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A Daily Topical Decontamination Regimen Reduces Catheter-Related Bloodstream Infections in Haematology Patients

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Running Title

Reducing CRBSI in haematology patients

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Highlights

- A topical decontamination regimen was introduced for haematology patients
- Incidence of catheter-related bloodstream infections reduced significantly
- Infection-free catheter survival times improved
- *Staphylococcus aureus* infections were particularly reduced

ABSTRACT

Objectives. To assess impact of a topical decontamination regimen on rates of catheter-related bloodstream infections (CRBSI) in intensively-treated haematology patients.

Methods. A historically-controlled cohort study was used to evaluate the effect of applying chlorhexidine or Octenisan® body washes and nasal Prontoderm® ointment for 5 days around the time of Hickman line insertion on the incidence of CRBSI and infection-free catheter time. Lines inserted during a 24 month period prior to implementation of the decolonisation regimen were compared with those inserted during a 12 month period after the intervention was applied.

Results. During the post-intervention period, 163 lines were inserted in 147 patients, compared to 303 lines in 242 patients in the pre-intervention period. CRBSI rates in treated and untreated patients respectively were 6.8 and 35.0 cases per 10,000 line-days by 21 days ($p = 0.009$), and 14.4 and 26.0 cases respectively per 10,000 line-days by 180 days ($p = 0.025$).

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The incidence rate of *Staphylococcus aureus* CRBSI in treated and untreated patients were 0.0 and 4.6 cases per 10,000 line-days respectively (p = 0.012). Multivariable Cox regression estimated an 81% probability (95% confidence interval 74% - 85%) that a treated line develops a CRBSI later than an untreated line by 21 days post-insertion.

Conclusions. Implementation of this safe and effective topical decontamination regimen enhances routine CRBSI-prevention measures for haematology patients requiring central venous line insertion.

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INTRODUCTION

Catheter-related bloodstream infections (CRBSI) are a common and serious complication of central venous line placement. They cause significant morbidity and mortality where they occur, and place a significant financial burden on health services [1-3]. Patients treated intensively for haematological malignancies are particularly vulnerable to the adverse effects of CRBSI where they occur, but placement of a central venous access device is often unavoidable; being required for delivery of chemotherapy, immunotherapy, and supportive treatments such as fluids, antibiotics and blood products [4]. Infection is one of the commonest causes of death in this population and CRBSI contribute significantly to the numbers dying from infectious complications [5]. CRBSI are also the commonest reason for premature line removal, often at a time when patients are neutropenic and requiring the greatest degree of supportive care, hindering both successful treatment of the septic episode and delivery of other necessary therapies during the intensive phase of treatment [4,6].

A number of different prevention strategies have been trialled with the aim of reducing CRBSI rates. Implementation of evidence-based 'bundles' of care have become almost universal. These variably specify infection control measures such as staff education and training; line insertion site; local antimicrobial dressing; daily review of central lines and removal of unnecessary lines. The composition of such care bundles varies between studies and their optimal composition remains a matter of debate. Even when well-established and consistently implemented, very few such packages of intervention reduce CRBSI rates to 0, leaving significant room for improvement [7,8]. Additional measures studied have included: use of antimicrobial-impregnated lines; antimicrobial line lock solutions; alcohol impregnated caps; antibacterial dressings and nasal mupirocin; however, data is lacking on the effectiveness of these measures in adult haematology patients, and associated adverse events have been reported [9-12].

The addition of topical chlorhexidine or Octenisan® combined with nasal Prontoderm® to traditional CRBSI prevention measures has not previously been studied in intensively-treated haematology patients. Given the excellent safety profiles and reported efficacy of these agents in other populations, this combination is deserving of further study in this high risk patient group [13-16].

In this study, we evaluate the efficacy of extended antimicrobial washes plus nasal Prontoderm® ointment in addition to routine CRBSI-prevention measures around the time of central line insertion to reduce CRBSI rates and improve infection-free catheter times in haematology patients.

MATERIALS AND METHODS

Study Design

This historically-controlled cohort study was designed to evaluate the impact of topical decolonisation therapy around the time of Hickman line insertion on the incidence of line infection and on infection-free catheter time in haematology patients.

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Setting

A large, tertiary care, adult haematology department in the UK, providing specialist haematology and stem cell transplantation services for a population of approximately 2 million. Hickman lines are routinely inserted for patients undergoing intensive chemotherapy treatment for acute leukaemia and those requiring autologous or allogeneic stem cell transplantation.

