# ANTIBIOTIC LOCK THERAPY (ALT) FOR MANAGEMENT OF CATHETER-RELATED INFECTION IN HOSPITAL UNIVERSITI SAINS MALAYSIA (HUSM)

**DR NUR AIN BINTI CHE AZMI**

DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER OF PATHOLOGY

(MEDICAL MICROBIOLOGY)


**SCHOOL OF MEDICAL SCIENCES**

**UNIVERSITI SAINS MALAYSIA**

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# LIST OF SYMBOLS

| Symbols/ abbreviations | Meaning |
|---|---|
| < | Less than |
| > | More than |
| % | Percentage |
| = | Equal to |
| x | Times or multiplication |
| °C | Degree Celsius |
| SD | Standard deviation |
| IQR | Interquartile range |
| spp. | Species |
| Et al | And others |
| CVCs | Central venous catheters |
| HD catheter | Haemodialysis catheter |
| MICs | Minimum inhibitory concentrations |
| ALT | Antibiotic lock therapy |
| CRBSIs | Catheter-related bloodstream infections |
| CRI | Catheter-related infection |
| CONS | Coagulase-negative staphylococci |
| MRCONS | Methicillin resistant Coagulase negative staphylococci |
| EPS | Extracellular polymeric substances |
| EDTA | Ethylenediaminetetraacetic acid |
| MDROs | Multidrug resistance organisms |

| Symbols/ abbreviations | Meaning |
|---|---|
| IDSA | The Infectious Diseases Society of America |
| UKJEH | Unit Kawalan Jangkitan dan Epidemiologi Hospital |
| HUSM | Hospital Universiti Sains Malaysia |
| LIS | Laboratory Information System |
| TWC | Total white count |
| ANC | Absolute neutrophil count |
| CRP | C-reactive protein |
| DM | Diabetes mellitus |
| HPT | Hypertension |
| ESRF | End stage renal failure |
| HLAR | High level aminoglycoside resistance |

# ABSTRAK


**Terapi kunci antibiotic (ALT) untuk pengurusan jangkitan berkaitan kateter di Hospital Universiti Sains Malaysia (HUSM).**

**Pengenalan**: Kateter vena pusat (CVC) digunakan secara meluas di hospital, terutamanya kepada pesakit kritikal, hemodialisis dan pesakit kanser. Walaupun digunakan dengan baik dan amalan kawalan jangkitan yang betul, jangkitan masih kekal sebagai komplikasi paling biasa berlaku bagi peralatan perubatan sedemikian. Dalam sesetengah keadaan di mana terdapat akses vaskular yang terhad, doktor boleh mencuba beberapa kaedah untuk menyelamatkan kateter. Terapi kunci antibiotik (ALT) yang direka untuk mencapai 100 hingga 1000 kali ganda kepekatan perencatan minimum (MIC) di dalam lumen, telah dicadangkan untuk menangani isu biofilem dalam patogen-patogen tersebut. Perkaitan antara penggunaan ALT dan hasil jangkitan berkaitan kateter (CRI) akan membantu kami untuk membuktikan penggunaan ALT dalam jangkitan berkaitan kateter. Tambahan pula, kadar kejayaan keseluruhan yang terdapat dalam setiap patogen yang menyebabkan jangkitan juga boleh membantu doktor memilih modaliti ALT yang sesuai.

**Metodologi**: Ini adalah semakan rekod retrospektif yang melibatkan pesakit dengan jangkitan berkaitan kateter yang didiagnos oleh doktor yang merawat di Hospital Universiti Sains Malaysia (HUSM) dari bulan Januari 2016 hingga bulan Disember 2019. Sebanyak 120 kes yang sesuai diberikan ALT untuk rawatan telah diambil untuk kajian ini. ALT boleh diberikan kepada mereka yang mempunyai jangkitan salur darah berkaitan kateter (CRBSI) yang tidak rumit atau kepada kolonisasi kateter di mana kateter vena

pusat (CVC) bertujuan untuk diselamatkan atas pelbagai sebab. Daripada jumlah ini, hanya 53 kes diambil kira analisis kerana mereka mengekalkan kateter terjangkit selepas rawatan sama ada dengan antibiotik sistemik sahaja atau oleh kedua-dua antibiotik, sistemik dan juga terapi kunci antibiotik (ALT). Semua data yang diperoleh telah dianalisis dengan menggunakan perisian SPSS versi 27 (SPSS Inc, Chicago, IL).

