CATHETER RELATED BLOOD STREAM INFECTION (CRBSI) IN ESRD SUBJECTS UNDERGOING HAEMODIALYSIS VIA TEMPORARY CENTRAL VENOUS CATHETER AT HUSM: A RETROSPECTIVE COHORT REVIEW OF 2 YEAR DATA

By

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Nor Azilawati bt Mohd Nawi

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Introduction: Since its introduction in 1964, hemodialysis has become one of the main modalities for the treatment of end-stage renal disease (ESRD). Central venous catheter (CVC) has become an important means in providing vascular access for hemodialysis treatment. Due to its nature as an indwelling catheter, there is an increased risk of developing catheter-related bloodstream infections (CRBSI). Hence, identifications of relevant risk factors for CRBSI development has become the paramount objective of this research endeavour.

Objectives: The aims of this study were to determine the prevalence of catheter-related bloodstream infections (CRBSI) among hemodialysis patient at Hospital Universiti Sains Malaysia using temporary central venous catheter and its associated factors, also to identify the commonest microorganism isolated and its antibiotic sensitivity.

Methodology: This is a retrospective cohort study involving a review of the medical records of 116 ESRD Hospital USM (HUSM) on haemodialysis via CVC from 1st January

2013 until 31st October 2014. Relevant details on the identified CRBSI risk factors such as age, gender, comorbidities, length of hospital stay prior to CVC insertion, duration of catheterization, HbA1c level, catheter insertion sites, haemoglobin level, WBC, serum albumin and urea levels, and aetiologies of End Stage Renal Disease (ESRD) were collected. The data was analysed using multiple logistic regression and the probability equation for predicting the development of CRBSI was computed. Level of significance was fixed at 0.05.

Results: : The prevalence of CRBSI is 19% (95% CI 11.9,26.1) with CRBSI rate of 3.5 bacteremia per 1000 catheter days. *S. aureus* (including MRSA) are the main microorganisms isolated among CRBSI cases (45.4%), followed by *P.aeruginosa* (22.7%) and others. Most of microbial isolates are susceptible to at least one type of antibiotics. Three significant risk factors for CRBSI were identified from multiple logistic regression analysis; duration of hospital admission before catheterization (adjusted OR:1.118 (95% CI: 1.030, 92.805), p value = 0.004), duration of catheterization in days (adjusted OR: 0.965 (95% CI 0.939, 0.992), p value = 0.005) and HbA1c levels (i) HbA1c 6.6-8.0% (adjusted OR: 1.143 (95% CI: 0.249,5.247), p value = 0.849) and ii) HbA1c ≥8.0% (adjusted OR: 5.613 (95% CI 1.023, 30.792), p value = 0.047).

Conclusion: The prevalence and CRBSI rate are comparable with other studies. Gram-positive cocci are still the predominant species isolated from HD subjects with CVC. Length of hospital stay prior to catheter insertion, duration of catheterization and $HbA1_c$ level were significant risk factors identified for CRBSI.

Dr Azreen Syazril Adnan: Supervisor

TABLE OF CONTENTS

CONTENTS **PAGE**

PAGE

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF ABBREVIATIONS

Agr	Accessory gene regulator
AUC	Area under receiver operating curve
AVF	Arteriovenous fistula
BMI	Body mass index
CAPD	Continuous ambulatory peritoneal dialysis
CI	Confidence intervals
CKD	Chronic kidney disease
CONS	Coagulase-negative staphylococci
CPN	Compounded admixture parenteral nutritions
CRBSI	Catheter-related bloodstream infections
CRF	Chronic renal failure
CTCAE	Common terminology criteria for adverse events
CVC	Central venous catheter
DM	Diabetes mellitus
ECG	Electrocardiogram
ESRD	End-stage renal disease
HABSI	Haemodialysis-associated bloodstream infections
HbA1c	Haemoglobin A1c
HD	Haemodialysis
HEMO	Hemodialysis (study's acronym)
HR	Hazard ratio
HUSM	Hospital Universiti Sains Malaysia
IHD	Ischaemic heart disease
IQR	Interquartile range
IPD	Intermitten Peritoneal Dialysis
JADDPKVP	Jangkitan aliran darah disebabkan penggunaan kateter vena pusat
LR	Likelihood ratio

MBC	Minimum bactericidal concentration
MCB	Multichamber bag
MRSA	Methicillin-resistant staphylococcus aureus
MSBP	Maximal sterile barrier precautions
MSSA	Methicillin-sensitive staphylococcus aureus
NG	Nisbah ganjil
NPV	Negative predictive value
NSTEMI	Non ST eleveation Myocardial Infarction
OGTT	Oral glucose tolerance test
OR	Odds ratio
PICC	Peripherally-inserted central catheters
PPV	Positive predictive value
PSM	Phenol soluble modulin
RBC	Red blood cells
ROC	Receiver operating curve
RRT	Renal replacement therapy
SD	Standard deviation
SE	Standard error
SK	Selang keyakinan
SSBP	Standard sterile barrier precaution
STEMI	ST elevation Myocardial Infarction
USRDS	United States Renal Data System
VIF	Variance Inflation Factor
WBC	White blood cell

LIST OF SYMBOLS

%	percentage
/	or
:	Ratio
<	less than
=	equal to
>	more than
®	trademark registered
µl	Mikrolitre
µm	Micrometre
1-β	statistical power
G	Gram
kg/m^2	Kilogramme per metre squared
M	ratio of control / cases
mg/Dl	milligram per decilitre
Min	Minute
Ml	Millilitre
Mm	Millimetre
mM	Milimolar
mmol/L	milimole per litre
N	number of subjects
ng/µL	nanogram per microlitre
ºC	degree celcius
P	short arm of chromosome
p_{stat}	p value
Pa	probability of exposure in cases
Po	probability of exposure in controls
Q	long arm of chromosome

q^{stat}	1-prevalence
T	Translocation
™	trademark unregistered
Vs	Versus
A	type 1 error
Δ	Precision
Λ	lambda
K	Kappa

ABSTRAK

JANGKITAN ALIRAN DARAH DISEBABKAN KATETER DIKALANGAN PESAKIT GINJAL TAHAP AKHIR YANG MENJALANI HEMODIALISIS MENGGUNAKAN KATETER VENA PUSAT SEMENTARA DI HUSM: KAJIAN RETROSPEKTIF KOHORT DATA TERKUMPUL SELAMA 2 TAHUN.

