sensitivity analysis.***further details reported elsewhere[30]

Figure 2: Kaplan-Meier curve for time to first BSI by CVC allocation (numbers show participants at risk and number of BSI events in brackets)

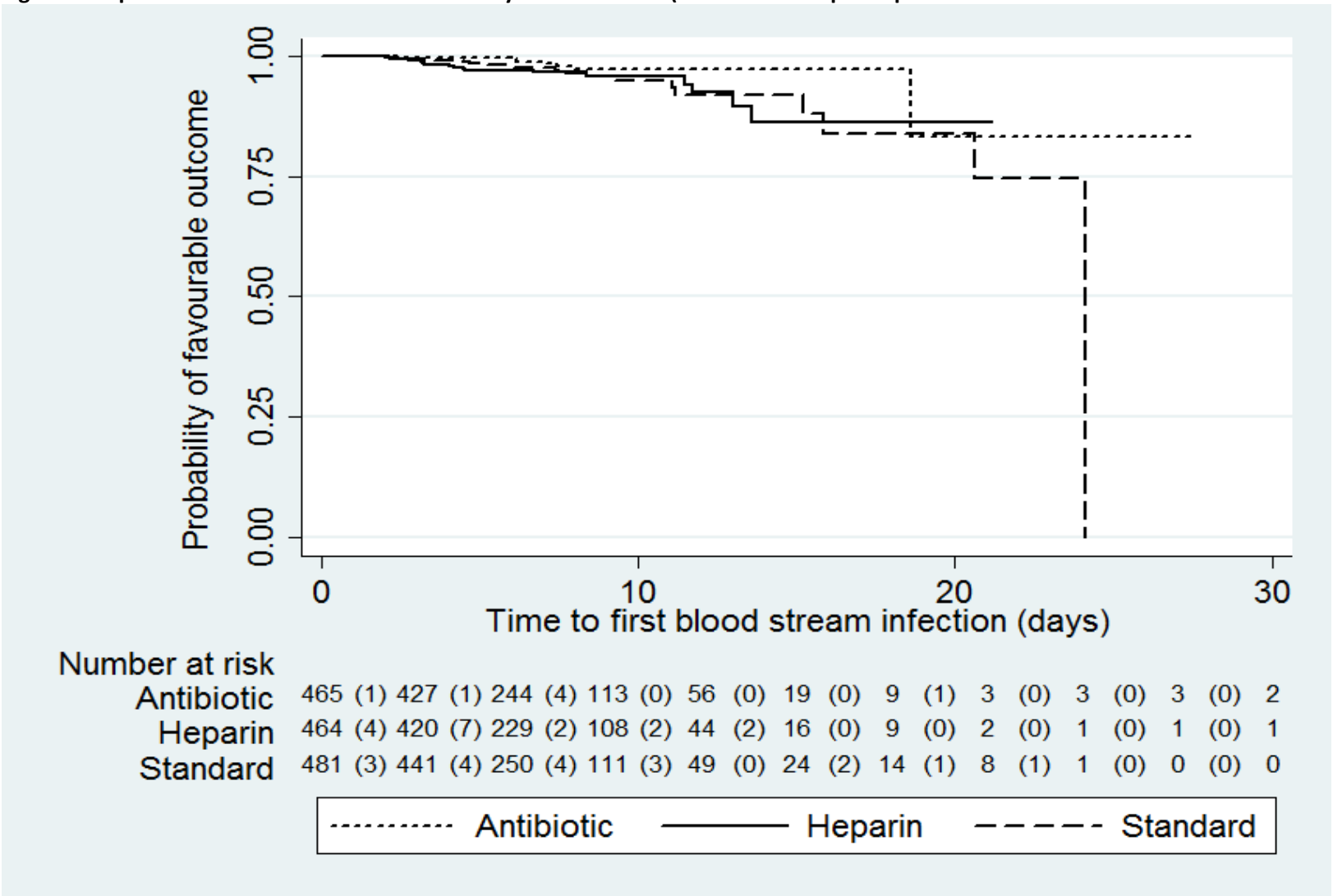


Table 1: Baseline characteristics, clinical condition at randomisation and details of the intervention (n=number of participants)