**Keputusan**: Daripada 53 kes CRI, hanya 36 (67.9%) kes diberikan ALT bersama-sama dengan antibiotic sistemik oleh doktor yang merawat. Kebanyakan kes (86.1%) adalah daripada wad onkologi di mana pesakit dengan kanser hematologi mewakili bahagian terbanyak yang menerima ALT. Kerintangan metisilin *Staphylococcus* koagulasi-negatif (MRCONS) telah didapati sebagai patogen yang paling biasa menyebabkan jangkitan berkaitan kateter dan telah diberikan ALT dengan kadar kejayaan 82.4%. Antara kes jangkitan berkaitan kateter (CRI) yang diberi rawatan gabungan antibiotik sistemik dan ALT, terdapat pengurangan ketara dalam tahap C-protein reaktif (CRP) sehingga 42% ($p=0.001$) dan kira-kira 83% dapat menyelamatkan kateter ($p<0.001$).

**Kesimpulan**: Gabungan terapi kunci antibiotik (ALT) bersama dengan rawatan antibiotik sistemik mungkin merupakan strategi yang berkesan dalam menyelamatkan kateter. Kajian lanjut mungkin diperlukan untuk menentukan keberkesanan ALT dalam populasi pesakit-pesakit tertentu.

# ABSTRACT

**Antibiotic lock therapy (ALT) for management of catheter-related infection in Hospital Universiti Sains Malaysia (HUSM).**

**Introduction**: Central venous catheters (CVCs) are used widely in hospitals, especially in critically ill patients, haemodialysis, and oncology patients. Despite all the excellent usage and proper infection control practices, infections remain the most common complications of such devices. In some conditions with limited vascular access, clinicians may attempt a few ways to salvage the catheter. Antibiotic lock therapy (ALT), designed to achieve 100 to 1000-fold minimum inhibitory concentrations (MICs) in the lumen, has been proposed to tackle the issue of biofilm in such pathogens. The association between the use of ALT and the outcome of a catheter-related infection (CRI) will help us justify the use of ALT in catheter-related infections. Furthermore, the overall success rate found in each pathogen causing the infection may also help clinicians choose the appropriate ALT modalities.

**Materials and method**: This was a retrospective record review involving patients with catheter-related infections diagnosed by treating clinicians in Hospital Universiti Sains Malaysia (HUSM) from January 2016 to December 2019. A total of 120 cases suitable for ALT were selected for this study. ALT can be given to those with uncomplicated CRBSI or catheter colonisation in which the CVCs were intended to be salvaged for various reasons. Out of this, only 53 cases were taken into the analysis as those that retained the CVCs after treatment either by systemic antibiotic alone or by both systemic

antibiotic and ALT. All the data that has been collected were analysed using version 27 of the SPSS software (SPSS Inc, Chicago, IL).

**Results**: Out of 53 cases of CRI, only 36 (67.9%) cases were given ALT together with systemic antibiotics by the treating clinicians. Most cases (86.1%) were from oncological wards where patients with haematological malignancy were the most common proportion of patients receiving ALT. Methicillin-resistant coagulase-negative staphylococci (MRCONS) were found to be the most common pathogens causing CRI and were given ALT with a success rate of 82.4%. Among the CRI cases that were given a combination treatment of systemic antibiotics and ALT, there was a significant reduction in CRP levels up to 42% ($p=0.001$), and about 83.3% were able to salvage the catheter ($p<0.001$).

**Conclusion**: A combination of antibiotic lock therapy together with systemic antibiotic treatment may be an effective strategy for salvaging the catheter. Further studies may be required to determine the effectiveness of ALT in specific populations of patients.

***Keywords***: Catheter-related infection, antibiotic lock therapy, outcome

# CHAPTER 1 INTRODUCTION

## 1.1 Background of the study

Central venous catheters (CVCs) are used widely in the hospital setting, particularly in critically ill patients, haemodialysis, and oncology patients. The main types of CVCs include non-tunnelled and tunnelled catheters, totally implantable venous access ports (TIVAP), and PICC lines (peripherally inserted central catheters). They are used for haemodialysis and monitoring patients' haemodynamic status, administering chemotherapy medications, and giving fluid and parenteral nutrition. They allow clinicians to deliver maximum effective management while avoiding the need for multiple punctures that cause pain to the patients. Despite all the excellent usage and proper infection control practices, infections remain the most common complications of such devices (Günther et al., 2016). These contribute to a more extended hospital stay and increase treatment costs with significant morbidity and mortality (Kelly *et al.*, 2011). Microorganisms that attain access to the extraluminal or intraluminal surface of the device will adhere and incorporate into biofilms which then cause haematogenous dissemination and infection. This biofilm formation has a much higher minimum inhibitory (MICs) for antibiotics when compared to non-biofilm-related infections (Yousif, Jamal & Raad, 2015). Hence, to combat this issue, antibiotic lock therapy (ALT) was designed to achieve 100-to-1000-fold higher MICs in the lumen compared to what can be achieved on systemic administration (Lebeaux *et al.*, 2014). This may help salvage the catheter, especially in conditions with limited venous access and in oncology patients where the catheter is precious (Böhlke, Uliano & Barcellos, 2015).