Pengenalan: Semenjak diperkenalkan pada tahun 1964, hemodialisis telah menjadi salah satu kaedah rawatan untuk pesakit ginjal tahap akhir. Kateter vena pusat telah menjadi salah satu cara untuk penyediaan akses salur darah bagi mencapai matlamat rawatan hemodialisis. Disebabkan ciri-ciri kateter vena pusat sebagai kateter yang menembusi kulit, terdapat peningkatan dari segi kadar jangkitan kuman disebabkan kateter jenis ini. Oleh itu, pengenalpastian faktor-faktor risiko yang relevan yang menyebabkan berlakunya jangkitan aliran darah disebabkan penggunaan kateter vena pusat (JADDKVP) adalah menjadi matlamat kajian ini.

Metodologi: Ini adalah kajian retrospektif kohort yang melibatkan rekod perubatan 116 pesakit ginjal tahap akhir yang menjalani hemodialisis di Hospital USM (HUSM) menggunakan kateter vena pusat bermula daripada 1 Januari 2013 sehingga 31 Oktober 2014. Maklumat-maklumat yang relevan berkenaan faktor-faktor risiko JADDKVP seperti usia pesakit, jantina, status penyakit lain, tempoh masa berada di hospital sebelum kateter dimasukkan, selang tempoh kateter digunakan, paras HbA1c, lokasi kateter dimasukkan, paras hemoglobin, sel darah putih, paras albumin dan urea dalam serum darah dan penyebab penyakit ginjal tahap akhir. Data kemudiannya dianalisis dengan regresi logistik berganda dan persamaan

kebarangkalian yang memberi ramalan berlakunya jangkitan aliran darah disebabkan kateter dihasilkan. Paras kepentingan ditetapkan pada 0.05.

Keputusan: Prevalens JADDKVP adalah 19.0% (95% selang keyakinan: 11.9,26.1) manakala kadar JADDKVP adalah 3.5 kes bakterimia bagi setiap 1000 kateter-hari. *S.aureus* (termasuk jenis MRSA) merupakan mikrorganisma utama yang didapati di kalangan kes JADDKVP (45.4%), diikuti *P.aeruginosa* (22.7%) dan lain- lain. Kebanyakan mikrorganisma yang diasingkan adalah sensitif sekurang-kurangnya terhadap satu jenis antibiotik. Terdapat tiga faktor risiko ketara yang menyebabkan JADDK ditemui melalui analisis regresi logistic berganda: panjang tempoh kemasukan di hospital sebelum kateter dimasukkan (nisbah kemungkinan terselaras: 1.118 (95% selang keyakinan: 1.030, 92.805) nilai p = 0.004), selang tempoh kateter digunakan (dalam unit hari) (nisbah kemungkinan terselaras: 0.965 (95% selang keyakinan: 0.939, 0.992), nilai p = 0.005) dan paras HbA1c (i) HbA1c 6.6-8.0% (nisbah kemungkinan terselaras: 1.143 (95% selang keyakinan: 0.249,5.247), nilai p = 0.849) and ii) HbA1c ≥8.0% (nisbah kemungkinan terselaras: 5.613 (95% selang keyakinan 1.023, 30.792), nilai p = 0.047).

Rumusan: Prevalens dan kadar JADDKVP adalah bersamaan seperti anggaran kajian-kajian yang lain. Bakteria kumpulan ‘cocci’ yang positif-Gram masih merupakan jenis utama bakteria yang didapati dikalangan kes-kes JADDKVP. Tempoh masa kemasukan ke hospital sebelum kateter dimasukkan, jangka masa kateter dan paras HbA1c telah dikenalpasti sebagai factor yang ketara menyebabkan JADDKVP.

ABSTRACT

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Conclusion: The prevalence and CRBSI rate are comparable with other studies. Gram-positive cocci are still the predominant species isolated from HD subjects with CVC. Length of hospital stay prior to catheter insertion, duration of catheterization and $HbA1_c$ level were significant risk factors identified for CRBSI.

CHAPTER ONE

INTRODUCTION

1.1 THE USE AND ECONOMIC BURDEN OF HAEMODIALYSIS THERAPY: A GLOBAL COMPARISON

Dialysis therapy was elementarily initiated in Malaysia in 1964, primarily for the treatment of acute renal failure (Lim *et al.*, 2008). This was subsequently followed by the institution of chronic haemodialysis in 1969, the first renal transplant in mid-1970s and continuous ambulatory peritoneal dialysis in 1981 (Lim *et al.* 2008). Since then, the epidemiological scene of the uptake of renal replacement therapy (RRT) has drastically increased; 50 patients on haemodialysis in 1980 compared to nearly 15000 haemodialysis patients in 2006 (Lim *et al.* 2008). Besides, there's also a hike in the haemodialysis acceptance rate which is about 3 per million population in 1981 to 116 per million population in 2006 (Lim *et al.* 2008). Apart from that, there is a large difference with respect to prevalence rate of haemodialysis usage between 1980 and 2006; 4 per million and 550 per million, respectively (Lim *et al.* 2008).

Based on the 21st report of the Malaysian dialysis and transplant registry 2013, the prevalence rate of dialysis is 1065 per million populations in 2013 (Malaysian Society of Nephrology 2013), which is about twice the prevalence rate in 2008. This can be translated into a doubling of dialysis acceptance rate from 112 per million population in 2004 to 223 per million population in 2012 (Malaysian Society of Nephrology 2013). Therefore, the increased need for haemodialysis may result in further requirements for permanent and temporary vascular access, leading to a much

higher occurrence of catheter-related complications such as thrombosis and infections.