		Standard		Antibiotic		Heparin	
		n	%	n	%	n	%
Patient characteristics		**502**	**100**	**486**	**100**	**497**	**100**
Emergency (deferred consent)		333	66.3	320	65.8	331	66.6
Elective (prospective consent)		169	33.7	166	34.2	166	33.4
Male		285	56.8	291	59.9	277	55.7
Age	<3 months	159	31.7	159	32.7	175	35.2
	3-12 months	129	25.7	123	25.3	116	23.3
	1-10 years	174	34.7	154	31.7	174	35.0
	11+ years	40	8.0	50	10.3	32	6.4
Weight at admission	< 3kg	41	8.2	38	7.8	56	11.3
	3-10kg	278	55.4	280	57.6	273	54.9
	>10 kg	183	36.5	166	34.2	168	33.8
	Missing	0	0.0	2	0.4	0	0.0
Admitted for surgery		174	34.7	171	35.2	181	36.4
PICU assessment (from linked PICANet data)		**479**	95.4	**456**	93.8	**473**	95.2
Primary reason for admission	Cardiovascular	235	49.1	233	51.1	250	52.9
	Endocrine/metabolic	30	6.3	34	7.5	30	6.3
	Infection	39	8.1	30	6.6	31	6.6
	Cancer	9	1.9	6	1.3	8	1.7
	Respiratory	102	21.3	86	18.9	84	17.8
	Neurological	22	4.6	31	6.8	29	6.1
	Trauma	18	3.8	10	2.2	18	3.8
	Other	24	5.0	26	5.7	22	4.7
	Unknown	0	0.0	0	0.0	1	0.2
Paediatric Index of Mortality (PIM2)	<1%	54	11.3	48	10.5	48	10.1
	1-5%	264	55.1	236	51.8	247	52.2
	5-<15%	116	24.2	123	27.0	119	25.2
	15-<30%	34	7.1	31	6.8	39	8.2
	30%+	11	2.3	18	3.9	20	4.2
Clinical condition at randomisation		**502**	100.0	**486**	100.0	**497**	100.0
< 72h <u>before</u> randomised	CVC in situ	95	18.9	91	18.7	83	16.7
	Anticoagulants received	50	10.0	59	12.1	61	12.3
	Antibiotics received	286	57.0	276	56.8	284	57.1
	Positive blood culture	40	8.0	25	5.1	36	7.2
At randomisation	Infection suspected	214	42.6	181	37.2	199	40.0
	Immune compromised	44	8.8	31	6.4	29	5.8
CVC details (inserted CVCs)		**481**	95.8	**465**	95.7	**464**	93.4
Deferred consent, CVC inserted		314	65.3	301	64.7	302	65.1
Inserted at same hospital	ICU	276	57.4	264	56.8	259	55.8
	Theatre	5	1.0	4	0.9	7	1.5
	Other	2	0.4	3	0.6	1	0.2
Inserted at other hospital*	ICU	5	1.0	6	1.3	3	0.6

	Theatre	3	0.6	8	1.7	7	1.5
	Other	23	4.8	16	3.4	23	5.0
Missing		0	0.0	0	0.0	2	0.4
Prospective consent, CVC inserted		167	34.7	164	35.3	162	34.9
	ICU	15	3.1	23	4.9	16	3.4
Inserted at same hospital	Theatre	152	31.6	141	30.3	144	31.0
	Other	0	0.0	0	0.0	1	0.2
Triple lumen CVC		450	93.6	421	90.5	422	90.9
CVC inserted into femoral vein		253	52.6	217	46.7	235	50.6

*CVCs were inserted by the retrieval team prior to transfer to PICU.

Table 2: Endpoint frequency according to CVC allocation (ITT analyses) and CVC received (safety analyses). Values for *n* refer to number of participants (%) unless otherwise stated.