Hickman Line Insertion and Care

Hickman lines were placed or supervised by senior vascular radiologists in specialist angiographic laboratories. Under local anaesthesia, line insertion was preferentially into the right internal jugular vein under ultrasound guidance using Seldinger technique. Strict aseptic technique was followed, including: use of surgical chlorhexidine or betadine hand wash; sterile gown, gloves, surgical cap and face mask by operator; sterilisation of insertion site with 2% chlorhexidine solution and use of sterile drapes.

Following insertion, line sites were dressed and inspected regularly. No difference in line insertion technique, peri-procedural management or post-procedural ward care was implemented during the study period other than the defined intervention.

Intervention

A skin and nasal decontamination regimen was introduced by the hospital with the aim of reducing CRBSI rates, in October 2013. This consisted of a 5 day course in total of decolonisation with daily topical chlorhexidine or Octenisan® (Schülke & Mayr UK Ltd) washes and three times per day bilateral nasal Prontoderm® (B. Braun Medical Ltd), administered by the patient themselves where possible or by staff members if required, with a patient information sheet provided to facilitate this. The course began 2 days before planned line insertion date, continued through the day of insertion and for 2 days afterwards therefore was a total of 5 days with 2 of these being prior to the date of line insertion.

Patients

Haematology patients having Hickman lines inserted were identified through the Radiology department database. Patients included in the pre-intervention group had Hickman lines inserted during a 24 month period from 1/1/11.

To allow a run-in period for staff to become familiar with the regimen, patients included in the post-intervention group had lines inserted during a 12 month period from 1/4/14. Lines inserted in other hospitals or outside the Radiology department were not included in the study.

Dates of line removal were ascertained from the trust's coding database; through receipt of a line tip by the Microbiology department; or by review of patient notes, allowing duration of line presence to be calculated. All lines were followed up until removal or 180 days post insertion, whichever came sooner.

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Laboratory Methods

Culture of all line lumens along with peripheral blood was routinely performed in response to the development of fever in patients with a Hickman line. Blood was incubated in the Microbiology laboratory using the Bactec FX® continuously monitored blood culture system (Becton-Dickinson and co). Time to positivity was recorded within the Laboratory Information Management System via a direct interface. Following subculture from positive bottles, organisms were speciated using the MALDI Biotyper® (Bruker) and susceptibility testing performed in line with BSAC/EUCAST guidelines using a multipoint breakpoint agar or disc method [17].

Tips of lines removed due to suspected infection were sent for culture, performed by semi-quantitative roll plate method in line with the UK Standards for Microbiology Investigations [18]. Identification and susceptibility testing of cultured organisms was as detailed above.

Definitions

Line infections were classed as definite if 1 of the following 3 criteria were fulfilled: indistinguishable organism in peripheral and line culture with line culture positive ≥2 hours earlier than peripheral; indistinguishable organism in 2 simultaneous line cultures with one culture positive ≥2 hours earlier than the other if peripheral blood culture not sent; organism grown in line or peripheral blood culture indistinguishable from organism cultured from line tip post-withdrawal. Definitions adapted from Centers for Disease Control and Prevention definition [19].

Line infections were classed as probable if fulfilling 1 of the following 3 criteria: indistinguishable organism in peripheral and line culture with < 2hours differential time to positivity and line removed within 7 days due to clinical suspicion of line infection with otherwise unexplained pyrexia; culture of indistinguishable organism from both lines with negative peripheral culture and otherwise unexplained pyrexia; repeated positive cultures from same line lumen >24 hours apart with indistinguishable organism and otherwise unexplained pyrexia.

Organisms were classed as indistinguishable if of the same species and ≤1 different antibiotic susceptibilities using standard panel of agents.

Outcomes

Main endpoints were CRBSI-free catheter time and overall incidence rate of early-onset CRBSI, occurring up to 21 days post line insertion. To evaluate longer-term effects of the intervention, we also assessed episodes of CRBSI up to 180 days of line insertion. Staff compliance with the protocol was determined by prescription of decolonisation therapy. Patient adherence to therapy was not assessed.

