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- 1 **Title: Pragmatic randomised, controlled trial of impregnated central venous catheters for**
2 **preventing bloodstream infection in children**
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- 9

10 **Abstract**

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

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

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

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

29 (ClinicalTrials.gov Identifier:NCT01029717)

30 **Funding:** UK National Institute for Health Research.

31

32 **Introduction**

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

40

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

49

50 Despite the large number of randomised controlled trials, there is relatively weak evidence to guide
51 policy about adoption of impregnated CVCs for all who need them, particularly children. Firstly,
52 there are inherent biases in the use of CR-BSI - the primary outcome used in all previous trials - as
53 this could overestimate benefits of antibiotic impregnation.^{11, 15} CR-BSI requires positive cultures of
54 the same organism from the CVC tip and from blood, which excludes many patients with BSI and
55 may favour antibiotic impregnated CVC tips through inhibition of bacterial growth in culture media.¹⁶
56 Secondly, few studies have been conducted in the context of the low infection rates associated with
57 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

69 **Methods**

70 **Design, study population and intervention**

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

79

80 Children <16 years were eligible if they were admitted or being prepared for admission to a
81 participating PICU and were expected to require a CVC for 3 or more days. For children admitted to
82 PICU following elective surgery, we sought prospective parental consent during pre-operative
83 assessment. For children who required a CVC as an emergency, we sought parental consent after
84 randomisation and stabilisation (deferred consent) to avoid delaying treatment. Parents consented
85 to the use of their child's data for the trial, to follow-up using routinely recorded clinical data, and to
86 an additional 0.5ml of blood being collected for PCR testing whenever a blood culture was clinically
87 required. Further details are given in the protocol (see supplementary material).

88

89 **Randomisation and masking**

90 Children were randomised at the bedside or in theatre (operating room) immediately prior to CVC
91 insertion. The clinician or research nurse opened a pressure sealed, sequentially numbered, opaque
92 envelope containing the CVC allocation. Randomisation sequences were computer generated in a
93 1:1:1 ratio by an independent statistician in random blocks of three and six, stratified by method of

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

96

97 CVC allocation was not blinded to the clinician responsible for inserting the CVC (due to different
98 colour strips for antibiotic and heparin CVCs) but since CVCs looked identical whilst in situ, allocation
99 was concealed from patients, their parents and PICU personnel responsible for their care. Labels
100 identifying the type of CVC were held securely in a locked drawer in case unblinding was required.

101 Participant inclusion in analyses and occurrence of outcome events were established prior to release
102 of the randomisation sequence for analysis and for the data monitoring committee.

103

104 **Comparisons and end points**

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

107

108 The primary outcome was time to the first BSI based on blood cultures taken between 48 hours after
109 randomisation and 48 hours after CVC removal (or prior to death). All blood culture samples included
110 in the primary outcome were clinically indicated, defined by recorded evidence of infection (one or
111 more of: temperature instability, change in inotrope requirements, haemodynamic instability, or poor
112 perfusion) or removal of the CVC due to suspected infection. Blood cultures were recorded as positive
113 for the primary outcome if any organism was isolated that was not a skin commensal or if coagulase-
114 negative staphylococci (or other skin commensals) were isolated and there were two or more positive
115 cultures of the same organism within 48 hours of each other. A clinical committee reviewed all
116 primary outcomes involving positive cultures without knowledge of CVC allocation status. A sensitivity
117 analysis assumed that the primary outcome occurred for those with a record of clinical indication but
118 no blood culture taken in the primary outcome time window.

119

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

128

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

136

137 Safety analyses compared CVC-related adverse events (including unexplained thrombocytopenia
138 after insertion of CVC), mortality, and antibiotic resistance to minocycline ($>0.5 \mu\text{g/ml}$) or rifampicin
139 ($>1.0 \mu\text{g/ml}$) based on etest strips applied to organisms isolated from BSI ([www.biomerieux-](http://www.biomerieux-diagnostics.com/etest)
140 [diagnostics.com/etest](http://www.biomerieux-diagnostics.com/etest)). Incomplete laboratory testing and reporting limited analyses of resistance in
141 positive blood cultures and prevented analysis of resistance in cultures from the CVC tip (as specified
142 in the protocol).