		Standard		Antibiotic		Heparin	
Intention to treat analyses		*N=502*	%	*N=486*	%	*N=497*	%
Primary outcome							
Bloodstream infection		18	3.59	7	1.44	17	3.42
Median time to first BSI in days (IQR)		7.5	(4.5, 11.2)	6.9	(6.0, 8.0)	4.2	(3.1, 8.4)
Organism type	non skin	15[$]	2.99	6	1.23	16	3.22
	skin	3	0.60	1	0.21	1	0.20
Organism group*	gram positive[$$]	10	0.02	3	0.01	10	0.02
	gram negative	6	0.01	4	0.01	5	0.01
	Candida	2	0.00	0	0.00	3	0.01
Secondary outcomes							
Catheter-related BSI		12	2.39	3	0.62	10	2.01
BSI rate per 1000 CVC days (95% CI)		8.24	(4.72, 11.77)	3.30	(1.01, 5.60)	8.79	(5.03, 12.55)
Number/1000 days		21/2.548		8/2.389		21/2.421	
BSI or culture negative infection**		112	22.31	103	21.19	102	20.52
Thrombosis		125	24.90	126	25.93	105	21.13
Median time to CVC removal in days (IQR)		4.28	(2.30, 6.97)	4.31	(2.13, 7.0)	4.20	(2.24, 6.97)
Mortality ≤ 30 days after randomisation		42	8.37	39	8.02	28	5.63
Post-hoc analyses							
Median time to PICU discharge in days (IQR)		5.1	(2.8, 10.0)	4.4	(2.2, 9.3)	4.9	(2.3, 8.9)
Median time to hospital discharge in days (IQR)		12.0	(6.4, 25.6)	12.0	(6.7, 22.7)	12.1	(6.4, 22.5)
Safety analyses		*N=533*		*N=451*		*N=479*	
CVC related adverse events		9	1.69	14	3.10	8	1.67
Mortality ≤ 30 days after randomisation		45	8.44	35	7.76	29	6.05

[$] = includes 1 mixed BSI pathogen and skin organism; [$$] = includes 6 BSI due to coagulase negative staphylococci ; * = groups add to more than total due to multiple types of organisms isolated on same occasion in some patients; ** composite measure of BSI including the primary outcome or a negative blood culture combined with a positive 16S PCR result for bacterial DNA, 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.

Table 3: Risk differences and relative effect measures by CVC allocated (ITT analyses). (*=rate ratio; ^=risk ratio. Significant hazard ratios are in bold (p<0.05)