Besides, the raising prevalence rate of dialysis also occurred in other populations. For instance, a study by Cusumano *et al.* (2013) also demonstrated an increase in the prevalence rate of ESRD patients requiring renal replacement therapy (RRT) in Latin America from 119 patients per million population in 1991 to 568 patients per population in 2008, with the highest reported prevalence rates in Puerto Rico (1170 patients per million population), Uruguay (1079 patients per million population) and Chile (1036 patients per million population) . Haemodialysis is the primary mode of RRT (342 patients per million population) followed by peritoneal dialysis (119 patients per million population) and finally vascular grafts (106 patients per million) (Cusumano *et al.*, 2013). Apart from that, based on the data provided by the Korean Insan Prof. Byung-Suk Min Memorial ESRD Patient Registry, the prevalence rate of dialysis among ESRD patients in Korea is 1010 patients per million population (Jin *et al.* 2015). The same trend is also observed among Chinese ESRD patients residing in Beijing; a raising prevalence rate of haemodialysis was observed which is from 94 patients per million population in 2007 to 147.3 patients per million population in 2010 (Zuo *et al.* 2013). However, the current dialysis treatment rate among Sub Saharan African countries is still below 20 patients per million population, reflecting the lack of reliable renal registries and inadequate nephrology resources (funding, poor facilities and insufficient support) (Naicker 2013). With respect to those of Caucasian origin, the last report from the Italian Registry of Dialysis and Transplant (RIDT) showed that the prevalence rate of dialysis among Italian population with ESRD is 788 patients per million population (Roggeri *et al.*, 2014). In Ukraine, the latest estimate of prevalence rate of dialysis is

96.6 per million population (Kolesynk *et al.*, 2014). Hence, from all these observations we could conclude that the prevalence rate of dialysis is increasing worldwide. The prevalence rate of haemodialysis in Malaysia can be considered to be relatively lower than other countries, attributable to better preventive measures and provision of healthcare services adopted by the Malaysian government. Nevertheless, our attention on preventive measures should not be deviated, as the number of ESRD patients requiring haemodialysis is increasing at an alarming rate in our locality. Further actions such as intensive patient education, secondary prevention programmes in retarding the kidney disease progression are required to curb and eventually reverse this worrying trend.

The cost of haemodialysis has become a constant source of financial burden to ESRD patients. With respect to Malaysian context, the estimates of the cost of haemodialysis are only provided by three studies. Based on the estimate provided by a multicentre study involving 44 haemodialysis and 11 continuous ambulatory peritoneal dialysis (CAPD) centres by Hooi *et al.* (2005), the cost of haemodialysis ranged from RM 79.61 to RM475.79 per haemodialysis session and the mean cost is RM 169 per session. This is comparatively higher considering CAPD treatment which was estimated ranging between RM 1400 to RM 3200 per patient month (mean RM 2186 per patient month) (Hooi *et al.*, 2005). Besides, the cost per life year saved is much higher with haemodialysis (RM 33642) than with CAPD (RM 31635). This reflects a sudden drop in the cost-effectiveness of haemodialysis which was found to be the highest (haemodialysis centre: RM 21620 per life year saved, home dialysis: RM 23375 per life year saved) compared to CAPD (RM 30469 per life year saved) and IPD (RM 36016 per life year saved) in 1999 (Lim *et al.*, 1999). The findings on CAPD made by Morad *et al.* (2005) would not be used as a comparison

in here and thus further discussed since dubious and less comprehensive method was employed for cost calculation (which was only based on basic cost whilst other indirect costs such as transportation, loss of productivity and costs due to complications and extra medication are not included in the analysis).

In other countries around the globe, the cost of haemodialysis is substantially high. In a report by de Abreu *et al.*, (2013), the total mean cost of maintenance haemodialysis per patient year at Sao Paolo, Brazil is at a staggering amount of US$ 28570. Besides, according to USRDS 2012 annual report, the cost of haemodialysis per patient per annum was approximately USD 66750 (USRDS 2012). These data are further corroborated by Saran and Sabry (2012) who showed that the total average cost of each haemodialysis session is approximately around USD297 (1,141 Saudi Riyal). In addition, Ranasinghe *et al.* (2011) showed that the cost of each dialysis session in Sri Lanka is LKR 6377 (equivalent to USD 56). The exorbitant cost of haemodialysis has thus been summarized in a review by Karopadi *et al.* (2013) who demonstrated that HD treatment is between the range of 1.25 and 2.35 times of peritoneal dialysis cost in most developed countries. The authors also commended the Malaysian government's efforts in reducing the cost for PD by waiving import duty for CAPD (Karopadi *et al.,* 2013). The haemodialysis treatment cost will also be escalated if catheter-related complications occur, as such exacerbates the financial impact on the ESRD patients. Therefore, it is imperative that effective preventive measures be implemented and complications can be avoided. These can be achieved if the putative risk factors for each complication are fully known.

1.2 HAEMODIALYSIS CATHETERS AND INFECTIONS

Since the past two decades, the duration of catheter use and placement rates have surged (USRDS 2012). Around 80% of patients in North America received their weekly haemodialysis via catheters, with a catheter use rate of 50% 4 months after the initiation of haemodialysis (Canadian Organ Replacement Register 2012, USRDS 2012). Delayed in AVF creation, time requirement for access maturation, frequent complication and need for new access site become a common reason for temporary catheter insertion. As a result, infection has now become the commonest cause of morbidity and second most common cause of mortality among HD recipients, with sepsis-associated mortality rate of more than 100 times than the general population (Schaubel *et al.,* 2000, Sarnak and Jaber, 2000). Besides, it was estimated that 30% of patients using central venous access for haemodialysis will experience at least a single bacteraemia or septic episode per year (Ishani *et al.,* 2005). This is further supported by the findings of Astor *et al.* (2005) and Hoen *et al.* (1998) who revealed catheter use for haemodialysis access has higher risk of bacteraemia than those via arteriovenous fistula (AVF) (estimated relative risk and hazard ratio are 7.6 and 1.5, respectively). Consequently, CRBSI result in longer ICU stay and higher cost to the healthcare sector (estimated between USD 3000 to USD 56167 per episode), making its prevention imperative to ensure and maximize the safety of HD patients (Palomar *et al.,* 2013).