143

144 **Study procedures**

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

152

153 **Sample size**

154 We based the sample size calculation for the primary analysis on a relative risk (RR). We assumed
155 detection of a RR of 0.5 in patients with a baseline risk of 10% would change policy. We assumed the
156 RR would remain relatively constant across baseline risks while the absolute risk difference would be
157 more variable. 1200 children in a 2:1 ratio (impregnated:standard) were required to achieve 80%
158 power to detect a RR of 0.5 at a 5% level of significance, based on an estimated BSI rate of 10% and
159 allowing for 5% loss to follow-up. A lower than expected BSI rate of 5% would have 62% power to
160 detect a RR of 0.5 or 80% power for a RR of 0.32.

161

162 The Independent Data Monitoring Committee recommended continuation of the study until 30
163 November 2012 after: reviewing the first 209 children; an interim analysis of 650 children using the
164 Peto-Haybittle stopping rule for the primary outcome; recruitment had reached the original target of
165 1200 pre-schedule in June 2012 and there were no safety concerns. The recommendation for
166 continuation aimed to exhaust available funding.

167

168 **Statistical analysis**

169 Outcome data were analysed according to the intention to treat principle. Safety analyses included
170 the subset of children for whom CVC insertion was attempted, grouped by CVC actually received.

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

184

185 **Study oversight and role of funders**

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

194

195

196 **Results**

197 **Study population**

198 Overall, 1859 children were randomised (501 prospective, 1358 emergency). However, 984/1358
199 (72%) emergency patients subsequently provided deferred consent, leaving 1485 participants for final
200 analysis (Figure 1). Reasons for non-consent are reported in Figure 1. Of the 1485 randomised
201 participants, 75 (5%) did not receive a CVC: in 53 insertion was attempted but unsuccessful and in 22
202 CVC insertion was not attempted (16 no longer required, 5 reason not known and 1 patient died). Of
203 those receiving a CVC, more of those randomised to standard CVC received the allocated type of CVC
204 (93%; 468/502 allocated to standard; 90%; 437/486 to antibiotic, and 89%; 440/497 to heparin;
205 Figure 1). The majority of CVCs received but not allocated CVCs were standard CVCs (69%; 45/65;
206 Figure 1). All randomised and consented participants were followed up until 48 hours after CVC
207 removal or attempted CVC insertion.

208

209 **Baseline characteristics**

210 Table 1 shows that over half (58%) of children were aged under 12 months at admission, with one-
211 third aged less than 3 months. One third of children had surgery prior to admission to PICU and half
212 had cardiovascular problems as their primary diagnosis at admission. CVC insertion took place in the
213 operating room for 437/493 (89%) in the prospective consent (elective) group, but in only 34/917
214 (4%) of the deferred consent (emergency) group

215

216 **Endpoints**

217 *Primary outcome*

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

222 primary outcome of BSI was recorded for 42 children: standard 18/502 (3.6%); antibiotic 7/486
223 (1.4%); heparin 17/497 (3.4%). Gram positive organisms accounted for the majority of BSI (23/42;
224 55%) of which 6 (14%) were positive for coagulase negative staphylococci (Table 2). Details of all
225 organisms isolated in the primary outcomes are given in supplementary Table 1. All outcomes are
226 reported by CVC type in Table 2.

227

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

234

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

244

245 *Secondary outcomes*

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

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

255

256 *Safety*

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

264

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

272

273 **Discussion**

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

283

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

296

297 Limitations include the limited power of the study to detect differences in the primary outcome
298 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.