	Any impregnated vs standard (primary analysis)			Antibiotic vs standard (secondary analysis)			Heparin vs standard (secondary analysis)			Antibiotic vs heparin (secondary analysis)		
	risk difference (95% CI)	hazard ratio (95% CI)	p value	risk difference (95% CI)	hazard ratio (95% CI)	p value	risk difference (95% CI)	hazard ratio (95% CI)	p value	risk difference (95% CI)	hazard ratio (95% CI)	p value
Primary outcome												
Time to first bloodstream infection	-1.14 (-3.04, 0.75)	0.71 (0.37, 1.34)	0.29	-2.15 (-4.09, -0.20)	**0.43 (0.20, 0.96)**	**0.04**	-0.17 (-2.45, 2.12)	1.04 (0.53, 2.03)	0.90	-1.98 (-3.90, -0.06)	**0.42 (0.19, 0.93)**	**0.03**
Secondary outcomes												
CR-BSI	-1.07 (-2.58, 0.45)	0.55^ (0.25, 1.21)	0.13	-1.77 (-3.28, -0.27)	**0.25^ (0.07, 0.90)**	**0.03**	-0.38 (-2.20, 1.44)	0.84^ (0.36, 1.96)	0.68	-1.39 (-2.81, 0.02)	0.30^ (0.08, 1.11)	0.09
Rate of BSI per 1000 CVC days	-2.21 (-6.36, 1.94)	0.73* (0.40, 1.34)	0.31	-4.94 (-9.14, -0.73)	**0.40* (0.17, 0.97)**	**0.04**	0.55 (-4.60, 5.70)	1.07* (0.55, 2.06)	0.85	-5.49 (-9.89, -1.08)	**0.38* (0.16, 0.89)**	**0.03**
Time to first BSI or culture negative infection	-1.46 (-5.90, 2.98)	0.95 (0.75, 1.20)	0.65	-1.12 (-6.26, 4.03)	0.95 (0.72, 1.23)	0.73	-1.79 (-6.87, 3.30)	0.95 (0.73, 1.25)	0.67	0.67 (-4.41, 5.75)	0.99 (0.75, 1.25)	0.93
Time to CVC thrombosis	-1.40 (-6.02, 3.22)	0.98 (0.79, 1.22)	0.88	1.03 (-4.40, 6.46)	1.24 (0.96, 1.60)	0.49	-3.77 (-8.99, 1.44)	0.88 (0.68, 1.14)	0.34	4.80 (-0.50, 10.10)	1.25 (0.96, 1.62)	0.11
Time to CVC removal		1.04 (0.93, 1.16)	0.53		1.02 (0.90, 1.17)	0.67		1.05 (0.92, 1.19)	0.51		0.99 (0.87, 1.13)	0.87
Mortality ≤ 30 days after randomisation		0.80^ (0.54, 1.20)	0.28		0.96^ (0.61, 1.51)	0.85		0.65^ (0.40, 1.07)	0.09		1.46^ (0.86, 1.11)	0.14
Post-hoc analyses												
Time to PICU discharge		1.08 (0.97, 1.20)	0.17		1.07 (0.95, 1.22)	0.27		1.08 (0.96, 1.23)	0.21		0.98 (0.86, 1.11)	0.73
Time to hospital discharge		1.04 (0.93, 1.16)	0.47		1.03 (0.91, 1.16)	0.68		1.05 (0.93, 1.19)	0.42		0.98 (0.87, 1.11)	0.77

Supplementary material

Appendix Table A1: Type of organism isolated from positive blood cultures including in the primary outcome

Category	Organism	Type of CVC				
		Standard	Antibiotic	Heparin	Antibiotic or Heparin	Total
Non-skin organisms						
Gram positive	*Staphylococcus aureus*	1	1	3	4	5
	Meticillin-resistant Staphylococcus aureus	1	0	0	0	1
	Enterococcus spp.	2	0	4	4	6
	Streptococcus spp	2	1	1	2	4
Gram negative	*Serratia marcescens*	1	1	0	1	2
	Pseudomonas aeruginosa	2	1	1	2	4
	Gram negative bacillus	1	0	1	1	2
	Enterobacteriaceae	1	2	0	2	3
	Klebsiella spp.	0	0	1	1	1
	Cellulomas spp.	0	0	1	1	1
	Raoultella panticola and *Enterobacter spp.*	1	0	0	0	1
Gram positive+Gram negative	*Enterococcus spp.* and *Klebsiella pneumonia*	0	0	1	1	1
Fungi	*Candida spp.*	2	0	3	3	5
Skin organisms (based on normal skin flora/commensals)						
Gram positive	*Coagulase-negative staphylococcus*	3	1	1	2	5
Gram positive skin and gram positive non-skin organisms	*Coagulase-negative staphylococcus* and *Enterococcus spp.*	1	0	0	0	1
Total		18	7	17	24	42

Appendix Table A2: Sensitivity analysis for the primary outcome (including clinically indicated BSI with no sample taken in time window) N=number of participants

	N randomised	Primary outcome		Clinical indication but no sample taken in time window		Total included in sensitivity analysis		Hazard ratio (95% CI)	p-value
		N	%	N	%	N	%		
Any impregnated vs standard	983	24	57.14	9	52.94	33	55.93	0.67 (0.39, 1.15)	0.15
Standard	502	18	42.86	8	47.06	26	44.07		
Antibiotic vs standard	497	7	16.67	6	35.29	13	22.03	0.54 (0.29, 1.02)	0.06
Heparin vs standard	486	17	40.48	3	17.65	20	33.90	0.83 (0.47, 1.49)	0.54
Antibiotic vs heparin								0.64 (0.32, 1.27)	0.20
Total	**1485**	**42**		**17**		**59**			

