COMPARISON OF CATHETER RELATED BLOODSTREAM INFECTION RATE BEFORE AND AFTER THE IMPLEMENTATION OF CENTRAL VENOUS CATHETER CARE BUNDLE IN HOSPITAL USM

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LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMNS

CDC	Centre for Disease Control and Prevention
CFU	Colony-forming units
CLABSI	Central line associated bloodstream infection
CLSI	Clinical and Laboratory Standard Institute
CRBSI	Catheter related bloodstream infection
CVC	Central vascular catheter
ESBL	Extended-spectrum beta-lactamase
GNB	Gram-negative bacteria
GPB	Gram-positive bacteria
HCAI	Healthcare-associated infections
HUSM	Hospital Universiti Sains Malaysia
HCW	Healthcare-worker
ICN	Infection control nurse
ICU	Intensive care unit
MOH	Ministry of Health
PVC	Peripheral vascular catheter
UKJEH	Unit Kawalan Jangkitan dan Epidemiologi Hospital
WHO	World Health Organisation

PERBANDINGAN KADAR JANGKITAN MELALUI ALIRAN DARAH YANG BERKAITAN DENGAN KATETER SEBELUM DAN SELEPAS PELAKSANAAN BUNDEL KATETER LALUAN PUSAT VENA DI HOSPITAL USM.

ABSTRAK

Pengenalan: Jangkitan melalui aliran darah yang berkaitan dengan kateter boleh menyebabkan sepsis dan membawa maut. Ia juga menyebabkan penigkatan kos rawatan. Langkah pencegahan seperti pelaksanaan bundel kateter laluan pusat vena telah terbukti dapat mengurangkan kadar jangkitan. Matlamat kajian ini adalah untuk mengetahui kesan pelaksanaan bundel ini ke atas kadar kelaziman insiden jangkitan melalui aliran darah yang berkaitan dengan kateter dan ejen mikroorganisma penyebab jangkitan di Hospital USM.

Kaedah: Ini adalah kajian kohort ke atas pesakit yang mempunyai kateter laluan pusat di Hospital USM daripada April 2016 sehingga Disember 2017. Pesakit yang berumur 18 tahun keatas yang memenuhi kriteria definisi jangkitan melalui aliran darah yang berkaitan dengan kateter adalah termasuk dalam kajian ini, manakala pesakit yang telah mempunyai kateter saluran darah adalah terkecuali. Data dari April 2016 hingga Disember 2016 adalah dijadikan sebagai data pra-intervensi. Manakala intervensi dilakukan dari Januari 2017 hingga Mac 2017 dan diikuti dengan pemerhatian selepas intrevensi dari April hingga Disember 2017. Pelaksanaan bundel ini adalah berdasarkan garis panduan Pusat Kawalan dan Pencegahan Penyakit(CDC) tahun 2009. Maklumat pesakit diperolehi daripada rekod pesakit dan juga system informasi makmal. Keputusan kajian dianalisa secara diskriptif dan menggunakan analisa statistic SPSS versi 24 dan 2-point Poison Rate.

Keputusan: Sejumlah 126 kes CRBSI telah direkodkan yang melibatkan 57% (n=72) and 43% (n=54) pesakit semasa sebelum dan selepas intervensi. Kadar insidens lazim ialah 0.88 per 100 *admission-days* sebelum intervensi, berbanding 0.39 per 100 *admission-days* selepas intervensi. Keputusan ini adalah signifikan secara statistik ($p<0.001$). Kadar incidence CRBSI berdasarkan kiraan berdasarkan 1000 *catheter-days* ialah 18.1 (95% confidence interval: 13.3-22.0) per 1000 catheter-days. Mikroorganism Gram-positif adalah lebih dijumpai semasa pre-intervensi berbanding dengan Gram-negatif selepas intervensi. Mikroorganisma yang paling kerap diisolat ialah *Staphylococcus aureus* (50%, n=11), *Enterococcus fecalis* (18.2%, n=11), and *Pseudomonas aeruginosa* (15.4%, n=4). Kadar kepatuhan kepada bundel ialah dalam lingkungan 85-100%.