In spite of the institution of well-documented effective prophylactic schemes and the ubiquitous disseminations of clinical practice guidelines for the prevention of vascular access-related infections, the rates of catheter-related infections continue to be significantly high (Lok and Foley, 2013). Pronovost and colleagues (2006) have identified five evidence-based procedures which will greatly cut the risk of CRBSI

when implemented properly; good hand washing practices, the utilization of full-barrier provision during the insertion of CVCs, the use of chlorhexidine during cleaning of the skin, avoidance of femoral sites for CVC insertion and prompt removal of unneeded catheters. This evidence-based CRBSI prevention protocol has been demonstrated to cut the median rate of CRBSI from 2.7 per 1000 days to 0 case per 1000 days (Pronovost *et al.* 2006), a finding that has been further corroborated by Peredo *et al.* (2010) who showed an absolute relative risk reduction (ARR) of 0.74 ((95% CI 0.20 , 0.84) , p value = 0.015). Hence, the identification of risks factors and contexts which posed the HD patients at high infection risks is paramount so that further improvements can be made to the existing protocols for the prevention of CRBSI.

1.3 TYPES OF HAEMODIALYSIS CATHETERS

In general, there are two major types of catheters used for haemodialysis; non-tunnelled or temporary and tunnelled or permanent catheters. The non-tunnelled catheters are meant for short term use and are made of rigid materials like hard polyurethane or polyvinyl with tapered end to permit quick percutaneous insertion via Saldinger technique. Nevertheless, the newer generation of this catheter type (like the ones made of silicone) are usually made of softer materials with adjustable cannula that can be utilized to steady the catheter for insertion. Besides, they can also provide a higher rate of blood flow (400 ml/ min or greater vs 200 to 250 ml / min) compared to the previous model. These non-tunnelled catheters are devoid of retention cuffs and therefore should not be inserted into a subcutaneous tunnel. They are in different shapes (curved or straight) which enable them to be easily inserted at required insertion sites (femoral, internal jugular etc). The usual post-insertion lifetime for this type of catheters is usually between several days to several weeks.

On the other hand, tunnelled catheters have Dacron cuffs that can be adjusted and positioned into subcutaneous tunnels. The cuff functions as a fibrotic shield, preventing the migration of bacteria from the surrounding skin tissues into the bloodstream. Tunnelled catheters are usually made of soft polyurethane and usually introduced into the skin via a peelable sheath or trocar. The first original brand of this catheter, PermCath®, was marketed by Quinton Instrument Company which was based at Salt Lake City, Utah, USA. A new design subsequently superseded the large oval, two-lumen PermCath®; Vas Cath™ and Tesio™. These new designs were then proven to be more effective than PermCath® in preventing the complications related to the use of transcutaneous devices. Figure 1.1 and 1.2 represent the schematics of a cuffed tunnelled catheters:

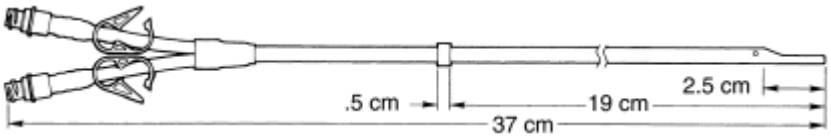

Figure 1.1: The schematic representation of a cuffed tunnelled catheter

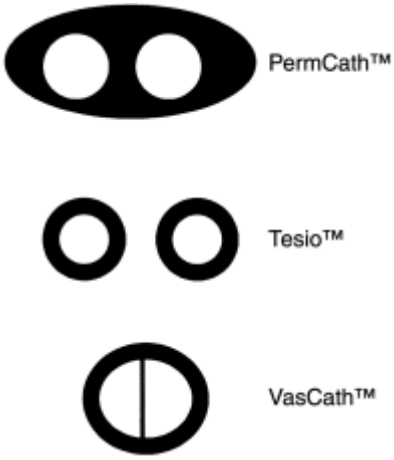

Figure 1.2: The transverse view of three commonly used cuffed tunnelled catheters (Schwab and Beathard 1999, with permission)

CHAPTER TWO

LITERATURE REVIEW

2.1 THE PATHOGENESIS AND DIAGNOSIS OF CRBSI

According to Trautner and Darouiche (2004), there are four primary routes by which catheters maybe contaminated by the infectious agents:

- Colonization by migrating skin microorganisms from sites of insertion into catheter tracts or along catheter surfaces which results in catheter tip colonization.
- Direct contaminants: fluids and unhygienic hand procedures/contacts which result in catheter or catheter hub contaminations
- Haematogenous dissemination of infections from other foci which is subsequently sown at the catheter site (uncommon)
- Contamination of infusate such as heparin flush (rare).

Among the four routes above, the first two are undoubtedly the most important. Hub contamination and skin sites colonization can be attributed to endogenous flora on the patient's skin or exogenous flora that are transferred from the healthcare's workers hands to the patient's skin or catheter hub during catheter insertion. Nevertheless, there are two main differences in terms of microbial migratory patterns depending upon where the initial contaminants occur; those which gain entry through the skin insertion sites will usually migrate upon the surface of the catheter whilst those microorganisms which contaminated the catheter hub will tend to migrate on the luminal surface of the catheters (Crnich and Maki 2002, Raad and Hanna 2002). The types of endogenous flora that are usually found to reach the

catheter site from the skin sites are coagulase-negative staphylococci and *S. aureus* whilst those which generally contaminated the catheter hubs are Stenotrophomonas sp, Pseudomonas sp, enterococci and Candida sp.

On the contrary, haematogenous spread of flora from remote sites such as the urinary tract is more of mechanistic conjectures than a possible certainty. Thus, the removal of catheters may not be necessary after well-recorded infections from secondary sites (Raad and Bodey 1992, Anaissie *et al.* 1995). Even though sepsis associated with contaminated infusates such as parenteral nutrition and lipid solutions has been well-documented, these occurrences can be considered rare with different pathological mechanisms that are beyond the scopes of this review. However, a recent study by Turpin *et al.* (2014) showed that the administration of parenteral nutrition via ready-to-use-three-chamber bag (MCB) was associated with the lowest hazard of CRBSI compared to administration via single bottle (SB) (hazard ratio: 2.53 (95% CI 1.66,3.86), p value <0.05) and hospital compounded admixture (CPN). Besides, they also found out that the use of MCB incurred the lowest hospitalization cost and thus the most cost-effective method in preventing CRBSI (Turpin *et al.* 2014).