325

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

334

335 **Implications**

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

347

348 **Research in context**

349 **Evidence before this study**

350 We searched PubMed, initially for systematic reviews or meta-analyses, using the clinical queries filter for
351 therapy studies or terms for meta-analysis and (catheter* OR central OR venous OR intravenous) (impregnated
352 OR bonded OR coated OR antibiotic OR heparin) and infection. We found 5 systematic reviews published since
353 2008. The two most recent reviews were both published in the Cochrane Library. One included any type of CVC
354 impregnation, but excluded children (56 RCTs, 5 antibiotic vs standard; 1 heparin vs standard).¹³ The other
355 compared heparin bonded with standard CVCs in children (2 trials).²⁸ All the trials evaluated in these two
356 reviews were included in an earlier systematic review and network meta-analysis by Wang et al which
357 comprised direct and indirect mixed treatment comparisons of 45 RCTs evaluating CR-BSI (6 antibiotic vs
358 standard none in children; 3 heparin vs standard, 2 in children). For antibiotic (minocycline-rifampicin)
359 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
360 We found one subsequent randomised controlled trial which compared antibiotic (minocycline and rifampicin)
361 and standard CVCs for children undergoing heart surgery.¹⁹ The trial of 288 participants was terminated early
362 because of a low event rate (3 catheter associated BSI in each group). The mixed treatment comparison for
363 heparin-bonded vs standard CVCs produced a pooled odds ratio of 0.20 (0.06, 0.44), and for antibiotic
364 compared with heparin CVCs (indirect comparisons only), OR 1.18 (0.28, 3.29).¹⁴ A previous cost-effectiveness
365 analysis based on trials in adults estimated that impregnated CVCs would be cost effective even at baseline
366 risks of BSI as low as 0.2%.¹²

367 **Added value of this study**

368 This is the first trial to evaluate antibiotic and heparin CVCs in children and in the context of low BSI rates
369 associated with improved asepsis practices. We add new evidence of effectiveness of antibiotic CVCs for any
370 BSI, showing a 57% reduction compared with standard CVCs in children. We confirmed the effectiveness of
371 antibiotic CVCs found in systematic reviews of trials in adults, with a 75% reduction in the risk of CR-BSI (HR 25;
372 0.07, 0.90) compared with standard CVCs, for the first time in children. We also report for the first time that
373 antibiotic CVCs are superior to heparin CVCs. These results are based on secondary analyses so need to be
374 interpreted with caution. Our results are consistent with previous studies showing no effect of antibiotic
375 impregnation on mortality or adverse effects.