Kesimpulan: Kadar insidens CRBSI menurun selepas pelaksanaan bundel kateter laluan pusat vena. Kadar keberkesanan pelaksanaan kepatuhan kepada bundel ini juga sangat baik. Mikroorganisma Gram-negatif adalah lebih banyak ditemui selepas pelaksanaan bundel ini.

COMPARISON OF CATHETER RELATED BLOODSTREAM INFECTION RATE BEFORE AND AFTER THE IMPLEMENTATION OF CENTRAL VENOUS CATHETER CARE BUNDLE IN HOSPITAL USM.

ABSTRACT

Introduction: Catheter related bloodstream infection (CRBSI) increases risk of bloodstream infections and sepsis-related death which leads to longer hospitalisation and created significant medical and economic burden. The implementation of the CVC Care Bundle has shown to decrease the incidence of CRBSIs worldwide. This study aimed to analyse the incidence rate of CRBSI following implementation of CVC Care Bundle in Hospital USM.

Methodology: This was a cohort study conducted in all patients admitted to Hospital USM within April 2016 till December 2017 who had CVC inserted on them. Patient who aged more than 18 years old and newly admitted patient for various indication of catheterisation were included in the study, whereas patients who already had other central venous devices were excluded in the study. Data of CRBSI cases from April 2016 to December 2016 was taken as pre-intervention data. Intervention was done for three months from January 2017 to March 2017 followed by post-intervention from April 2017 to December 2017. Implementation that was done include strict practices of CVC Care Bundle based on CDC guidelines in year 2009. Patient's information was obtained from medical record and laboratory information system. The results were presented as descriptive and statistically analysed using SPSS version. Comparison of incidence rate of CRBSI was done using 2-Sample Poisson Rate as a $p<0.05$ was considered statistically significant.

Result: A total of 126 cases of CRBSI were documented which consist of 57% (*n*=72) and 43% (*n*=54) patients pre and post-intervention respectively. The incidence rate of CRBSI was 0.88 per 100 admission days, compared to 0.39 per 100 admission days during post-intervention. The result was statistically significant ($p <0.001$). The incidence of CRBSI based on 1000 catheter days was of 18.1 (95% confidence interval: 13.3-22.0) per 1000 catheter-days. Gram-positive organism was the most common causative organism during pre-intervention whereas Gram-negative organism dominating during post-intervention. The most common organisms isolated were *Staphylococcus aureus* (50%, n=11), *Enterococcus fecalis* (18.2%, n=11), and *Pseudomonas aeruginosa* (15.4%, n=4). The compliance rates to CVC care bundle were in the range 85-100%.

Conclusion: Incidence rate of CRBSI reduced following the implementation of CVC Care Bundle. Compliance rates towards CVC care bundle were excellent. Gram-negative organism was the most common causative organism following intervention.

CHAPTER 1

INTRODUCTION

1.1 Background

Central venous catheters (CVCs) are commonly inserted in critically ill patients for various indications such as administration of fluids, medications, blood products nutrition (TPN) and monitoring hemodynamic status. European Prevalence of Infection in Intensive Care (EPIC) study in 1995 has reported about 78% of critically ill patients had intravenous catheter (Vincent *et al.*, 1995). The presence of this CVC may cause complications such as arterial puncture, bleeding, occlusive thrombosis, bloodstream infections and sepsis-related death.

Catheter related bloodstream infection (CRBSI) is among the problematic health care associated infection (HCAI). CRBSI associated with significant morbidity, increased duration of hospital stay and furthermore increases the usage of broad-spectrum antibiotics which later can promotes bacterial resistance (Dimick *et al.*, 2001). The medical and economic burden of CRBSI is huge, which estimated excess healthcare cost of $18, 000 (Zhou *et al.*, 2015). The economic impact of each CRBSI episode is significant, with the Centers for Disease Control and Prevention (CDC) estimating direct costs ranging from $5,734 to $22,939 per episode (Dumyati *et al.*, 2014).

CRBSI lead to longer hospitalisation and additional expenditures, CRBSI-related ICU costs increase, regardless of medical specialties as reported by E.Tacconelli *et al*, 2009. Indeed, Nakamura *et al.* reported that the estimated additional mean costs of each case of CRBSI in Japan were $57,090 (Nakamura *et al.*, 2015). Thus, strategies are needed to prevent these infections include the implementation of the central venous catheter (CVC) bundle as this infection causes substantial morbidity, mortality and incurs high costs.