The duration of time from the first insertion of central venous catheters to the first appearance of bacteria-embedded biofilms can be variable. Passerini and co-workers (1992) demonstrated using electron microscopy that biofilm formation can occur as early as 24 hours post insertion of central venous catheters. Nevertheless, the colonization of catheter's external surfaces is predominant in short-term indwelling catheters that are placed for less than 10 days whilst the colonization of intraluminal surfaces of the catheters is only prevalent after the introduction of long-term indwelling catheters such as subcutaneous ports, peripherally-inserted central

catheters (PICC) and tunnelled CVC and this may occur only after 30 days following the insertion of such catheters (Raad *et al.* 1993). However, the probability of such catheter colonization will culminate in overt bloodstream infections is quantitatively dependent upon the number of microorganisms isolated from the catheter surfaces by roll-plated methods and the dissimilarities with respect to the pathogenesis of CRBSI between the usage of short-term and long-term catheters may result in the differences of optimal preventive options for both types of CRBSI.

There are several well-reported metastatic complications of CRBSI. In a review by Lok and Mokrzycki (2011), the followings are the most frequently encountered metastatic complications of CRBSI:

Table 2.1 : Metastatic complications of CRBSI (Lok and Mokrzycki 2011)

CRBSI metastatic complications	**Prevalence (%)**
Endocarditis	3-7
Death	6-34
Osteomyelitis	1.5-15
Septic arthritis	2-5
Septic emboli (eg brain)	1-2
Other abscesses	1.5
Septic pulmonary emboli	0.4
Large atrial thrombi	rare (<0.1)

The diagnosis of CRBSI is currently based upon satisfying one of the following 3 criteria (Mermel *et al.* 2009):

i) Identical microorganisms isolated from blood culture and semi-quantitative (roll-plate) culture (>15 colony-forming units (cfu)) or quantitative (sonication) broth culture (>10^2 cfu) of the tips of catheters

ii) Similar microorganisms isolated from blood culture obtained through venoepuncture and catheter lumen, provided microbial growth were detected sooner (2 hours or more incubation time) in the latter sample. [differential time to positivity method]

iii) Same microorganism isolates detected from both percutaneous blood samples and blood obtained from catheter hub, with 3-fold higher colony-forming units in the latter. [quantitative blood culture method]

Nevertheless, there have been a few criticisms have been hurled upon the use of differential time to positivity (DTP) as a mean of diagnosing CRBSI. Kaasch *et al.* (2013) observed that DTP does not reliably predict CRBSI secondary to *S.aureus* in routine clinical setting (positive predictive value (PPV) of 0.46 (95% CI: 0.28,0.65) and negative predictive value (NPV) of 0.70 (95% CI: 0.58,0.80)). This finding contradicts the observations made by Blot *et al.* (1999) who demonstrated that DTP is an easy and reliable diagnostic method for CRBSI confirmation among cancer patients with CVC. Hence, both methods / criteria are now regarded as acceptable standards for diagnosing CRBSI (Mermel *et al.*, 2009).

2.2 THE PRINCIPAL MICROORGANISMS IMPLICATED FOR CRBSI

According to Saad (1999) and Lok *et al.* (2003), the microorganisms that are most commonly isolated from catheter sites are Gram-positive bacteria, with

methilline-sensitive *S.aureus* is the commonest (21 to 43%) followed by methicillin-resistant *S.aureus* (MRSA). With respect to Gram-negative species, Pseudomonas and Stenotrophomonas species are the main microorganism isolates for the majority of CRBSI cases (Mokrzycki *et al.* 2006). Nevertheless, the primary types of microorganism isolated may vary from one study to another. For instance, Patil *et al.* (2011) reported that the primary isolates identified from catheter tips and blood cultures are *S.epidermidis* (45%), followed by *S.haemolyticus* and *S.aureus* (15% each). Apart from that, there are also differences in the types of microorganism isolates between those developing early-CRBSI (defined as development of CRBSI in less than 24 hours after the removal of colonized catheters) and late-CRBSI (CRBSI develops 24 hours after the removal of colonized catheters). A study by Guembe *et al.* (2014) demonstrated significantly higher number of coagulase-negative staphylococci (CONS) in early-CRBSI than late-CRBSI cases, whilst MRSA isolates were significantly found in greater numbers in late-CRBSI than early-CRBSI. Therefore, this lends evidential supports to the variability of the types of microorganisms primarily implicated for CRBSI.

2.3 THE THERAPEUTIC MANAGEMENT OF CRBSI

According to the guideline produced by the Infectious Disease Society of America (IDSA) for the diagnosis and management of intravascular catheter-related infections in 2009, penicillinase-resistant penicillin such as nafcillin or oxacillin should be given to methacillin susceptible staphylococci (Mermel *et al.* 2009). Cefazolin 2g given every 8 hours or vancomycin 15mg/kg twice daily (12 hourly) can be reserved as an alternative agent to penicillinase-resistant penicillin (Mermel *et al.*, 2009). For MRSA, vancomycin (using the same dose as above), daptomycin (6-8mg/kg/day) or linezolid are the recommended treatments for CRBSI (Mermel *et al.*,

2009). For Gram negative bacilli, on the other hand, the choice of antibiotics should be guided by the local antimicrobial susceptibility data and CRBSI severity (Mermel *et al.,* 2009). Based on the recent report on local susceptibility data by Abdul Gafoor *et al.* (2014), intravenous vancomycin and ceftazidime (Fortum®) or cefepime are the antibiotics of choice since they provide the greatest coverage for all types of bacteria (Gram-positive and negative alike, both MRSA and methicillin-sensitive *S.aureus* (MSSA)) implicated for CRBSI. Besides, the catheter should always be removed if CRBSI is found to be due to *S.aureus*, Pseudomonas sp. or Candida sp. and this should be replaced with a new temporary catheter (Mermel *et al.,* 2009). If catheter removal is not indicated due to the absence of metastatic infection or resolution of symptoms 2-3 days after the start of antibiotics, the catheter can be left in place with a concurrent adjunctive use of antibiotic lock administered after the end of each dialysis sessions (Mermel *et al.,* 2009).