Appendix Table A3: Regression analysis for the primary outcome (time to first bloodstream infection)

Analysis	Variable	Comparator	Hazard Ratio	95% CI	p-value
Primary	Antibiotic or heparin CVC	standard	0.71	(0.38, 1.33)	0.29
	Deferred consent	prospective	0.87	(0.40, 1.90)	0.73
	Suspected infection	no suspected infection	0.69	(0.33, 1.42)	0.31
Secondary	Heparin CVC	standard	1.05	(0.54, 2.05)	0.89
	Antibiotic CVC	standard	**0.40**	**(0.17, 0.96)**	**0.04**
	Deferred consent	prospective	0.87	(0.40, 1.90)	0.35
	Suspected infection	no suspected infection	0.68	(0.33, 1.40)	0.30
Secondary	Antibiotic CVC	heparin	**0.39**	**(0.16, 0.95)**	**0.04**
	Deferred consent	prospective	0.85	(0.30, 2.45)	0.76
	Suspected infection	no suspected infection	0.99	(0.40, 2.43)	0.98

Appendix Table A4: Number of children experiencing a BSI or culture negative indicators of a blood stream infection.

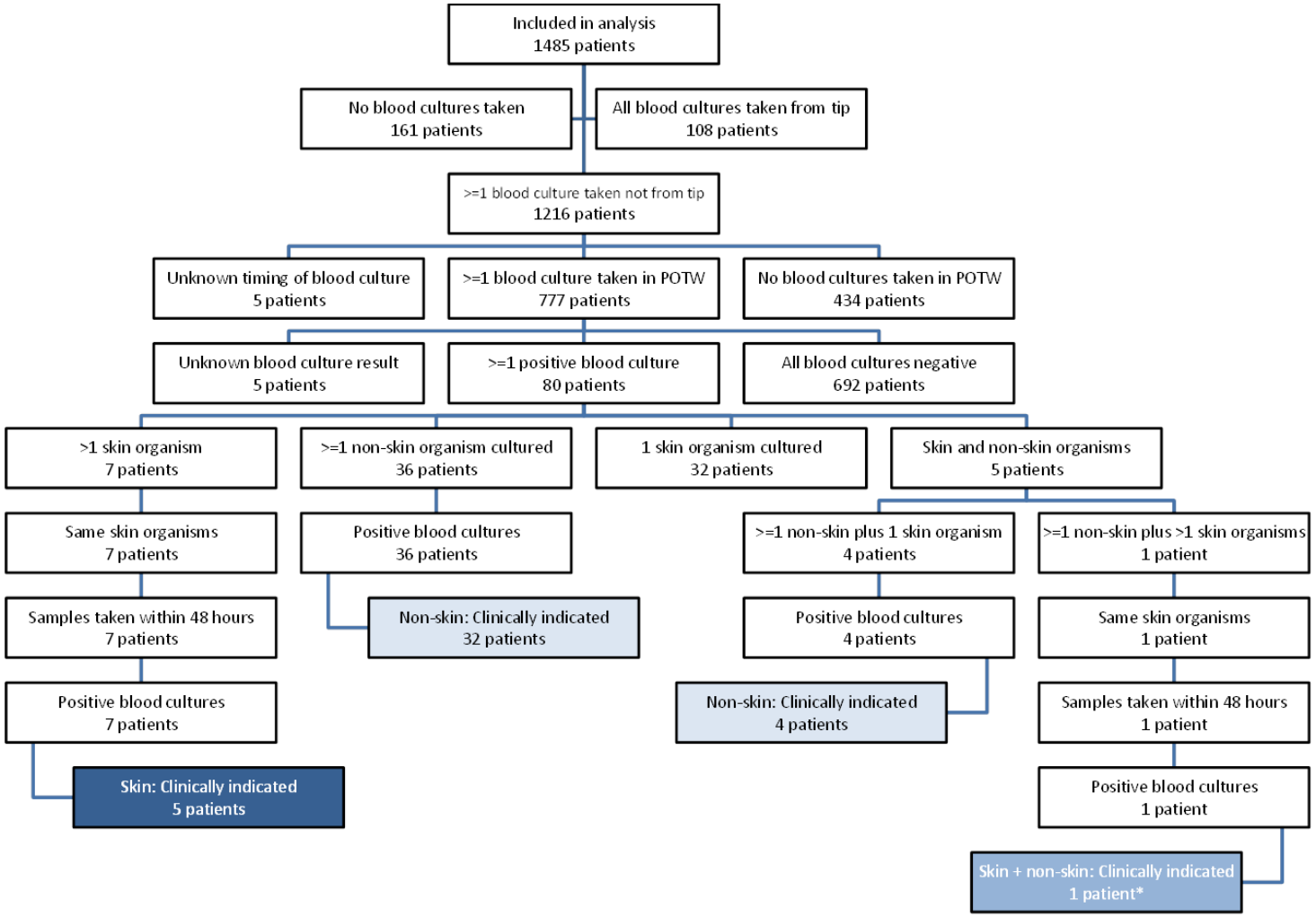
Treatment	Number randomised	Number experiencing BSI or culture negative blood stream infection											Total*
		Primary outcome	Any of the clinical indicators of infection and (negative) blood culture taken and										
			High bacterial DNA load from a PCR positive result only	Change in antibiotic on same day or next day only	ii. CVC removal for infection only	Primary outcome and removed for infection	Primary outcome and antibiotic change	Removed for infection and antibiotic change	PCR positive and antibiotic change	Primary outcome, removed for infection and antibiotic change	Removed for infection, PCR positive and antibiotic change	All 4 criteria	
Standard	502	2	2	79	6	1	8	7	1	6	0	1	112
Antibiotic or Heparin	983	4	2	135	19	0	12	24	1	7	0	1	
Antibiotic	486	0	1	71	12	0	6	11	1	1	0	0	103
Heparin	497	4	1	64	7	0	6	13	0	6	0	1	102
Total	1485	6	4	214	25	1	20	31	1	13	0	2	317