Central venous catheter (CVC) Care Bundle is one of the preventive strategies that was implemented by CDC in 2009 with the aim is to prevent these infections. The central line bundle is a group of evidence-based interventions that has shown to reduce the risk of central line-associated bloodstream infection (O'grady *et al.*, 2011; Zhou *et al.*, 2015).

CVC Care Bundle incorporates evidence-based science into practices, and is recommended in international CRBSI guideline. The bundle involves several components. Those include educating and training healthcare personnel who insert and maintain catheters; using of maximal sterile barrier precautions during central venous catheter insertion; the use of a > 0.5% chlorhexidine skin preparation with alcohol for antisepsis and also care for maintenance of the catheter (O'grady *et al.*, 2011).

The bundles were shown to reduce the rates of CVC related infections for more than a decade. Recent study had demonstrated that consistent application of evidence-based practices can lead to significant, sustained reductions in CLABSI rates. A study was conducted by Salama *et al.* between January 2010 and February 2012 demonstrated that implementation of CVC post-insertion bundle was associated with a reduction in CLABSI /1000 central line days from 14.9 to 11.08 infections in intensive care unit of general teaching hospital in Kuwait (Salama *et al.*, 2016).

The use of this bundle has been shown to decrease the incidence of CRBSIs worldwide (Khalid *et al.*, 2013; Pronovost *et al.*, 2010). A multimodal intervention done by Ghinwa Dumyati et al. (Dumyati *et al.*, 2014) in 2014, which included engagement and education of nursing staff on an evidence-based bundle for CVC insertion and maintenance, along with measurement and feedback of CRBSI rates and a review of CRBSI cases, resulted in a sustainable reduction in CRBSI rates outside the ICU across 6 diverse hospitals.

One study conducted by Rosenthal *et al.* addressed that the education, performance feedback, and outcome and process surveillance of CLABSI rates significantly improved infection control adherence, reducing the CLABSI incidence by 54% and the number of CLABSI-associated deaths by 58% in INICC hospitals during the first 2 years (Rosenthal *et al.*, 2010).

A landmark study included 103 ICUs in Michigan in 2006 by Pronovost *et al.* demonstrated that strict adherence to a bundled practice of hand hygiene, full barrier precautions, chlorhexidine skin antisepsis, femoral site avoidance, and early removing unnecessary central line could dramatically reduce the rate of CRBSI to nearly 0% (Pronovost *et al.*, 2006). This rate of zero was also sustained at the 18-month follow-up.

A similar study was conducted by Schulman *et al.* in 18 neonatal ICUs in New York resulted overall state-wide rates of CRBSI declined from 6.4 cases/1000 catheter-days to 2.1cases/1000 catheter-days by establishing a central line maintenance checklist, using hand hygiene, sterilizing skin with chlorhexidine and removing unnecessary catheters (Schulman *et al.*, 2011).

Son CH *et al.* in 2011 demonstrated that central line-associated bloodstream infection (CLABSI) rates outside the ICU are similar to those in the ICU, but the number of non-ICU patients at risk is substantially larger, leading to a greater burden of infection compared with the ICU setting.

Compliance with the bundle was a protective factor against the development of CRBSI with staff adherence to the bundle in ICUs in Colombia was over 80% as reported by Osorio *et al.* (Osorio *et al.*, 2013). However the overall compliance of bundle in ICUs at regional teaching hospital in Taiwan by study Hung-Jen *et al.* was much lower; was only 50.3% (Tang *et al.*, 2014). Compliance to maximal sterile barrier was low due to emergency condition. Therefore we introduced the CVC kit with checklist and enough sterile drapes to improve compliance among healthcare-workers.

Reducing the number of CRBSI cases can be translated to reduction of the hospital acquired infection and the final outcome is the reduction in the hospital expanses. Apart from sophisticated devices, other important measures in preventing CRBSI are the education and the compliance among healthcare-workers towards the CVC Care Bundle. The effort to reduce the number of CRBSI cases should be multidisciplinary, involving healthcare professionals' example doctors who order and insert the catheters, staff nurses, medical attendants who maintain and taking care of the catheters and infection control personnel.