## 1.2 Literature review

### 1.2.1 Catheter-related infection

Undoubtedly, central venous catheters (CVCs) are essential in managing patients for hemodialysis, chemotherapy, antibiotic administration, and monitoring fluid in critically ill patients. However, their usage also has been associated with complications such as catheter-related bloodstream infections (CRBSIs), catheter colonization, exit site infections, and tunnel infections (Shahar *et al.*, 2021). Due to their immunocompromised state, those at risk for these complications include hemodialysis patients and oncology patients.

According to the Clinical and Laboratory Standards Institute (CLSI), for the diagnosis of catheter-related bloodstream infection (CRBSI) to be made, the blood culture from the catheter should grow 2 hours earlier before the peripheral blood culture, and they should be of the same organism and similar sensitivity pattern (CLSI M47, 2022). For such an infection to happen, the microorganisms must have access to the extraluminal or intraluminal surface of the device. They will adhere, incorporate into the biofilm and later produce infection or even cause hematogenous dissemination. The intraluminal source is the most frequent cause of bacteraemia in long-term catheters. It is known that catheters in place for more than 30 days have a 40% higher risk of having biofilm–producing microbes attached to them. This microbial colonization at the catheter insertion site also plays a role in causing catheter-related bloodstream infection (CRBSI) (Mermel, 2011).

A study done in UKMMC on haemodialysis patients using tunneled dialysis catheters found that the prevalence of catheter-related bloodstream infection (CRBSI) was 4.2%, and catheter colonization was 4.8%. The most common isolates in both groups

were Gram-positive organisms, particularly coagulase-negative staphylococci (CONS) and methicillin-sensitive *Staphylococcus aureus* (MSSA) (Shahar *et al.*, 2021). This finding also corresponds with one study in Spain in which the predominant isolate among catheter colonizers was *Staphylococcus epidermidis* (Alonso *et al.*, 2019). Meanwhile, in China and Bangladesh, catheter colonizers were predominantly Gram-negative organisms, *Acinetobacter* spp. and *Pseudomonas* spp. respectively for each state (Afroz *et al.*, 2015; He *et al.*, 2019). These differences in the catheter colonizer epidemiology may be caused by different analysis techniques for the method of identification and different hospital environments and weather that contribute to the variation of microbial colonization. Thus, knowing the microbiological profile and antibiotic susceptibility pattern of catheter-related infection in our setting would help the clinician choose suitable antibiotics for empirical therapy and thus improve infection control measures in the hospital.

### 1.2.2 Antibiotic lock therapy (ALT)

The catheter-related infection has been a complicated issue, especially in oncology patients due to their immunosuppressive state and in haemodialysis patients when the clinician has limited options for venous access. The most common approach would be catheter removal. However, the decision to remove CVC depends on the isolated organism and the patient's clinical condition. Infection by *Staphylococcus aureus* and *Candida* spp. frequently require catheter removal as they are associated with a higher mortality rate, while infection by Gram-negative organisms may be related to a better salvage rate (Mermel *et al.*, 2009; Soman *et al.*, 2016). On the other hand, re-insertion of CVC is associated with an increased risk of pneumothorax and bleeding and is costly. So, we should find ways to salvage the catheter without worsening the outcome (Zanwar *et*

*al.*, 2019). It has been suggested that in patients with a catheter-related infection where the catheter would have to be remained in place due to specific reasons, antibiotic lock therapy can be given to the retained catheter (Mermel *et al.*, 2009). Antibiotic lock therapy (ALT) can achieve 100 to 1000-fold higher minimum inhibitory concentration (MICs) in the lumen than achieved upon systemic administration. The antibiotic solution is left to dwell within the lumen for a few hours to days depending on the choice of antibiotic given. The concentration of the solution is such that enough is given to fill the lumen but not spill into the systemic circulation. Most studies found that the duration of ALT should be two weeks. Antibiotics such as vancomycin, ceftazidime, and cefazolin are stable in heparin solutions at $25^0$ C and $37^0$ C for a few days (Mermel *et al.*, 2009).