*Number of participants with BSI indicators in an exclusive descending hierarchy based on specificity of indicator for BSI (total n=317): BSI =42; PCR positive = 5; CVC removed for infection =56; change or start of antibiotics same or next day = 214

Appendix Table A5: Results of antibiotic resistance testing reported for 12 patients with a positive blood culture included in the primary outcome.

	E test result	
CVC allocation	**Minocycline**	**Rifampicin**
Standard		
-Colifom bacilli	Resistant	Resistant
-*Enterococcus faecalis*	Resistant	Resistant
-*Serratia marcescens*	Resistant	Resistant
-*Staph aureus*	Sensitive	Sensitive
-Meticillin resistant *Staphylococcus aureus*	Sensitive	Sensitive
Antibiotic		
-*E.coli*	Resistant	Resistant
-Staphylococcal spp	Resistant	Resistant
Heparin		
-*Klebsiella pneumoniae*	Resistant	Resistant
-*Klebsiella pneumoniae*	Resistant	Resistant
-*Staph aureus*	Sensitive	Sensitive
-*Coagulase negative staphylococci*	Sensitive	Sensitive
-*Enterococcus hirae* and	Resistant	Sensitive
Coagulase negative staphylococci	Sensitive	Resistant

Appendix Figure 1: Diagram shows samples taken, positive cultures, and clinically indicated positive cultures in the primary outcome time window that meet the criteria for the primary outcome. *The non-skin organism was from a sample taken at 47 hours and 55 minutes after randomisation (POTW = primary outcome time window)**.**



Appendix Figure 2: Number of children included in the primary outcome, the rate of BSI and catheter-related BSI according to time since randomisation