1.2 Definition of CRBSI

A CVC was defined as an intravascular catheter terminating at or close to the heart or in a great vessel and used for infusion, withdrawal of blood, or hemodynamic monitoring (Horan *et al.*, 2008). CRBSI was defined according to Centers for Disease Control and Prevention/National Healthcare Safety Network surveillance criteria as bacteremia/fungemia in a patient with an intravascular catheter (the line was in use during the 48-hour period before the development of the bloodstream infection) with positive blood culture (central and peripheral fulfilled requirement based on time to positivity), clinical manifestations of infection (ie, fever, chills, and/or hypotension), and no apparent source for the bloodstream infection except the catheter (Dimick *et al.*, 2001; Horan, 2004b; Horan *et al.*, 2008; O'grady *et al.*, 2011). CRBSI rate was calculated using denominator of cases per 1000 catheter-days (Horan, 2004b). However the incidence rates can be calculated by other method that is based on 100 admission days (Control and Prevention, 2012).

1.3 Types of central venous catheter and indication of central venous catheterisation

There are four types of central venous catheter available include non-tunnelled, tunnelled, peripherally inserted and totally implantable catheters. Catheters can be inserted through a peripheral vein or a proximal central vein, most commonly the internal jugular, subclavian, or femoral vein.

Antimicrobial agents, such as antiseptics or antibiotics coated onto or incorporated into the catheter polymer, as a way to prevent bacterial colonisation and the development of CRBSI. Some of the antimicrobial CVC available are silver, chlorhexidine and silver sulfadiazine, benzalkonium chloride, and minocycline rifampicin. A relatively large number of trials have been carried out on the chlorhexidine silver sulfadiazine CVC and many have achieved a significant reduction both in microbial colonisation of the catheters and in CRBSI (Heard *et al.*, 1998; Maki *et al.*, 1997).

The most extensively studied antimicrobial CVCs are those coated with chlorhexidine–silver sulfadiazine (CSS). These antiseptics act synergistically against microorganisms. Chlorhexidine disrupts the microbial cytoplasmic membrane, thus facilitating the uptake of silver ions, which subsequently bind to the DNA and prevent replication. These CVCs were originally marketed with both antimicrobial agents on the external surface only and remained effective for up to 15 days (Elliott, 2007). A systematic review and meta-analysis of antimicrobial central venous catheters in adults reported that use of chlorhexidine–silver sulfadiazine and minocycline–rifampicin CVCs were significantly reduces catheter colonisation and incidence of CRBSI (Casey *et al*., 2008).

Impregnating the surface of the catheter with antiseptic or antimicrobial substances (such as chlorhexidine and silver sulfadiazine) reduces CRBSI. A Cochrane review of the effectiveness of this approach for reducing CRBSI in adults which included 56 studies and 16 512 catheters with 11 different types of impregnation, bonding, or coating (Lai *et al.*, 2013). The study reported that patient who had impregnated catheters had lower rates of CRBSI (absolute reduction in CRBSI was 2%). Thus, catheter impregnation reduced the risk of catheter related bloodstream infections and catheter colonisation.

The draft epic 3 guidelines recommend that impregnated lines should be used only in patients who are expected to have a catheter in place for more than five days and in units where the CRBSI rate remains high (Loveday *et al.*, 2013). Von Eiff *et al.* reported that the catheters remain effective for up to only 15 days in situ (Von Eiff *et al.*, 2005). Furthermore, the chlorhexidine resistance has not been reported yet with the clinical use of these devices (Rupp *et al.*, 2005; Von Eiff *et al.*, 2005). Instead, the problem has been identified with the catheters was hypersensitivity reactions.

The indications for central venous catheterisation include access for giving drugs and fluids, extracorporeal blood circuits like renal replacement therapy, plasma exchange and total parenteral nutrition, and haemodynamic monitoring and interventions like central venous pressure, central venous blood oxygen saturation, pulmonary artery pressure, and for repeated blood sampling. Most of the contraindications to central venous catheterisation are thrombocytopenia, vessels thrombosis, stenosis, or disruption, and any infection overlying insertion site.

1.4 Risk factors for CRBSI

Associated risk factors of CRBSI were duration of central venous catheter use (O'grady *et al.*, 2011; Pronovost *et al.*, 2006) length of hospitalization time, long-term indwelling central venous catheter, and insertion of central venous catheter in intensive care unit; use catheter for parenteral nutrition and administration of blood products, underlying disease such as neutropenia and diabetes mellitus, sepsis at insertion and administration of one or more antibiotics before insertion (Almuneef *et al.*, 2006).