Nevertheless, in a much more recent systematic review and management of haemodialysis catheter-related infection, Aslam *et al.* (2014) recommended that treatments with either guidewire exchange or antibiotic lock solution provide a more superior treatment success rate compared to systemic antibiotic alone (Antibotic lock solution: OR:2.08 (95% CI, 1.25 to 3.45), p value <0.010; guidewire exchange: OR:2.88 (95% CI: 1.82 , 4.55), p value <0.001). Besides, the authors also found that the proportions of cured cases were highest in those infected with CONS, followed by gram-negative rods and *S.aureus* (Aslam *et al.,* 2014). Furthermore, guidewire exchange was found to be the most effective modality in resolving *S.aureus*-associated CRBSI when comparisons were made against systemic antibiotic use OR:3.33 (95% CI: 1.17, 9.46) p value = 0.020) or antibiotic lock solution (OR:4.72 (95% CI: 1.79, 12.46)p value = 0.002). Hence, guidewire exchange has now become

the preferential modality over systemic antibiotic use or antibiotic lock solution alone for the therapeutic management of CRBSI.

2.4 A REVIEW OF RISK FACTORS FOR CATHETER-RELATED BLOODSTREAM INFECTIONS

The risk factors for CRBSI can be classified into four major groups; host related factors, catheter-related factors, pathogen-related factors and haemodialysis-related factors. For the first one, older age has been associated with raising risk of CRBSI (mean age in bacteraemia vs non bacteraemia subjects: 64.6 years vs 59.8 years , p value <0.05) (Jean *et al.* 2002).

Besides that, impairment of immunity due to neutrophil and monocyte dysfunctions, derangement in T-cell and humoral response activation secondary to uraemia, hyperparathyroidism and excessive iron load may also be incriminated for CRBSI occurrence (Jaber 2005). Moreover, the coexisting diabetes mellitus (39% (CRBSI) vs 18% (non-CRBSI) , p value<0.001), low haemoglobin (mean serum Hb in BSI vs non BSI patients: 10.51g/dL vs 11.14 g/dL, p value <0.001) and hypoalbuminaemia (34.3 g/dL (CRBSI) vs 36.9 g/dL (non-CRBSI), p value < 0.001) may also induce CRBSI development in subjects who received haemodialysis via CVC (Fysaraki *et al.* 2013, Tanriover *et al*. 2000). Apart from those factors above, previous hospitalization and history of previous bacteraemia also pose subjects who opt for CVC as a mean of haemodialysis access (Tokars *et al.*, 2001). Nevertheless, all risk factors above required further investigation in our local setting since the effect sizes (relative risk, odds ratio) obtained from the above studies are still inconclusive which may negate the existence of clinical significance (for instance, the difference in haemoglobin concentration between CRBSI and non

CRBSI subjects are small (mean difference: 0.6 g /dL) in Fysaraki *et al.* (2013) study).

For catheter-associated risk factors, duration of catheter use has been singled out as one of the most important catheter-associated risk factors. Lemaire and colleagues (2009) demonstrated that the use of permanent dual catheter for haemodialysis exceeding 90 days increased the odds of CRBSI by 1.85 (95% CI 1.35, 2.55; p value <0.05). Their findings were further corroborated by those of Jean and associates (2002) who showed longer duration of dialysis catheter use in CRBSI subjects than non CRBSI subjects (mean days of catheter use: 648 days 296 days, p value t-test <0.001). Apart from that, sites of catheter insertion have been found to be a significant risk factor for CRBSI. For instance, Kairaitis and Gottlieb (1999) found that CRBSI occurs more common if internal jugular vein was chosen as the insertion site than subclavian vein (. This is supported by Develter *et al. (*2005) who showed 79.8% increase in risk of developing catheter-related bacteraemia if the catheter was placed in right internal jugular vein than other sites of insertion. However their findings were not statistically significant (95% CI 0.983,3.625; p value =0.068). Nevertheless, the generalizability of the findings from both studies are hampered by 2 factors; 1) the studies only utilized subjects using tunnelled catheters, 2) the use of subclavian vein predisposes subjects to a greater risk of catheter-related central venous stenosis. As a result, the routine use of subclavian vein as a haemodialysis access site is thus contraindicated and further investigations are required to ascertain the benefits associated with it.

Besides, prompt withdrawal of catheter after a positive test result for isolates on catheter tips is associated with low risk (around 4.1%) of developing late CRBSI (Guembe *et al.* 2014). Interestingly, despite the low risk of developing late-CRBSI,

it is still associated with high rate of crude mortality (Guembe *et al.* 2014). Hence, it is imperative that catheter should cared for and taken out even before colonization occurs. Besides, the techniques used for the insertion of catheter and types of sterile barrier precautions used may also influence the rate of CRBSI. For instance, Haga *et al.* (2013) found that the use of direct puncture for catheter insertion and maximal sterile barrier precaution (MSBP) resulted in significant reductions of CRBSI rate per 1000 catheter days when compared to Seldinger method for catheter insertion and standard sterile barrier precaution (SSBP) methods, respectively (p values = 0.025 and 0.030, respectively). Apart from that, the use of antimicrobial or antiseptic coating of catheters (eg. antibiotic lock therapy) may also decrease the risk of CRBSI (Shah *et al.* 2013). Nevertheless, the success rate in preventing CRBSI is variable which may be due to the inefficacy of antibiotic locking solution to kill microbes in a biofilm. This is further corroborated by Kropec *et al.* (1993) and Ramirez de Arellano *et al.* (1994), both demonstrated that a 100 to 1000-fold higher antibiotic concentrations were required to eradicate bacteria in biofilms (sessile bacteria) than free-floating bacteria (planktonic bacteria).

With regard to pathogen-related risk factors, *S.aureus* nasal carriage has been studied the most. Again, it was Jean and associates (2002) who first successfully demonstrated the relationship between the presence of *S.aureus* nasal colonization and CRBSI. They observed a shorter median time for catheter survival before the occurrence of first bacteraemia episode in those with positive *S.aureus* nasal carriage than those without *S. aureus* nasal colonization (median time to first catheter-associated bacteraemia: 128. days vs 209.5 days, p value<0.001). Besides that, a short treatment with mupirocin ointment (<5 days) has been shown to successfully eradicate *S.aureus* nasal carriage which results in a reduction of CRBSI caused by

S.aureus (Betjes 2011). Therefore, these evidences consolidate the roles of *S.aureus* nasal carriage in CRBSI. Besides that, antibiotic resistance pattern, bacterial virulence, and bacterial propensity for biofilm formation also played great roles in the occurrence of CRBSI. These factors would not be reviewed since they will not be evaluated in this study.