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

381 **Implications of the available evidence**

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

385

386

387 **Contributions**

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

393

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424

425 **References**

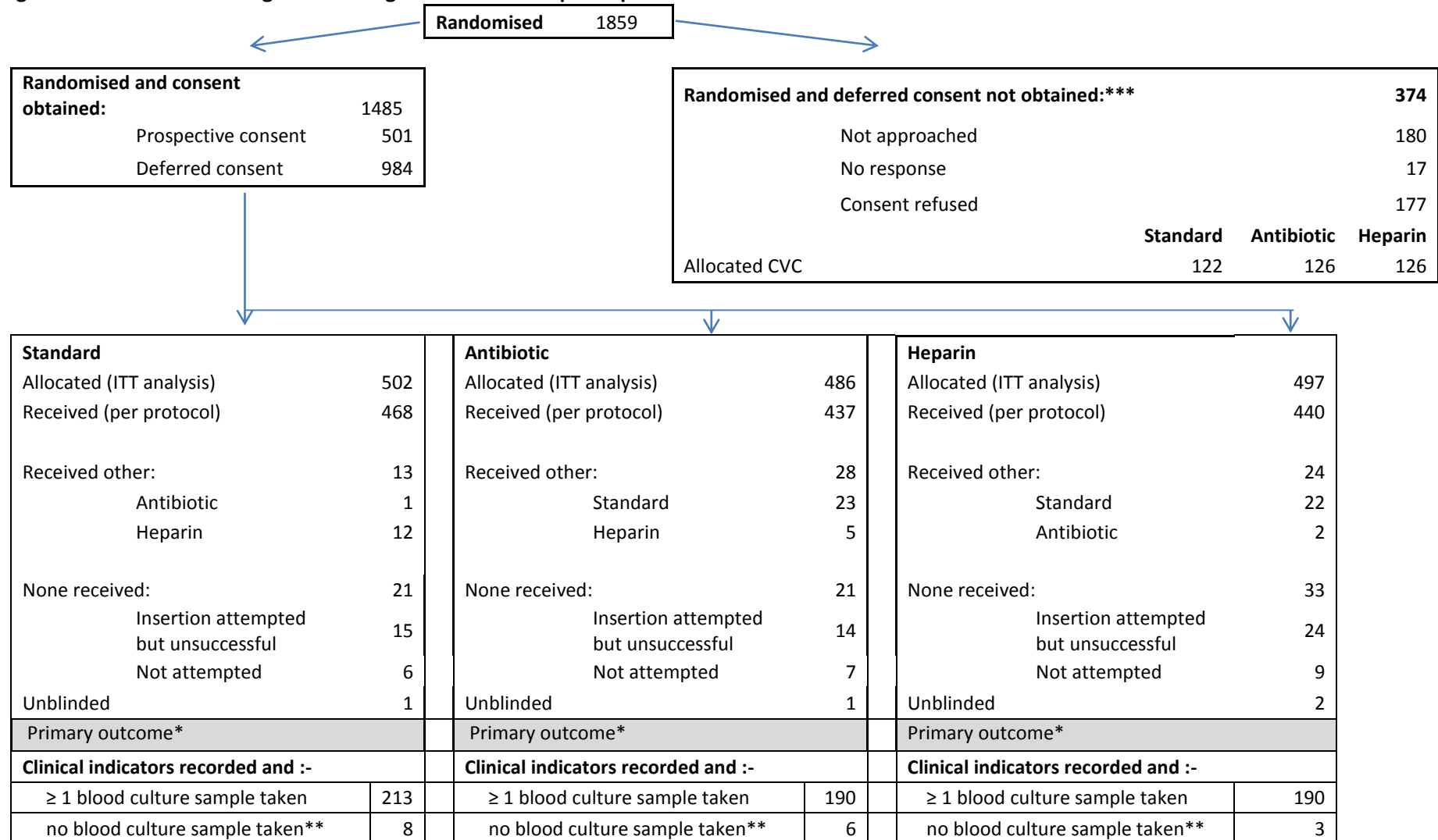
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Figure 1: CONSORT flow diagram showing numbers of trial participants



* 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 elsewhere³⁰

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)