The higher the risk of catheter-related infection would be expected when the longer used of CVC. Indeed, the duration of catheterisation was important risk factor in the development of CRBSI in some studies (Arruda *et al.*, 1997; Tacconelli *et al.*, 2009; Tan *et al.*, 2007). However, there were studies showed no relationship between prolonged catheterisation and incidence of infection (Eyer *et al.*, 1990; Gowardman *et al.*, 1998). The CRBSI cases had a significant on duration of catheter days and lengths of hospital stays but no differences on hospital mortality (Jaroen Cheewinmethasiri et al., 2014).

The site for CVC insertion that was associated with the higher risk of CRBSI remained controversial. No randomised trial had satisfactorily compared infection rates of CRBSI for catheters placed in jugular, subclavian and femoral area. Merrer *et al*. performed a randomized controlled trial comparing complications of femoral and subclavian venous catheterisation in critically ill patients and found that femoral catheterisation was associated with a higher incidence of clinical sepsis with or without bloodstream infection which did not reach statistical significance (p=0.07) (Merrer *et al.*, 2001).

CDC Guidelines for Prevention of Intravascular Catheter-Related Infections in 2011 recommended avoid using of the femoral vein for central venous access in adult patients whereas avoid the subclavian site in hemodialysis patients as it can lead to subclavian venous stenosis (Goetz *et al.*, 1998; O'grady *et al.*, 2011; Parienti *et al.*, 2008). The evidence for avoiding femoral catheter was based on higher risk for deep venous thrombosis and higher colonization rates (Goetz *et al.*, 1998; Trottier *et al.*, 1995).

The presence of multiple lumen of CVC increased the risk of CRBSI. A study by Almuneef *et al*. reported that the presence of multiple lumen of CVC increased the risk of CRBSI almost 10-fold in their PICU (Almuneef *et al.*, 2006). The frequent sampling through the lines might increase the opportunity for introduction of microorganisms into the catheters.

Catheters which placed under emergency situations, during which optimal aseptic conditions had been significantly associated with higher risk of catheter-related infection compared to elective situation (Goetz *et al.*, 1998; Mermel *et al.*, 1991). Patient with renal problem were at risk of CRBSI, particularly patients undergoing hemodialysis due to uraemia, vascular access, and the combination of surgery and immunosuppressive therapy (Rojas *et al.*, 2013).

1.5 Pathogenesis of CRBSI

There are four common routes for contamination of catheters: migration of skin organisms at the insertion site into the cutaneous catheter tract and along the surface of the catheter with colonization of the catheter tip; this is the most common route of infection for short-term catheters; direct contamination of the catheter or catheter hub by contact with hands or contaminated fluids or devices; less commonly, catheters might become hematogenously seeded from another focus of infection; and rarely, infusate contamination might lead to CRBSI (Crnich and Maki, 2002). Extraluminal colonisation from the skin colonised the line during insertion or migrated along the catheter tract which could occur early after line insertion.

The adherence properties of microorganism are important in the pathogenesis of CRBSI. *Stahylococcus aureus* as example can adhere to the host protein such as fibrinogen and fibronectin that commonly present on catheter by expressing the clumping factors that bind to protein adhesins (Mehall *et al.*, 2002). Furthermore the proteins facilitate the adherence of microorganisms such as coagulase negative staphylococci, *S.aureus*, *Pseudomonas aeruginosa* and *Candida species* of an extracellular polymeric substance of exopolysaccharide that form a microbial biofilm layer (Donlan, 2002). This biofilm, allow them to battle with host defence mechanism and protects them from chemotherapeutic agents and opsonophagocytosis and furthermore make them less susceptible to antimicrobial agents (Donlan, 2000; Farber *et al.*, 1990).

1.6 Incidence of CRBSI

The prevalence of CRBSI in Malaysia was around 3.2-9.43 per 1000 catheter days reported by Sulong *et al.* in 2008, whereas in a study conducted at ICU Hospital UKM; overall rate was 6.4 per 1000 catheter days (Sulong *et al.*). However, the prevalence was much lower in developed countries at 1.8- 5.2 per 1000 catheter-days (Daniels and Frei, 2013). In Europe, the rate of catheter-related bloodstream infections in intensive care units (ICUs) was between 1- 4.2 per 1000 catheter days (Almuneef *et al.*, 2006).