Lastly, with respect to haemodialysis-related factors, haemodialysis adequacy parameters were firstly identified as significant risk factors for CRBSI by Bloembergen *et al.* (1996). They showed that a 5% increase in urea reduction ratio (URR) and 0.1 increase in kt/V are significantly associated with 12.4% and 9% reductions in the risk of developing CRBSI. However, their findings were negated by the observations made by the investigators of HEMO study who established the lack of association of between CRBSI and haemodialysis adequacy parameters. They also did not find any significant association between CRBSI and types of dialysis membrane flux (high or low flux) (Allon *et al.*, 2003). These conflicting pieces of evidence requires further investigation to place the roles of both haemodialysis adequacy parameters and types of dialysis membrane flux as risk factors for CRBSI on a firmer footing.

2.5 RATIONALE OF THE STUDY

Despite many prior studies have investigated and identified nearly all major CRBSI determinants, the measures of risk (relative risk, odds ratio) provided are inconsistent from one study to another. Besides, the risk factors for CRBSI are still not clearly characterized in Malaysian setting, especially in subjects requiring haemodialysis via temporary CVC . Therefore, this research endeavour aims to shed some light on this scientific equipoise. Moreover, two additional benefits will be obtained from this research

- The identification of CRBSI risk factors will assist in the prolongation of catheter survival and reduce other risks of early catheter failure. This will result in early interventions that will aid to prevent CRBSI at the earliest possible time.
- The information on the types of isolated microorganisms that are responsible for CRBSI and their sensitivities to antibiotics will guide and steer the patient management towards a more rapid clinical intervention.

2.6 CONCEPTUAL FRAMEWORK

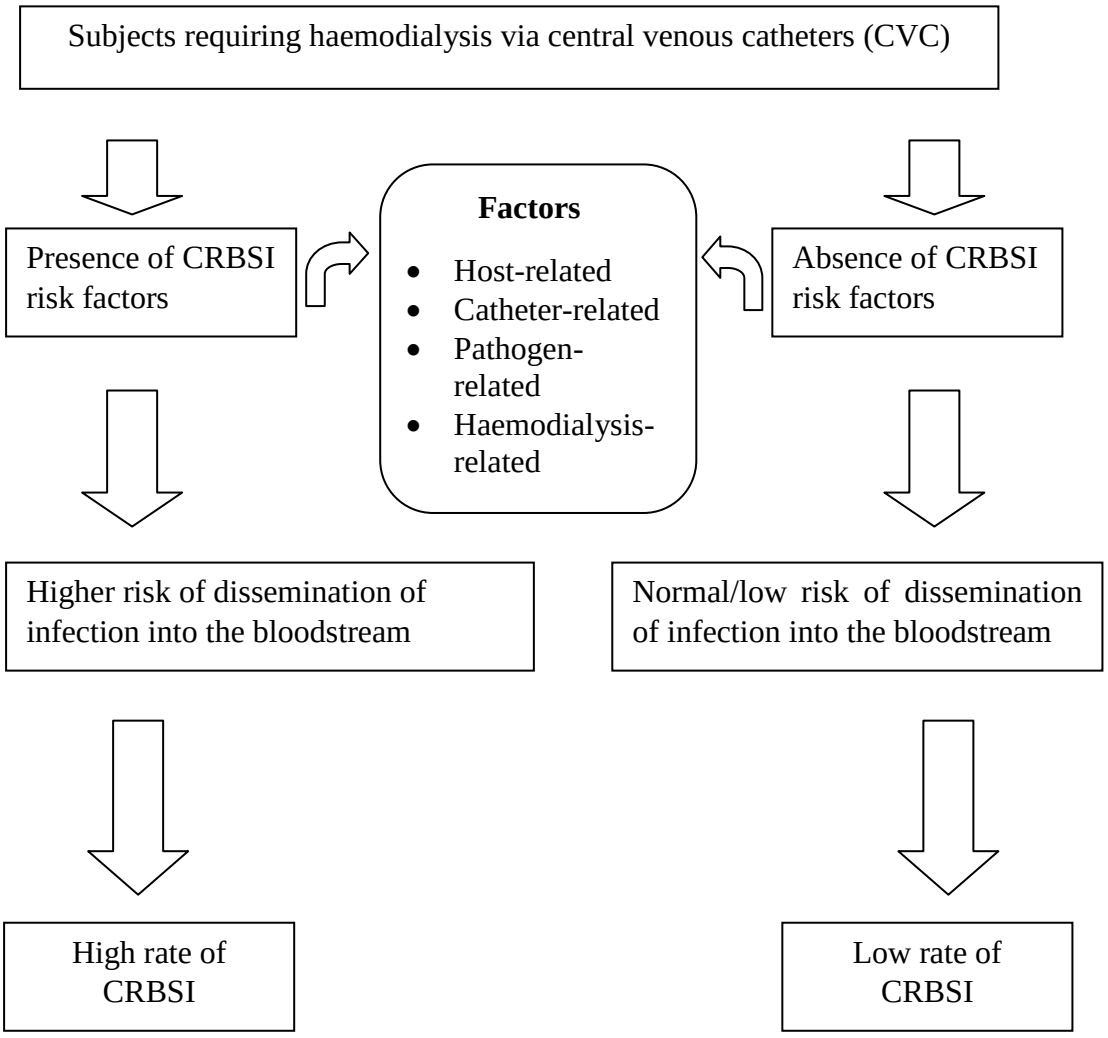

Figure 2.1: Relationship between the risk factors and rates of CRBSI

CHAPTER THREE

OBJECTIVES

3.1 GENERAL OBJECTIVE

To determine the prevalence of catheter-related bloodstream infections (CRBSI) and its associated factors.

3.2 SPECIFIC OBJECTIVES

1) To estimate the prevalence of CRBSI in patients undergoing haemodialysis via temporary central venous catheter.