### 1.2.3 Antibiotic activity against biofilm

Biofilms are a community of microbes attached and embedded in a glycocalyx or a matrix of extracellular polymeric substances (EPS). This EPS density differs within the biofilm, being the densest in the layers immediately surrounding the microbial colony, usually situated at the deeper part. Comparable, the more superficial layers have less density, thus forming channels within and around the biofilm matrix. Such channels enable the movement of nutrients, waste products, quorum-sensing molecules, and other substances (including antibiotics), similar to how the circulatory system functions in multicellular organisms. Biofilms represent a form of adaptive resistance that results in significant reductions in antibiotic susceptibility ranging from 10- to 1,000-fold (based on minimum inhibitory concentrations [MIC]). Biofilms may retard the distribution of antibiotics through charge interactions, size exclusion, matrix viscosity, and potential adsorption to proteins. EPS can also inactivate antibiotic molecules before they reach biofilm cells. Due to the high content of polyanionic, positively charged antibiotics (such

as aminoglycosides) can bind to EPS and have particularly weak distribution in biofilms (Justo & Bookstaver, 2014).

Besides that, biofilm cells may also show some resistance factors such as increased efflux pumps, stress response regulons, and inactivating enzymes and thus express a slower rate of growth. The killing effect of antibiotics with a growth-dependent mechanism of action is often reduced in these static biofilm cells. So, the ideal antibiotic treatment of biofilm should have ample penetration into EPS and has dynamic activity against biofilm cells. Ion chelators such as ethylenediaminetetraacetic acid (EDTA) and citrate may be used as additives as they also show synergistic activity with antibiotics (Justo & Bookstaver, 2014).

### 1.2.4 Ideal ALT solutions

Preferably, any lock solution should have a few characteristics to be used as a treatment modality. Those characteristics include the following:

a) The scope of activity should include common pathogens. Although most CRBSIs are secondary to Gram-positive organisms, long-term use of CVCs in high-risk patients increases the likelihood of developing Gram-negative and fungal pathogens.

b) The ability to penetrate biofilms and act at concentrations 100 to 1000 times higher than standard concentrations. Some additives like EDTA and citrate can disrupt biofilms.

c) Using compatible anticoagulants such as heparin or citrate can reduce the risk of occlusion. Thus, this would further improve the ability to use the lock solutions more widely.

d) Extended stability. The ability to mass-produce lock solutions and apply longer expiry dates will improve ALT continuity at points of care. In addition, room temperature storage is an added benefit compared to refrigerated storage.

e) Low risk of toxicity and adverse events. The small amount used in the intraluminal space does not pose a high risk of toxicity. Nevertheless, when used in high concentrations, certain drugs, such as aminoglycosides and citrate, are associated with severe toxicity and should be avoided in ALT. Catheter occlusion also can occur with ALT, especially in the absence of a low-dose anticoagulant in the solution.

f) Less potential for resistance. Resistance concerns are mitigated when systemic antibiotics are used concurrently as lock solutions in treatment modalities.

g) Cost-effectiveness. Certain drugs, such as linezolid and daptomycin, can be costly, especially when used for prophylaxis in large populations. Therefore, before initiating lock therapy with such expensive agents, careful considerations should be given to maximize formulation efficiency and stability.

### 1.2.5 Examples of ALT

Ampicillin and cefazolin are stable and well tolerated in combination with heparin, potentially providing treatment options for sensitive Gram-positive pathogens. Extended-spectrum beta-lactam antibiotics such as piperacillin, piperacillin/tazobactam, and ticarcillin/clavulanic acid have also shown stability and compatibility with heparin. As for carbapenem-based solutions, the data are scanty. Perhaps more data are needed for

this in the future because CRBSIs with multidrug-resistant organisms (MDROs) have increased over time with limited treatment options (Labriola, 2019).

Aminoglycosides such as amikacin and gentamicin can also be used for ALT. However, there is a concern regarding the chemical stability of high gentamicin concentrations (up to 40 mg/mL) when mixed with heparin. This problem can be solved by using other additives such as citrate or EDTA. (Chauhan *et al.*, 2012). Amikacin, on the other hand, when used in higher concentrations (more than 10 mg/mL), can result in ototoxicity. Therefore, these concentrations increase the risk to the patient, especially if they accidentally enter the systemic circulation during flushing, and thus should not be used in lock solutions (Saxena, Panhotra & Naguib, 2002).