A multimodal intervention done by Dumyati *et al.* (Dumyati *et al.*, 2014) in 2014, which included engagement and education of nursing staff on an evidence-based bundle for CVC insertion and maintenance, along with measurement and feedback of CRBSI rates and a review of CRBSI cases, resulted in a sustainable reduction in CRBSI rates outside the ICU across 6 diverse hospitals.

However there were several studies reported of higher rate of CRBSI. Study by Almuneef *et al.* in 2005 at PICU of King Abdulaziz Medical City (Riyadh) reported incidence rate of CRBSI 20.06 per 1000 catheter-days (Almuneef *et al.*, 2006). Another study was conducted by Salama *et al.* between January 2010 and February 2012 demonstrated that implementation of CVC post-insertion bundle was associated with a reduction in

CLABSI /1000 central line days from 14.9 to 11.08 infections in intensive care unit of general teaching hospital in Kuwait (Salama *et al.*, 2016).

There were various reports from developed and developing countries with variable rates (Khuri-Bulos *et al.*, 1999; Stover *et al.*, 2001; Yogaraj *et al.*, 2002). This variability depends on unit-related parameters such as sample size and settings, patient's comorbidities such as severity and type of illness, and catheter-related parameters such as type of catheter, site (route), conditions under which the catheter was inserted whether emergent of elective insertion, skill of person inserted the catheter and finally type of infusate and apparatus used. France presented the lowest incidence rate of CRBSI among the industrialised countries which was about 0.9 per 1000 catheter days (Group, 2009).

1.7 Aetiological agent of CRBSI

Most CRBSIs come from either the patient's skin or the hands of medical personal, so that many literatures note that staphylococci, specifically *S.aureus* and *S.epidermidis* are the most common organism implicated in CRBSIs (Hooven and Polin, 2014; Sengupta *et al.*, 2010). These organisms are able to colonise the catheter and difficult to treat because easily resistant to systemic antibiotic as they embedded themselves in a biofilm (Deva *et al.*, 2013).

However the causative etiological agents of CRBSI in other countries like Taiwan and China was reporting increase of Gram-negative bacteria isolated (Tao *et al.*, 2011; Wu *et al.*, 2006). A study was done by Tan *et al*. (Tan *et al.*, 2007) reported the most common organism was Gram-negative organism with the percentage of 80.5% and the most common organism isolated was *Klebsiella pneumoniae* (38.9%).

A 3-year prospective study by Lorente *et al.* in intensive care unit (ICU) of the Hospital Universitario de Canarias (Tenerife), between 1 May 2000 and 30 April 2003 reported a total of 53 microorganisms were responsible for the 53 CRBSI cases, of which 38 (71.70%) were Gram-positive bacteria, 12 (22.64%) were Gram-negative bacteria and 3 (5.66%) were yeasts (Lorente *et al.*, 2005). In addition, a report of CRBSI from Spain had also shown the same predisposition that Gram-positive bacteria were higher in the proportion compared to other microorganism (Rodríguez-Créixems *et al.*, 2008).

1.8 Clinical presentations and complication of central venous catheterisation.

Clinical signs for CRBSI are not specific. Fever and chills are the most sensitive clinical finding but is not specific. The presence of inflammation or pus at the catheter exit site is more specific but less sensitive. Furthermore, local catheter inflammation and phlebitis could exist in the absence of CRBSI (Walshe *et al.*, 2002). Therefore physician consider a diagnosis of CRBSI in patients with signs of systemic infection in the absence of other identifiable source.

Despite the benefits of central venous lines to patients, more than 15% of patients were developed catheter related complications. The use of antimicrobial CVCs needs to be carefully decided as the complications related to central venous catheters are common and may cause serious morbidity and mortality. Complications are divided into immediate and delayed, then subdivided into mechanical, embolic, and infectious. Air embolism may occur at any point during the lifetime of line and can be related to poor technique during line insertion, use of the line, or line removal.