2) To identify the main microorganism isolates involved in CRBSI and their patterns of antibiotics sensitivities.

3) To determine the risk factors of CRBSI in patients with central venous catheter for haemodialysis.

3.3 RESEARCH QUESTIONS

1) What is the prevalence of CRBSI in patients who underwent haemodialysis via temporary central venous catheter at HUSM?

2) What are the principal microorganisms isolated in patients with CRBSI and the patterns of antibiotics sensitivities at HUSM?

3) What are the risk factors that are significantly associated with CRBSI in patients with central venous catheter for haemodialysis in HUSM?

3.4 RESEARCH HYPOTHESES

1,2) No research hypotheses are required for the first two objectives since they are readily answered by simple descriptive analyses. Therefore, no two competing hypotheses (null and alternative) are needed

3) **Null hypothesis:**. There is no specific factors associated with an increase risk of CRBSI among haemodialysis patient on temporary central venous catheter

Alternative hypothesis: There are certain factors which are associated with an increased risk of CRBSI among haemodialysis patient on temporary central venous catheter.

CHAPTER FOUR

METHODOLOGY

4.1 STUDY DESIGN

This is a retrospective cohort study involving a review of medical records of Hospital USM CKD patients undergoing haemodialysis via central venous catheter acquired from HUSM registry.

4.2 PERIOD OF DATA RECRUITMENT AND STUDY DURATION

Data was collected on CKD patients with temporary central venous catheter for haemodialysis who were treated and recorded in the HUSM registry between 1st January 2013 and 31st October 2014. Therefore, the total duration of retrospective observation window is 22 months.

The duration of research (proposal presentation, application for ethical approval, data collection, and thesis write-up) was from April 2014 until November 2014 (8 months).

4.3 STUDY AREA

This study was conducted at Haemodialysis Unit of HUSM which is the tertiary centre of referral for CKD patients from the east coast states of Malaysia (Kelantan and Terengganu). On the average, CKD unit provides treatment for 200 to 300 patients per annum.

4.4 REFERENCE POPULATION

All ESRD patients undergoing haemodialysis through central venous catheter in Kelantan and who are at risk of CRBSI.

4.5 SOURCE POPULATION

All ESRD patients who required haemodialysis via central venous catheter at HUSM and were also at risk of CRBSI.

4.6 SAMPLING FRAME

ESRD patients with criteria as above and who also fulfilled inclusion and exclusion criteria.

4.7 STUDY SUBJECTS

ESRD patients who met the criteria as above and also consented to study participation.

4.8 INCLUSION AND EXCLUSION CRITERIA

4.8.1 Inclusion criteria

i) Age at least or more than 18 years old at the time of catheter insertion

ii) End stage renal failure patient that require haemodialysis via temporary central venous catheter.

iii) No evidence of bacteraemia or sepsis at the time of catheter insertion

4.8.2 Exclusion criteria

i) Patients who were on antibiotics after the insertion of catheter and prior to the diagnosis of CRBSI. This is ascertained through documentation details in the medical records.

ii) Pregnancy

iii) Patients who require for new catheter reinsertion through a new or the same exit sites

iv) Central catheter use for purposes other than haemodialysis

4.9 SAMPLING METHOD

Convenient sampling, a subset of non-probability sampling, was used due to the inadequate number of patients upon initial survey of the HUSM medical registry for ESRD patients undergoing haemodialysis at CKD unit.

4.10 SAMPLE SIZE DETERMINATION

Sample size was calculated using Power and Sample Size (PS) software version 3.0.43 (Dupont and Plummer, Vanderbilt, USA; 2011). For objective 1 and 2, single proportion formula was used for calculating sample size. The formula is as follows:

$n= (1.96/ \Delta)^2 p(1-p)$. Precision ($\Delta$) was chosen at 10% (0.10) to ensure the sample size calculated would be practical and achievable since higher precision (for instance, Δ=5%) would result in a very large sample size that is deemed impossible to achieve in this single-centre study. Therefore, the most optimal precision was selected to ensure the achievement the most optimal precision for objective 1 and 2.

i) <u>Objective 1: Prevalence of CRBSI</u>

For objective no 1, two approximate prevalence estimates of CRBSI in ESRD patients using temporary CVC for haemodialysis are provided by two different studies; a) Kim *et al.* (2006) – 11.7%, and b) Bleyer *et al.* (2005) – 8.4%. Since the relationship between prevalence and incidence rate is described by the following formula (Fletcher *et al.* 2012):

Prevalence rate ≈ [Incidence rate] x [Duration of the disease in a steady state],

Therefore, the incidence rate as reported by Kim *et al.* (2006) and Bleyer *et al.* (2005) can be regarded as an approximate prevalence rate of CRBSI in ESRD patients who have non-tunneled CVC for haemodialysis since the duration of the

disease is very short (CRBSI is a non-chronic disease). The estimate provided by Kim *et al.* (2006) was finally chosen as the more reliable one due to the larger sample size used for its estimation.

$n= (1.96/ \Delta)^2 p(1-p)$

Prevalence of CRBSI: 11.7% (Kim *et al.* 2006)

Precision (Δ) = 0.05

$n = (1.96 /0.05)^2 (0.117) (1-0.117)$

n = 40 subjects

Drop out rate = 20%

n_{total} = 40 subjects + 20% = 44 subjects

ii) <u>Objective 2: Prevalence of main microorganism implicated for CRBSI</u>

S. aureus (both methicillin sensitive and resistant) is considered as the main microbial isolate in CRBSI cases. Four prevalence estimates were extracted from the previous literature for ESRD patients using temporary central venous catheter:

a) Nabi *et al.* (2009): n= 7/11 (63.7%).

b) Altaee *et al.* (2007): n =11/19 (57.8%)

c) Kaze *et al.* (2014): n = 12/17 (70.6%)

d) Nielsen *et al.* (1998): n= 14/25 (56%). This is the best estimate since it was based on the largest sample size.

Nevertheless, since the estimates provided by a, b and c are quite close to each other, the prevalence estimate of *S.aureus* as the main microbial isolate found in CRBSI was hence decided to be approximately 60%.

$n= (1.96/ \Delta)^2 p(1-p)$