

# Accuracy of bacterial DNA testing for central venous catheter-associated bloodstream infection in children with cancer

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## Executive summary

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# Executive summary

## Background

Central venous catheters (CVCs) are widely used for children with cancer to infuse anti cancer drugs and to administer complex drug and hydration schedules, blood products and parenteral nutrition. CVCs are required for up to 2 years during the cancer treatment. They are a major risk factor for bloodstream infection in this group of patients.

Children undergoing treatment for cancer may develop bloodstream infection from a variety of sources, including the CVC. Although intravenous (i.v.) antibiotic treatment is required whatever the source of infection, distinguishing CVC-associated bloodstream infection from other sources is important as additional interventions may be required, such as antibiotic treatment given slowly or in higher concentrations to target intraluminal biofilm bacteria and, in some cases, removal of the CVC.

Methods used in adults to distinguish the CVC from other sources of infection require additional blood sampling from a peripheral vein or removal of the CVC, which is not always acceptable for children. Another problem for the diagnosis of CVC infection in patients undergoing treatment for cancer is the widespread use of antibiotics for both prophylaxis and treatment, which reduce the sensitivity of blood culture, and other diagnostic methods that require recovery of viable microbes.

Early and specific diagnosis of CVC-associated bloodstream infection has the potential to lead to more effective, CVC-targeted treatment and to reduce the risk of serious complications. Early targeted treatment, such as antibiotic locks, may also reduce the risk of CVC removal, thereby avoiding the operative risks and trauma of reinsertion.

The overall aim of our study was to improve the detection and treatment of CVC-associated bloodstream infections in children with cancer admitted with fever. The study involved the evaluation of diagnostic accuracy of a quantitative molecular method for the detection of bacterial DNA (deoxyribonucleic acid), based solely on blood samples drawn through the CVC. We analysed the prognostic risk of CVC removal and duration of i.v. antibiotic treatment days in relation to presenting clinical features, blood culture results and bacterial DNA test results, and we carried out a series of systematic reviews of treatment options for CVC-associated infection. We evaluated the clinical effectiveness of different test–treatment strategies to reduce i.v. antibiotic treatment days and unnecessary CVC removals, and, finally, we considered the implications of our findings for further research.

## Objectives

1. To determine the diagnostic accuracy of a novel molecular test for CVC-associated infection in children with cancer admitted with fever.
2. To determine the extent to which bacterial DNA and other prognostic markers discriminate between sequelae of CVC-associated infection, including CVC removal and duration of i.v. antibiotic treatment days.
3. To conduct systematic reviews to determine the effectiveness of treatment options targeted at CVC-associated bloodstream infection.

4. To survey current clinical practice to determine the use of antimicrobial locks for prophylaxis or treatment of CVC-associated infection and perceived barriers to their use.
5. To estimate the potential benefits of different test–treatment strategies measured by i.v. antibiotic treatment days saved and avoidance of unnecessary CVC removals.

## Methods

The diagnostic accuracy study involved eight paediatric oncology centres in the UK and was co-ordinated through the Children's Cancer and Leukaemia Group (CCLG). Children aged 0–18 years with a CVC or implanted CVC port considered to be required for a minimum of 3 months were invited to participate in the study. Eligible patients were enrolled when they presented with a febrile episode if they had not received i.v. antibiotic therapy during the preceding 2 weeks. Samples were collected at the time of presentation to hospital with fever for routine blood cultures and for bacterial DNA testing. Clinical data were collected at the time of admission and at 4 weeks after presentation using standard questionnaires. Definitions of CVC-associated infection were agreed before the start of the study and these allowed classification of fever episodes into probable, possible, unlikely and unclassifiable groups. The results of the accuracy study have been published [Millar *et al.* Molecular diagnosis of vascular access device-associated infection in children being treated for cancer or leukaemia. *Clin Microbiol Infect* 2008;**14**(3):213–20].

The study of prognostic markers used the same data set as the diagnostic accuracy study, but with additional information up to 6 months after the presenting admission with fever. Analyses were restricted to the first episode of fever. Two test results were considered in all analyses in addition to the bacterial DNA results: these were blood culture and clinical signs of CVC-associated infection (fever, chills, rigors or hypotension associated with CVC manipulations).