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Statistical Methods

Per-protocol analysis was carried out to determine the impact of decolonisation therapy on the incidence of CRBSI and infection-free line survival time. Incidence rates of CRBSI were calculated as number of new infections per 10,000 line-days and compared between treatment arms by calculating incidence rate ratios with exact 95% confidence intervals (95% CI) and Mid-P tests. Time at risk for CRBSI (infection-free survival time) was calculated as number of days between line insertion and line removal for episodes without CRBSI and as interval between line insertion and onset of first infection for episodes with CRBSI. Kaplan–Meier estimates of infection-free survival were obtained and survival curves were compared between treatment groups using log-rank test. Differences in baseline covariates were assessed using chi-square or Fisher's exact test for categorical variables and Mann-Whitney U-test for continuous variables. Multivariable Cox proportional hazards regression was used to obtain adjusted hazard ratios (HR) and 95% CIs correcting for differences in baseline covariates. The probability that a line in the decolonisation therapy group develops a CRBSI later than an untreated line insertion was estimated as P = 1 - HR/(1 + HR) [20].

Lines removed earlier than 21 days of insertion were considered censored observations in the survival analysis of early-onset CRBSI. Study end was defined at 180 days post line insertion. Cluster-robust standard error estimation was used in Cox regression to account for potential dependencies between different line-insertion episodes in the same patient. Statistical significance was defined at $p \leq 0.05$.

Various sensitivity analyses were performed to assess the likely effects of decolonisation therapy under different conditions. As decolonisation therapy was not prescribed in 19 (11.7%) of the inserted lines during the post-intervention period, an intention-to-treat analysis was carried out comparing CRBSI rates and infection-free times between assignment arms (pre-intervention vs. post-intervention). The data were also analysed on a modified intention-to-treat basis excluding the 19 lines that did not receive treatment during the post-intervention period. Finally, all analyses were repeated by excluding probable infections.

RESULTS

Baseline Data

During the pre-intervention period, 303 lines were inserted in 242 patients for a total of 24,212 line-days. In the post-intervention period, 163 lines were inserted in 147 patients with a total of 13,648 line-days. Decolonisation therapy was prescribed for 144 (88.3%) of the 163 inserted lines in the post-intervention period resulting in a total of 12,348 line-days among treated patients and 25,512 line-days among untreated patients. Decolonisation therapy was chlorhexidine and Prontoderm® in 133 cases and Octenisan® and Prontoderm® in 11 cases.

Treatment arms were similar with respect to patient age, sex, receipt of total parenteral nutrition and history of diabetes. Treatment arms differed significantly in primary diagnosis, with patients who were prescribed therapy being more likely to have received stem cell transplants (Table 1).

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Incidence of CRBSI

A total of 2 early-onset CRBSIs were detected up to day 21 post-insertion in patients who received decolonisation therapy, compared with 22 in untreated line insertions. The rate of early-onset CRBSI was 81% lower among the treated line-insertions than among those untreated (6.8 vs 35.0 cases per 10,000 lines-days at risk, p = 0.009).

Overall, 17 CRBSI were identified within 180 days following line-insertion in the decolonisation therapy group, as compared with 62 in the untreated group. The rate of CRBSI was 45% lower among the treated line-insertion episodes than among those untreated (14.4 vs. 26.0 cases per 10,000 lines-days at risk, p = 0.025).

If probable infections were excluded from analyses, relative rate reductions were 82% (p = 0.056) for definite early-onset infections and 58% (p = 0.016) for definite any-onset infections, respectively (Table 2).

Among the 24 early-onset CRBSI detected in this study, the most common pathogens were coagulase-negative *Staphylococcus* (29.2%), *Staphylococcus aureus* (29.2%) and *Enterobacteriaceae* (20.8%). Among the 79 any-onset CRBSI, most common aetiologic agents included coagulase-negative *Staphylococcus* (30.4%), *Enterobacteriaceae* (22.8%), non-fermenting Gram-negative bacteria (16.5%), and *Staphylococcus aureus* (13.9%). Following decolonisation therapy, a trend to reduced CRBSI incidence was observed for each bacterial pathogen except for *Corynebacterium* and non-fermenting Gram-negative bacteria (Table 3). The reduction was statistically significant in the case of *Staphylococcus aureus*, where early-onset infections reduced from 11.1 to 0.0 cases per 10,000 lines-days at risk (p = 0.069) and any-onset infections reduced from 4.6 to 0.0 cases per 10,000 lines-days at risk (p = 0.012).