Vancomycin is one of the most well-studied glycopeptides used in ALT. It is documented that it is compatible with concentrations ranging from 0.1 to 10 mg/mL and heparin sodium 100 to 5000 units/mL for ALT. Furthermore, despite it exhibiting concentration-dependent antimicrobial killing activity, it is reported in many studies that it remains physically and chemically stable for up to 72 hours (Bookstaver *et al.*, 2013).

### 1.2.6 Outcome of CRI with the use of ALT

Long-term use of CVCs carries a significant risk of bloodstream infection. Although removing the CVCs is the best option, it is not always suitable for many patients with limited vascular access and high-risk surgical candidates. Several randomized studies have been performed using ALT as a treatment modality. A study by Qureshi et al. found that catheter salvage was achieved in 77.8% of paediatric haematology/oncology patients given ALT. However, relapses were high in cases of *Staphylococcus* spp. infection, in which IDSA guidelines did not recommend using ALT (Qureshi *et al.*, 2019). Meanwhile, a success rate of 66.7% was found in patients on home

parenteral nutrition that develop CRBSI. Their study also found a significant association between infection in patients who have undergone previous catheterization ($p < 0.001$) (Santarpia et al., 2016). Haemodialysis patients on tunnelled catheters, using Daptomycin as ALT to treat Gram-positive CRBSIs have shown more than 70% success rate with the coagulase-negative staphylococci (CONS) subgroup have achieved up to 88% success (Yen *et al.*, 2016). In a multivariate analysis done by Freire et al. on ALT outcome of long-term CVCs with CRBSI, ALT has shown statistical significance for both outcomes - treatment success (relative risk: 0.78, 95% confidence interval: 0.70 – 0.91, p-value = 0.03) and mortality (hazards ratio: 0.15, 95% confidence interval: 0.05 – 0.49, p-value = 0.04) (Freire *et al.*, 2018). Also, in a study by Raad et al., they found that patients that received ALT containing minocycline, EDTA, and 25% ethanol received a shorter duration of systemic antibiotic therapy with a median of 11 days ($p < 0.0001$). The catheter can also be salvaged for a median of 74 days after the onset of bacteraemia (Raad *et al.*, 2016). Meanwhile, another case series analysis found that up to 69.2% of CRBSI cases achieved blood culture sterilization with the use of ALT, and the CVCs could be retained in 42.3% of cases (Bookstaver, Gerrald & Moran, 2010).