The risks of mechanical lesions include arterial puncture, pneumothorax, cardiac tamponade, or nerve lesions and thrombotic complication with each CVC. One of the most frequently reported complications of CVC insertion is arterial puncture (Yilmazlar *et al.*, 1997). Incidence of pneumothorax has been reported to occur in 0.5% to 4% of the insertions (Plewa *et al.*, 1995), but the incidence was lower in other study by Tyburski *et al.* (Tyburski *et al.*, 1993).

The risk of catheter-related sepsis was be increased when the catheter was thrombosed (Timsit *et al.*, 1998) . Rate of catheter related thrombi and CRBSI in cancer patients was reported more than 50% (Wu *et al.*, 1999). The risk of getting CRBSI in patients with a CVC was reported to range between 1 and 10% (Adal and Farr, 1996). Incidence of infection as the complication of indwelling catheters was reported approximately 5.3 per 1,000 catheter days and an attributed mortality of 18% (O'grady *et al.*, 2011).

1.9 Diagnosis

Catheter related infection was suspected in a patient with an intravascular catheter (the line was in use during the 48-hour period before the development of the bloodstream infection) when any sign of local infection (induration, erythema, heat, pain, purulent drainage) and signs of systemic infection (fever, chills, and/or hypotension), with no apparent source of bacteremia except the catheter, and with the microbiological evidence that the catheter was the source of infection

Culture of the same organism was isolated both from the catheter segment and peripheral blood with the differential period of CVC culture versus peripheral blood culture positively of more than two hours, whether a positive semiquantitative (>15 Colony forming unit (CFU)/catheter segment) or by quantitative (>103 CFU/catheter segment) (O'grady *et al.*, 2011).

1.10 Laboratory investigation

According to IDSA guidelines, the semi-quantitative roll plate technique of 5cm catheter tip is recommended especially for short term catheter (less than 14 days) and quantitative broth culture (luminal flushing or sonication) for catheter which have remained in place for a longer time. However, other studies showed no difference between both approaches (Bouza *et al.*, 2005; Mermel *et al.*, 2009).

In general, detection of >15 colony forming units (CFU) is relevant for roll plate and quantitative broth culture (luminal flushing or sonication, positive if >102 CFU are detected). However it is less sensitive and unable to culture organisms that embedded intraluminal.

Simultaneous quantitative blood culture drawn through CVC yields CFU count five-fold higher or more than CFU count from simultaneously drawn blood from peripheral vein is the other methods (Mermel *et al.,* 2009). A meta-analysis study of diagnostic test showed that simultaneous quantitative blood culture was found to be the most accurate test for diagnosis of CRBSI with pooled sensitivity and specificity 75% and 97% respectively (Safdar *et al.,* 2005). However, the use of the simultaneous quantitative blood culture technique has been limited because it is labour intensive and expensive

1.11 Treatment

There was increasing evidence that antimicrobial lock applied within the catheter lumen were effective at preventing CRBSI. Some lock therapy such as citrate, alcohol, ethylene diamine triacetic acid (EDTA) has extra antimicrobial and biofilm removing properties. On contrast, heparin tends to antagonize the bactericidal properties of certain antibiotic like aminoglycosides. Moreover it also promotes biofilm formation unless at very low concentrations (Droste *et al.*, 2003; Shanks *et al.*, 2006).

Heparin catheter lock has become widely used as an antithrombotic agent in catheters since two decade ago as a result of studies published between 1979 and 1996 that showed heparin infusion effectively reduces catheter-related thrombus formation and may reduce catheter infection (Randolph *et al.*, 1998). Several prospective randomised studies have shown that an antimicrobial catheter lock is superior to heparin alone as a lock solution in preventing catheter infection (Garland *et al.*, 2002; Henrickson *et al.*, 2000; Safdar *et al.*, 2005).

The choice of antibiotic treatment was depend on individual preference, local or regional patterns, and/or recommendations from national or international guidelines. Decision whether the CVC should be removed or retained, with antibiotic catheter lock, and the duration and type of therapy depend on the type of organism causing the CRBSI. For example of coagulase negative staphylococci, catheter removal was once thought to be necessary, however almost 80% can be treated with glycopeptide antibiotics, such as vancomycin, without catheter removal. However, there is a 20% chance that the bacteraemia will recur if the CVC is not removed (Raad and Bodey, 1992).