CRBSI-Free Survival Times

The Kaplan-Meier estimates of 21 day infection-free rate after line insertion were 98.6% for the decolonisation therapy group and 92.8% for the untreated group. At 180 days following line insertion, estimated infection-free rate was 76.0% in the treated group and 66.5% in the untreated group (Figure 1). The log-rank test revealed a statistically significant difference between infection-free rates over time (p = 0.028).

Further investigation with a Cox proportional hazards analysis (Table 4), controlling for patient age, sex, primary diagnosis, type of transplant and history of diabetes, indicated that, at any given time, line-insertions that had been prescribed decolonisation therapy were significantly less likely to develop an early-onset CRBSI compared to those in the untreated group (adjusted HR = 0.24; 95% CI 0.17 – 0.35). This corresponds to an 81% probability (95% CI 74% - 85%) that a treated line develops an early-onset CRBSI later than an untreated line.

Extending follow-up time to 180 days of line insertion, our analysis showed a reduced risk of CRBSI in the decolonisation therapy group (adjusted HR = 0.61; 95% CI 0.46 – 0.79), with an estimated 62% chance (95% CI 56% - 68%) of treated lines developing a CRBSI later than untreated lines.

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Sensitivity Analyses

Table 5 presents the results of multivariable Cox regression for the risk of CRBSI under different conditions. Exclusion of probable infections did not alter the results in per-protocol analysis. Results were also similar when line insertions that were not prescribed decolonisation therapy during the post-intervention period (n = 19) were excluded from analysis.

An intention-to-treat analysis produced less pronounced and not statistically significant relative hazard reductions both for early-onset CRBSI (adjusted HR = 0.58; p = 0.199) and any-onset CRBSI (adjusted HR = 0.91; p = 0.477). The incidence rate of early-onset CRBSI during the post-intervention period was lower than the pre-intervention period (15.1 vs 32.1 cases per 10,000 lines-days at risk, respectively) but the difference was not statistically significant (p = 0.127). At 180 days post line-insertion, incidence rates of CRBSI were similar between the pre- and post- intervention periods (23.2 vs 20.2 cases per 10,000 lines-days at risk, respectively; p = 0.566).

DISCUSSION

We report a significant reduction in CRBSI rates and improved infection-free line survival times with the use of a dual skin and nasal decontamination regimen using chlorhexidine or Octenisan® washes and Prontoderm® nasal ointment, in a population of intensively-treated haematology patients with Hickman catheters.

Multiple factors contribute to the high rate of CRBSI in haematology patients and to the frequency of associated complications and mortality. These include prolonged neutropenia, immunosuppression and mucosal barrier breakdown, secondary to an often synergistic interaction between the underlying conditions themselves and the intensive cytotoxic therapy administered to treat them [3]. Central lines are also often in situ for longer periods in cancer patients compared to many others, another factor demonstrated to increase CRBSI risk [2,21].

Haematology patients are often treated intensively with curative intent or with the aim of inducing long-lasting remission with good quality of life. They therefore have much to gain from successful treatment but much to lose where infectious complications intervene to complicate and delay treatment. CRBSIs caused by drug-resistant organisms are frequent and present a particular challenge [22]. Given the difficulties in effectively treating such infections, and the high morbidity and mortality burden associated with them, prevention of CRBSIs is a particularly important goal in this patient population [3].

A reduction in CRBSI rates, such as that reported in our study, would be expected to translate into a clinically relevant reduction in serious complications including overwhelming sepsis and early line removal. The longer infection-free line survival times after decolonisation therapy will also facilitate delivery of necessary treatment and supportive therapy.

Reduction in early infection rate was particularly pronounced in this study, at a time when extraluminal route of infection predominates and measures to reduce contamination around the time of CVC insertion are therefore unsurprisingly most likely to improve infection rates [2,23]. The spectrum of causative organisms in our patient group was similar to that reported in previous studies of CRBSI in haematology and oncology patients, with the majority of cultured organisms being coagulase negative staphylococci, *Staphylococcus aureus*, Enterobacteriaceae, and other gram negative organisms [6,24,25]. Of all causative pathogens, reduction in *Staphylococcus aureus* CRBSI

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was most significant following implementation of our dual decolonisation regime, an organism commonly reported as a cause of early CRBSI [6,24,25].