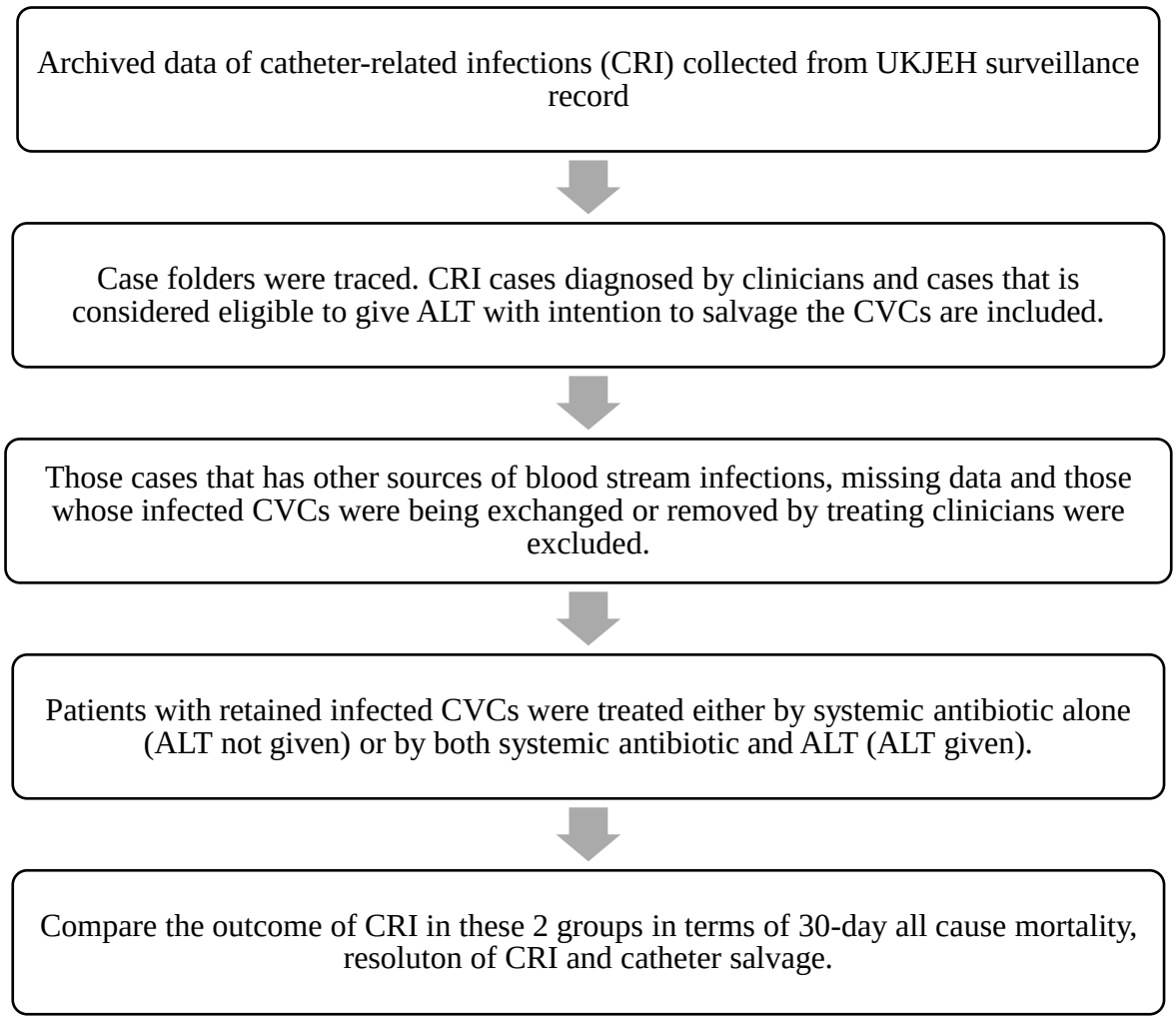
## 1.3 The rationale of the study

There has been a limited number of studies that have been done in Malaysia regarding the outcome of antibiotic lock therapy (ALT) in catheter-related infection. For example, a study by Rai et al. in 2016 only highlights the burden of catheter-related bloodstream infection (CRBSI) with mortality rates in Malaysia (Rai *et al.*, 2016). However, it did not describe the microbiological profile, antibiotic susceptibility pattern, and the outcome of ALT.

Few studies have been done on microbial colonization of CVCs. They found that the prevalence varies widely regarding the phyla and genera of the microorganism and the patient's population. Furthermore, with the increasing trend of multidrug-resistant organisms, the treatment of catheter-related infections and the choice of antibiotics have become more challenging. Thus, knowing the microbiological characteristics and their distribution on catheter surfaces will guide the clinician in improving the management of CVCs and treating catheter-related infections (He *et al.*, 2019).

Association found between the use of ALT, and the outcome of catheter-related infection will encourage clinicians to use ALT when managing catheter-related infection. In addition, the findings will further help in the prevention of CRBSI events.

## 1.4 Study flowchart



## 1.5 Research Question (s)

1. What is the proportion of catheter-related infection given ALT in HUSM?

2. What is the microbiological profile and antibiotic susceptibility pattern of catheter-related infection given ALT in HUSM?

3. What is the association between the use of ALT with the outcome of catheter-related infection?

## 1.6 Objectives

**General**: To study the use of antibiotic lock therapy (ALT) in Hospital Universiti Sains Malaysia (HUSM) as part of the management of catheter-related infection.

**Specific**:

1. To describe the proportion of catheter-related infection given ALT in HUSM.
2. To describe the microbiological profile and antibiotic susceptibility pattern of catheter-related infection given ALT in HUSM.
3. To determine the association between the use of ALT with the outcome of catheter-related infection.

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# CHAPTER 2 STUDY PROTOCOL

## 2.1 Title

Antibiotic lock therapy (ALT) for management of catheter-related infection in Hospital Universiti Sains Malaysia (HUSM).

## 2.2 Objectives

### 2.2.1 General objectives

To study the use of antibiotic lock therapy (ALT) in Hospital Universiti Sains Malaysia (HUSM) as part of the management of catheter-related infection.

### 2.2.2 Specific objectives

1. To describe the proportion of catheter-related infection given ALT in HUSM.
2. To describe the microbiological profile and antibiotic susceptibility pattern of catheter-related infection given ALT in HUSM.
3. To determine the association between the use of ALT with the outcome of catheter-related infection.

## 2.3 Methodology

### 2.3.1 Study design

This was a cross-sectional study with a retrospective record review involving patients with catheter-related infections diagnosed by treating clinicians from January 2016 to December 2019.

### 2.3.2 Study area

Hospital Universiti Sains Malaysia (Hospital USM), Kubang Kerian, Kelantan.