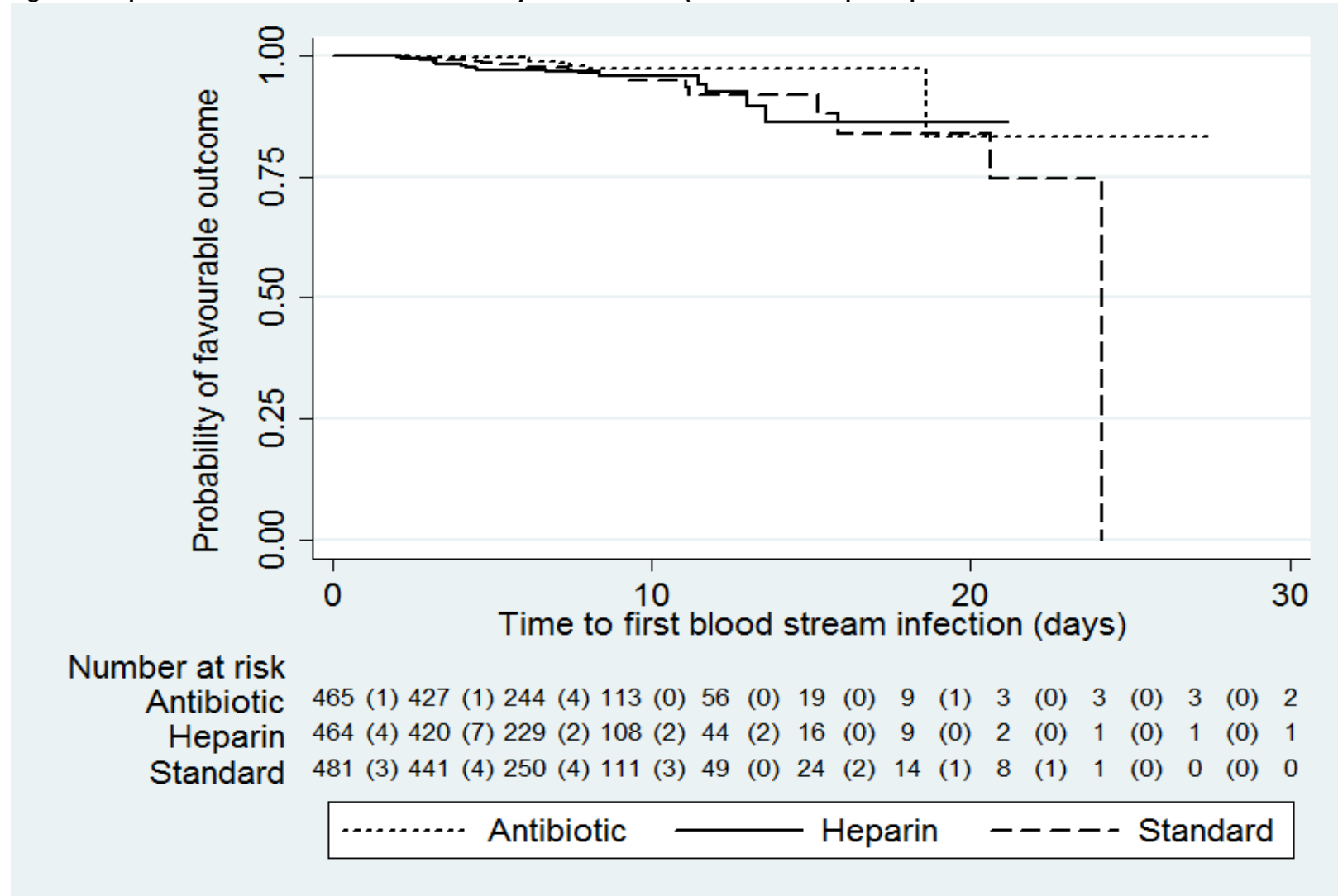


Table 1: Baseline characteristics, clinical condition at randomisation and details of the intervention (n=number of participants)

		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		152	31.6	141	30.3	144	31.0
	Theatre						
	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	
<i>Intention to treat analyses</i>	<i>N=502</i>	%	<i>N=486</i>	%	<i>N=497</i>	%
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)
<i>Safety analyses</i>	<i>N=533</i>		<i>N=451</i>		<i>N=479</i>	
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	<i>Staphylococcus aureus</i>	1	1	3	4	5
	<i>Meticillin-resistant Staphylococcus aureus</i>	1	0	0	0	1
	<i>Enterococcus spp.</i>	2	0	4	4	6
	<i>Streptococcus spp</i>	2	1	1	2	4
Gram negative	<i>Serratia marcescens</i>	1	1	0	1	2
	<i>Pseudomonas aeruginosa</i>	2	1	1	2	4
	<i>Gram negative bacillus</i>	1	0	1	1	2
	<i>Enterobacteriaceae</i>	1	2	0	2	3
	<i>Klebsiella spp.</i>	0	0	1	1	1
	<i>Cellulomas spp.</i>	0	0	1	1	1
	<i>Raoultella panticola</i> and <i>Enterobacter spp.</i>	1	0	0	0	1
Gram positive+Gram negative	<i>Enterococcus spp.</i> and <i>Klebsiella pneumonia</i>	0	0	1	1	1
Fungi	<i>Candida spp.</i>	2	0	3	3	5
Skin organisms (based on normal skin flora/commensals)						
Gram positive	<i>Coagulase-negative staphylococcus</i>	3	1	1	2	5
Gram positive skin and gram positive non-skin organisms	<i>Coagulase-negative staphylococcus</i> and <i>Enterococcus spp.</i>	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.