Reduction in infection rates was not statistically significant when analysed on an intention-to-treat basis, indicating that a programme to ensure good compliance must be introduced along with the policy of peri-procedural decolonisation. Compliance was assessed by review of drug charts to determine whether decolonisation therapy had been prescribed as per protocol. As most of the decolonisation therapy was self–administered and not necessarily in hospital, no further data on compliance is available beyond information on decolonisation prescription. Given that 100% compliance with the prescribed decontamination regimen is unlikely, and true compliance therefore likely to be less than that assumed by the analysis above, the magnitude of reported reduction in infection rate and improvement in infection-free line survival could be expected to be even greater than those reported here if 100% compliance were assured.

A higher proportion of patients underwent stem cell transplantation in the treatment group than the pre-intervention group. We hypothesise that this is due to the involvement of highly trained transplant nurse specialists overseeing care for this particular patient group and ensuring strict adherence to prescribing policies, as well as to a general increase in transplant activity within the department over the course of the study.

We recommend routine implementation of a peri-procedural decontamination regimen using chlorhexidine or Octenisan® body washes and nasal Prontoderm® application to reduce CRBSI rates and improve infection-free line survival in intensively treated haematology and stem cell transplant patients. This is in addition to the traditional bundle of infection-prevention measures including aseptic technique at time of line insertion, staff training and education, and rigorous adherence to hand washing policies. Given the importance of compliance in attaining the reported reduction in infection rate, meticulous attention to ensuring staff and patient adherence to decolonisation therapy is vital.

We suggest that a programme of staff education along with the provision of verbal and written patient information on the rationale for such a regimen will aid compliance, and that specialist haematology nurses are well placed to oversee the introduction and ongoing implementation of these measures. Audit of CRBSI rates in individual units before and after implementation of a peri-procedural decontamination regimen is recommended, as well as monitoring of compliance with prescription and administration policy. While compliance with prescription policy is relatively easily assessed, compliance with administration will necessarily be more challenging to measure. Asking patients to sign a pre-printed calendar with the dates and times of administration may be one method, albeit imperfect, by which an estimation of compliance with administration may be gained.

This particular dual decolonisation therapy regimen now has proven efficacy in both the critical care and haematology settings. Further research is necessary to determine whether these results can be extrapolated to other populations such as patients undergoing renal replacement therapy and those being treated for solid tumours. No cost-effectiveness analysis has been carried out in this study and is also an area requiring further investigation.

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Figure 1 Kaplan-Meier estimates of the probability of CRBSI-free survival

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Table 1. Comparison of baseline characteristics of Hickman line-insertion episodes per treatment arm

Characteristic	Treatment arm		
	Untreated lines (n = 322)	Treated lines (n = 144)	*P* Value
Line-days, median (total)			
Overall	59.0 (25512)	63.5 (12348)	0.176
At risk[a]	51.5 (23871)	59.0 (11821)	0.081
Patient age, median (IQR)	57 (45 - 65)	56 (47 - 65)	0.992
Female sex, n (%)	103 (32.1)	56 (38.9)	0.153
Primary diagnosis, n (%)			0.042
Myeloma	95 (29.5)	46 (31.9)	
Lymphoma	91 (28.3)	30 (20.8)	
Acute myelogenous leukaemia	59 (18.3)	23 (16.0)	
Acute lymphoid leukaemia	39 (12.1)	14 (9.7)	
Chronic myelogenous leukaemia	7 (2.2)	10 (6.9)	
Other[b]	31 (9.6)	21 (14.6)	
Total parenteral nutrition, n (%)	12 (3.7)	2 (1.4)	0.244
Diabetes, n (%)	17 (5.3)	11 (7.6)	0.322
Type of transplant, n (%)			<0.001
None	152 (47.2)	39 (27.1)	
Autologous	108 (33.5)	57 (39.6)	
Allogeneic	62 (19.3)	48 (33.3)	

[a] Line-days before onset of infection.

[b] Includes aplastic anaemia (n=15), chronic lymphocytic leukaemia (n=10), myelodysplastic syndromes (n=12), myelofibrosis (n=5), and non-haematological diagnosis (n=10).