We conducted three systematic reviews to determine the effectiveness of early versus deferred CVC removal, antimicrobial locks for treating CVC-associated infection and antimicrobial locks for preventing CVC-associated infection. We also conducted a questionnaire survey of 18 oncology centres, in collaboration with CCLG members, to obtain information about current practice and problems perceived with using antimicrobial locks for prophylaxis or treatment of CVC-associated infection.

We illustrated the potential benefits of different test–treatment strategies based on clinical signs of CVC infection or bacterial DNA results on admission prior to availability of blood culture results 48 hours later. We considered the treatment options of early removal of the CVC, early stopping of i.v. treatment for children at very low risk of bloodstream infection, antimicrobial lock treatment and standard care.

## Results

The accuracy study found that the bacterial DNA test detected two-thirds of children classified with probable CVC-associated infection and the specificity was 88% [95% confidence interval (CI) 84% to 92%]. Although high bacterial DNA concentrations were associated with subsequent CVC removal and duration of i.v. antibiotic treatment, the test did not improve the prediction of these outcomes over and above clinical signs of CVC-associated infection and blood culture results, although DNA was predictive of CVC removal and i.v. treatment duration on the day of admission, before blood culture results became available at 48 hours after sampling.

In the systematic reviews of treatment strategies, we found no trials that evaluated early removal of the CVC compared with delayed removal. Observational studies comparing early removal with retention and treatment were confounded by deferred removal in the sickest patients.

We found limited evidence that antibiotic lock treatment reduces the risk of recurrent CVC-associated infection or removal (pooled relative risk 0.7, 95% CI 0.47 to 1.05). We found 24 trials, published since 1994, on the use of antimicrobial locks to prevent CVC-associated infection. Overall, antimicrobial locks halved the risk of bloodstream infection in a variety of patient groups (pooled incidence rate ratio 0.43, 95% CI 0.36 to 0.51). Contrary to this evidence, our national survey of paediatric oncology centres found that locks are being used for treatment rather than prevention and that problems related to the formulation of lock solutions currently impede a shift to their prophylactic use in children. We found that most i.v. treatment days would be saved by early stopping of treatment for children at low risk of infection.

## Conclusions

We found strong evidence to support the use of antimicrobial locks for prevention of CVC-associated infection; however, few of these studies involved children with cancer. The study highlighted variation in the management of children with cancer and fever who were admitted from home. Our analysis does not support routine bacterial DNA testing on admission to detect CVC-associated infection, but we cannot exclude the possibility that repeated testing (as a marker of microbial load) may be of value in high-risk groups, for example to measure response to treatment.

## Recommendations for research

1. We recommend a trial to determine whether early discontinuation of i.v. antibiotic treatment in children with cancer presenting with fever is equivalent to standard care.
2. There is good evidence that antibiotic locks prevent CVC-associated bloodstream infection, but there may still be a need for effectiveness and cost-effectiveness studies in certain groups: for example, children and adults undergoing treatment for cancer, children and adults receiving long-term total parenteral nutrition. Initial laboratory studies are needed to determine the optimum formulations of lock solutions for home use and storage conditions. In addition, long-term follow-up studies are needed to evaluate the emergence of antimicrobial resistance. Additional clinical trials are required to compare different types of antimicrobial solutions.
3. Randomised, placebo-controlled trials are needed to determine the effectiveness of antibiotic locks for treating CVC-associated infection.
4. Controversy about the benefits of early CVC removal versus treatment in situ will remain until clinical trials have shown clear benefits for early CVC removal, according to the type of organism.
5. We do not recommend a randomised controlled trial involving the DNA testing methodology used in this study as a single test on admission of children with cancer presenting from the community with fever. However, improved methodologies (both sampling and analysis) may require further clinical studies. *Repeated* DNA testing should be evaluated as a marker of microbial load in children undergoing targeted treatment for CVC-associated infection to identify those with a persisting microbial load who require CVC removal.
6. Variation in practice between centres should be evaluated to determine the effectiveness of alternative practices. Linkage between routine data on individual patient admissions and

blood culture results, is now feasible and could offer an efficient way of evaluating the impact of variation in practice.

### **Trial registration**

This trial is registered as ISRCTN68138140.

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### **Publication**

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# NIHR Health Technology Assessment programme

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

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 03/39/13. The contractual start date was in June 2005. The draft report began editorial review in January 2010 and was accepted for publication in September 2010. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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