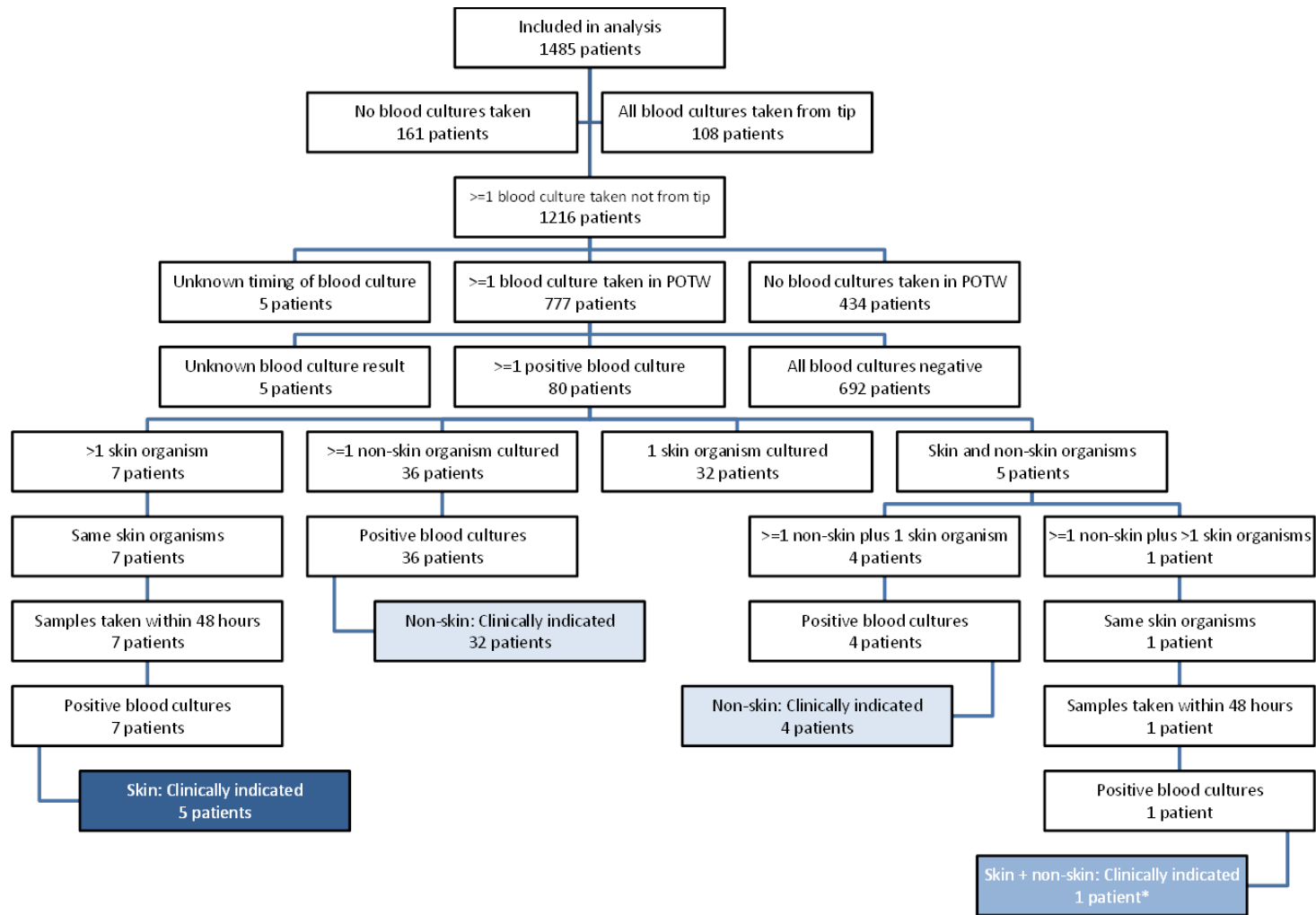
Treatment	Number randomised	Number experiencing BSI or culture negative blood stream infection											Total*	
		Primary outcome	Any of the clinical indicators of infection and (negative) blood culture taken and											
			High bacterial DNA load from a PCR positive result only	Change in antibiotic 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.

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

Randomisation	48 hours after randomisation		CVC removal		48 h after CVC removal
		Primary outcome of BSI			
		n=40		n=2	
		Rate of BSI per 1000 CVC-days			
	n=10	n=40			
		Catheter-related BSI (CR-BSI)			
		n=24		n=1	