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Table 2. Incidence rates of CRBSI and median times to infection according to treatment arm

Type of infection	Treatment arm: Untreated lines (n = 322)	Treatment arm: Treated lines (n = 144)	Incidence Rate Ratio (95% CI)	*P* Value
Early onset CRBSI[a]				
No. of infections	22	2		
Median time to infection (days)	13.5	11.0		
Line-days at risk[b]	6294	2936		
Incidence rate[c]	35.0	6.8	0.19 (0.02 - 0.79)	0.009
Early-onset definite CRBSI[a]				
No. of infections	12	1		
Median time to infection (days)	13.5	14.0		
Line-days at risk[b]	6348	2949		
Incidence rate[c]	18.9	3.4	0.18 (0.00 - 1.21)	0.056
Any-onset CRBSI[d]				
No. of infections	62	17		
Median time to infection (days)	37.5	62.0		
Line-days at risk[e]	23871	11821		
Incidence rate[c]	26.0	14.4	0.55 (0.30 - 0.96)	0.025
Any-onset definite CRBSI[d]				
No. of infections	39	8		
Median time to infection (days)	45.0	76.5		

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Line-days at risk[e]	24765	12175		
Incidence rate[c]	15.7	6.6	0.42 (0.17 - 0.91)	0.016

Abbreviations: CRBSI, catheter-related bloodstream infection; CI, confidence interval.

[a] Includes infections that occurred within 21 days of line insertion.

[b] Duration of lines was calculated until onset of infection for infected patients and up to line-removal or 21 days post insertion for uninfected patients.

[c] Number of infections per 10,000 line-days at risk.

[d] Includes infections occurring up to 180 days post line insertion.

[e] Duration of lines was calculated until onset of infection for infected patients and up to line-removal or 180 days post insertion for uninfected patients.

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Table 3. Incidence of CRBSI by type of aetiologic organism

	Untreated lines (n = 322)		Treated lines (n = 144)		
Infecting organism	**No. of infections**	**Incidence Rate[a]**	**No. of infections**	**Incidence Rate[a]**	**P value**
Coagulase negative staphylococcus					
Early onset CRBSI[b]	6	9.5	1	3.4	0.361
All CRBSI[c]	17	7.1	7	5.9	0.703
***Staphylococcus* aureus**					
Early onset CRBSI[b]	7	11.1	0	0.0	0.069
All CRBSI[c]	11	4.6	0	0.0	0.012
Alpha Haemolytic streptococcus					
Early onset CRBSI[b]	1	1.6	0	0.0	0.682
All CRBSI[c]	3	1.3	1	0.8	0.797
Enterococcus					
Early onset CRBSI[b]	1	1.6	0	0.0	0.682
All CRBSI[c]	1	0.4	0	0.0	0.669
Corynebacterium					
Early onset CRBSI[b]	1	1.6	1	3.4	0.636
All CRBSI[c]	3	1.3	1	0.8	0.797
Enterobacteriaceae					
Early onset CRBSI[b]	5	7.9	0	0.0	0.147
All CRBSI[c]	15	6.3	3	2.5	0.139
Non-fermenting Gram negative					
Early onset CRBSI[b]	0	0.0	0	0.0	1.000
All CRBSI[c]	9	3.8	4	3.4	0.887

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Anaerobe					
Early onset CRBSI[b]	1	1.6	0	0.0	0.682
All CRBSI[c]	2	0.8	0	0.0	0.447
***Mycobacterium* chelonae**					
Early onset CRBSI[b]	0	0.0	0	0.0	1.000
All CRBSI[c]	1	0.8	1	0.4	0.662
Total					
Early onset CRBSI[b]	22	35.0	2	6.8	0.009
All CRBSI[c]	62	26.0	17	14.4	0.025

Abbreviations: CRBSI, catheter-related bloodstream infection.

[a] Number of infections per 10,000 line-days at risk

[b] Includes infections that occurred within 21 days of line insertion.

[c] Includes infections occurring up to 180 days post line insertion.

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Table 4. Results of multivariable Cox proportional hazards regression analysis for the risk of catheter-related bloodstream infection