### 2.3.3 Study population

Reference population: All patients that have central venous catheters in HUSM.

Target population: All patients that have a catheter-related infection in HUSM from January 2016 until December 2019.

### 2.3.4 Sampling frame

Central venous catheter (CVC) surveillance records provided by Unit Kawalan Jangkitan dan Epidemiology Hospital (UKJEH) HUSM.

### 2.3.5 Subject criteria

Inclusion criteria: Those patients with CRI that are suitable to give ALT.

Exclusion criteria:

1. Missing data.
2. Patients that have other sources of bloodstream infection.
3. Patients who no longer have infected catheters after either being exchanged or removed.

### 2.3.6 Sample size estimation

For objectives 1 and 2, sample size calculation is not required since they are only descriptive studies.

For objective 3: to determine the association between the use of ALT with the outcome of catheter-related infection, the sample size estimation is as follows:

Based on a study done by Zanwar et al (Zanwar *et al.*, 2019), the probability of catheter salvage in the absence of ALT is 55%.

Meanwhile, the estimated probability of catheter salvage in the use of ALT is 80%.

Sample size, n = 54, with drop – out = 60

Thus, the estimated sample size is 60 x 2 = 120

This was calculated using the Sample size calculator software (Version 2.0) by Wan Nor Arifin – 2 proportion estimation formula – Hypothesis testing.

### 2.3.7 Sampling method and subject recruitment

Non-probability convenient sampling was used as the sampling method. All cases that meet the subject criteria were recruited in this study.

The consent form is not required for this study as it is a retrospective record review.

### 2.3.8 Operational definition

1. Catheter-related infection (CRI)

    a) Symptomatic catheter colonization: significant growth of microorganisms in the blood culture taken from the central catheter and no similar growth found in the paired peripheral sample. The patients must also have symptoms of infection such as fever and hypotension (Mermel *et al.*, 2009).

    b) Catheter-related bloodstream infection (CRBSI): microorganism growth in the central catheter grew at least 2 hours earlier than the paired peripheral sample and the patient had no other apparent source of bloodstream infection (Mermel *et al.*, 2009).

2. Antibiotic lock therapy (ALT)

ALT can be given to uncomplicated cases of CRBSIs involving long-term CVCs and catheter colonization. Uncomplicated CRBSI is defined as the resolution of bloodstream infections and fever within 72 hours in patients who have no manifestations of endocarditis or thrombophlebitis (Mermel *et al.*, 2009).

3. Outcome

Determines by 30-day all-cause mortality, catheter salvage and resolution of catheter-related infection.

a) 30-day all-cause mortality: Death within 30 days from the day of diagnosis (Freire *et al.*, 2018).

b) Resolution of catheter-related infection: Assessed by microbiological and clinical resolution of bacteraemia within 72 hours of the initiation of treatment and absence of deep-seated infections (e.g.: septic thrombosis or endocarditis) (Raad *et al.*, 2016).

c) Catheter salvage: A catheter was considered 'salvage' if there was an initial resolution, as mentioned above, followed by a repeat negative central culture for at least 14 days from the treatment (McGrath et al., 2018).

4. Overall success is defined as there is no mortality after 30 days of diagnosis, with the resolution of CRI and catheter salvage.

### 2.3.9 Research tools

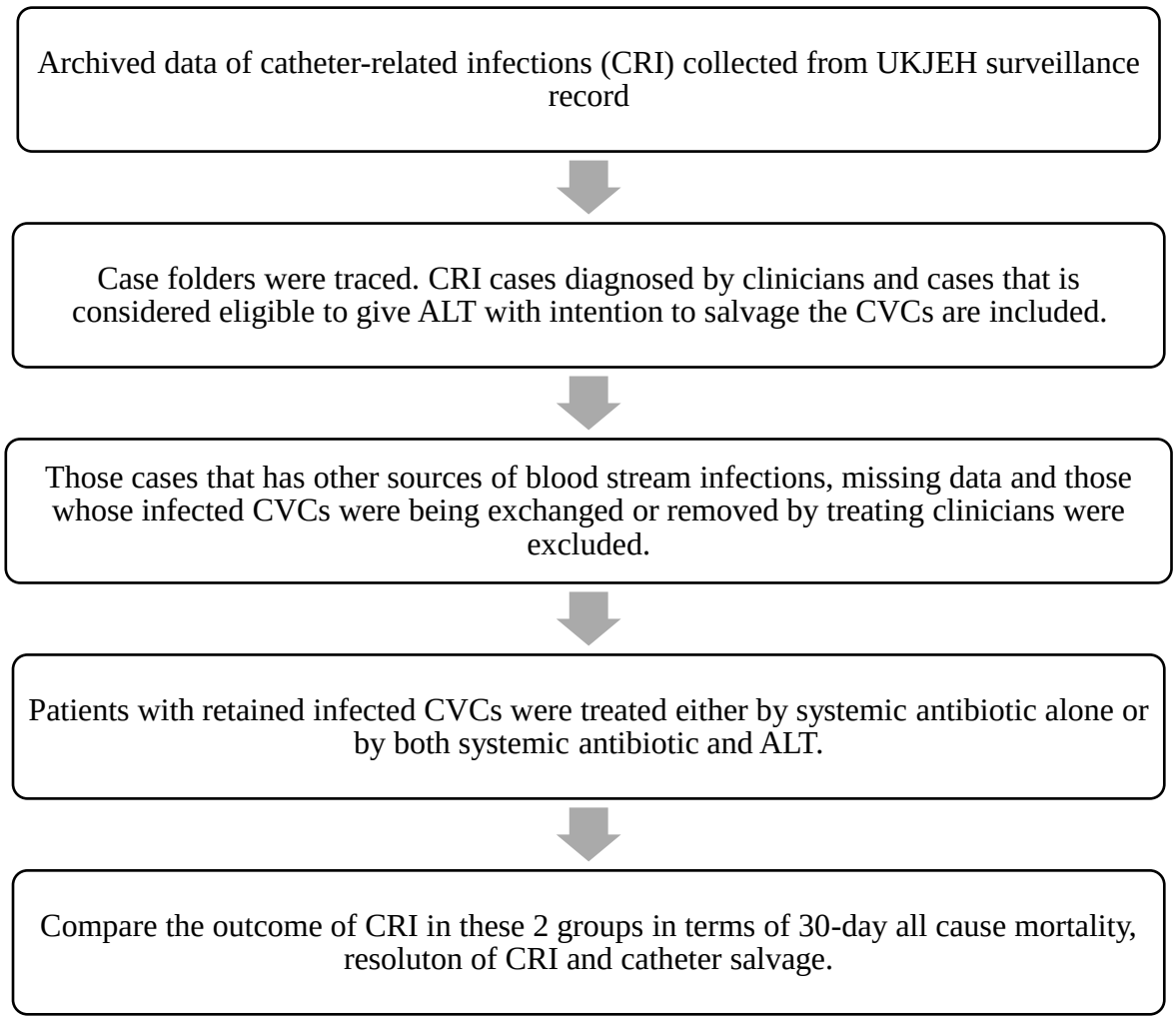
For diagnosis of catheter-related infections, the central venous catheter (CVC) surveillance records provided by Unit Kawalan Jangkitan dan Epidemiologi Hospital (UKJEH) HUSM were used to explore cases that were eligible for this study. The patient's case notes were traced and matched clinicians' diagnoses of catheter-related infections.

Laboratory information system (Lis) for laboratory data information. Data collected included blood culture and sensitivity results, total white count (TWC), absolute neutrophil count (ANC), and C-reactive protein (CRP).

Patient's record folder for demographic data, CVC details of patients, diagnosis at the time of infection (either catheter colonization or CRBSI), the use of systemic antibiotic ALT, progress and outcome measures.

## 2.4 Data collection method

Archived folders of patients with catheter-related infections (CRI) from January 2016 until December 2019 were reviewed. In addition, the records of patients who were given antibiotic lock therapy (ALT) were traced. The data and information on demographics and clinical and microbiological data were collected using a standardized checklist. All the information and data obtained were kept confidential by the investigator. The flow chart of the study was as follows.



## 2.5 Statistical analysis

In this analysis, all categorical data were presented in frequency and percentage, while the numerical data were presented in mean and standard deviation or median and interquartile range depending upon the normality of the distribution. Comparisons between the two groups were made using the Chi-Square test or Fisher's exact test, as appropriate. Wilcoxon Signed Ranks Test was used to analyse numerical data of the pre and post-test. The P level of less than 0.05 was considered statistically significant. Statistical analysis was performed using version 27 of the SPSS software (SPSS Inc, Chicago, IL).

## 2.6 Ethical approval

This study was approved by the Research Ethics Committee USM protocol code USM/JEPeM/20010035. Ethical approval was obtained for data collection from the patient's medical records. The medical information and data obtained were kept confidential by the investigator. The consent letter from the Director of Hospital USM to use patient data for research purposes was attached in the appendix.

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