	Early-onset CRBSI[a]			Any-onset CRBSI[b]		
Variable	**Adjusted HR**	**95% CI**	**P value**	**Adjusted HR**	**95% CI**	**P value**
Decolonisation therapy						
Untreated	1.00	-	-	1.00	-	-
Treated	0.24	0.17 - 0.35	<0.001	0.61	0.46 - 0.79	<0.001
Male sex	1.65	0.84 – 3.26	0.147	0.95	0.73 – 1.23	0.700
Age	1.00	0.98 – 1.01	0.518	0.99	0.98 – 1.00	0.194
Primary diagnosis						
Myeloma	0.73	0.23 – 2.37		1.07	0.63 – 1.80	0.812
Lymphoma	0.30	0.10 – 0.87		1.00	0.69 – 1.47	0.986
Acute myelogenous leukaemia	0.85	0.39 – 1.85		1.37	0.91 – 2.07	0.127
Acute lymphoid leukaemia	0.86	0.32 – 2.31		1.05	0.67 – 1.64	0.839
Other[c]	1.00	-	-	1.00	-	-
Diabetes	3.27	1.16 – 9.20	0.025	1.43	0.72 - 2.87	0.306
Type of transplant						
None	1.00	-	-	1.00	-	-
Autologous	0.23	0.10 - 0.54	0.001	0.37	0.26 – 0.52	<0.001
Allogeneic	0.30	0.11 - 0.85	0.024	0.55	0.38 – 0.79	0.001

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Abbreviations: CRBSI, catheter-related bloodstream infection; HR, hazard ratio; CI, confidence interval.

[a] Includes infections occurring up to 21 days post line insertion.

[b] Includes infections that occurred within 180 days of line insertion.

[c] Includes aplastic anaemia, CLL, chronic myelogenous leukaemia, myelodysplastic syndromes, myelofibrosis, and non-haematological diagnoses.

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Table 5. Results of multivariable Cox proportional hazards regression for the risk of catheter-related bloodstream infection under different conditions (sensitivity analyses)

	Per-protocol analysis[a]			**Intention-to-treat analysis[b]**			**Modified intention-to-treat analysis[c]**		
Type of infection	aHR[d]	95% CI	*P* value	aHR[d]	95% CI	P value	aHR[d]	95% CI	*P* value
Early-onset CRBSI, all[e]	0.24	0.17 - 0.35	<0.001	0.58	0.25 – 1.34	0.199	0.26	0.18 – 0.40	<0.001
Early-onset CRBSI, definite[e]	0.26	0.14 – 0.48	<0.001	0.69	0.20 – 2.31	0.541	0.26	0.10 – 0.69	0.008
Any-onset CRBSI, all[f]	0.61	0.46 - 0.79	<0.001	0.91	0.71 – 1.18	0.477	0.68	0.55 – 0.83	<0.001
Any-onset CRBSI, definite[f]	0.46	0.30 – 0.69	<0.001	0.86	0.58 – 1.27	0.454	0.52	0.39 – 0.71	<0.001

Abbreviations: aHR, adjusted Hazard Ratio; CI, confidence interval, CRBSI, catheter-related bloodstream infection.

[a] Compares line-insertion episodes that were prescribed decolonisation therapy (n = 144) to those that did not (n = 322).

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[b] Compares line-insertion episodes in the post-intervention period (n = 163) to those in the pre-intervention period (n = 303).

[c] Compares line-insertion episodes in the post-intervention period (n = 144) to those in the pre-intervention period (n= 303), excluding line insertion that were not prescribed decolonisation therapy during the post-intervention period (n = 19).

[d] Controlling for the effects of patient age, sex, primary diagnosis, type of transplant, and history of diabetes.

[e] Includes infections that occurred within 21 days of line insertion.

[f] Includes infections occurring up to 180 days post line insertion.

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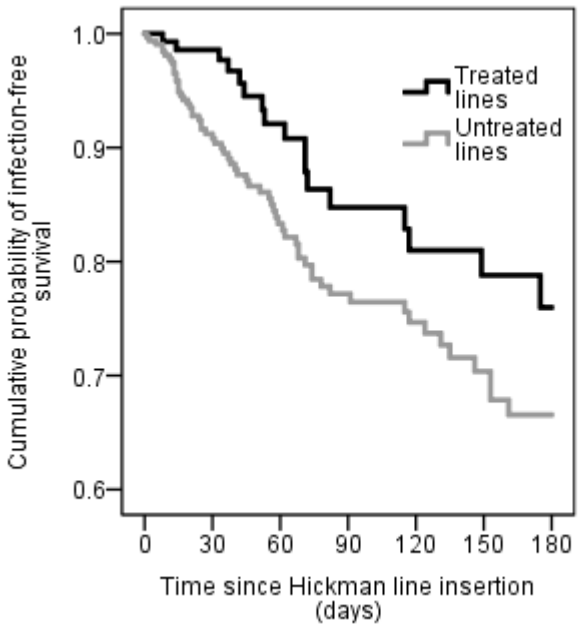

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