According to European Renal Best Practice (ERBP), preference should be given to antibiotics with a pharmacokinetic profile allowing administration after each dialysis session only (vancomycin, teicoplanin, cefazolin, ceftazidime and daptomycin) (Vanholder *et al.*, 2010). In settings where methicillin-resistant *S. aureus* (MRSA) was highly prevalent, vancomycin or teicoplanin was the first choice for empirical treatment (Allon, 2003).

Whereas the duration of therapy for uncomplicated *Staphylococcus aureus* CRBSI, a 10–14 day course of intravenous therapy is necessary if the CVC is removed (Dimick *et al.*, 2001). The type of antibiotics used should be based on the susceptibility of *S. aureus.* For Gram-negative bacteraemia, it is practical to remove the CVC and treat with a 1-week course of appropriate susceptible antibiotics. Whereas for candida species, several prospective studies have shown that CVC removal was associated with improved in patient outcome (Nucci and Anaissie, 2002; Raad *et al.*, 2004). According to IDSA guidelines, the duration of therapy for uncomplicated catheter-related candidaemia should be for two weeks duration since from the last positive blood culture (Mermel *et al.*, 2009).

1.12 Prevention

It is necessary to minimize CRBSI by monitoring its incidence and to implement preventive measures. More than a decade ago, the bundles were shown to reduce rates of CVC related infections. Recent study has demonstrated that consistent application of evidence-based practices can lead to significant, sustained reductions in CLABSI rates. The implementation of a CVL insertion care bundle was associated with a decrease in the total CLABSI/1000 central line days from 14.9 to 11.08 infections as reported by Salama *et al.* (Salama *et al.*, 2016)

A landmark study in 2006 by Pronovost *et al.* demonstrated that strict adherence to a bundled practice of hand hygiene, full barrier precautions, chlorhexidine skin antisepsis, femoral site avoidance, and judicious early line removal can dramatically reduce the rate of CRBSI to nearly 0% (Pronovost *et al.*, 2006).

European Renal Best Practice (ERBP) recommends the preventive measures as followings; catheter insertion should be performed under strict aseptic conditions, universal precautions and a sterile environment should be applied at any occasion when a venous catheter is manipulated, connected or disconnected, practice of antimicrobial locks applied within the catheter lumen, and the catheter exit site should be inspected and replaced when it is no longer clean (Vanholder *et al.*, 2010).

Evidence based recommendations for preventing intravascular catheter related infections includes 1) educating and training healthcare personnel who insert and maintain catheters; 2) using maximal sterile barrier precautions during central venous catheter insertion; 3) using a > 0.5% chlorhexidine skin preparation with alcohol for antisepsis and also care for maintenance of the catheter.

The using 2% chlohexidine gluconate in 70% alcohol was more benefit instead of povidone-iodine in preventing CRBSI as it was superior and rapid skin decontamination (Maki *et al.*, 1991; Mimoz *et al.*, 1996). Indeed, a meta-analysis had shown that daily bathing of ICU patients with chlorhexidine gluconate reduces healthcare related infection and CRBSI (O'horo et al., 2012).

Program of "Scrub the Hub," which purpose was to reduce infections, educate, and encourage healthcare-workers to disinfect the hub carefully every manipulation, as it had been widely practised and recommended. Several institutions have reached their goal of eliminating CRBSIs after implementing the same disinfection cap (DeVries *et al.*, 2014). As example, DeVries *et al.*, reported that CRBSI rate dropped 43%, comparing the pre-intervention rate of roughly 0.010/100 patient days to 0.0059/100 patient days during the post-intervention period.

1.13 Mortality of CRBSI

CRBSI are associated with serious morbidity and mortality. Mortality due to CRBSI is difficult to estimate due to multiple confounding factors that can be identified among selected patients. Gastmeier *et al.* estimated that mortality attributable to CRBSI ranges from 1000 to 1300 patients per year about 12-15% (Gastmeier *et al.*, 1999). Whereas mortality attributable to CRBSI was estimated at 17% by Endimiani *et al.*(Endimiani *et al.*, 2003). The higher rate of 21.8% was reported by a study by Hajjej *et al.* in Tunisian medical ICU (Hajjej *et al.*, 2014).

1.14 Rationale of study

Although there were many studies about CRBSI worldwide but it seem limited study done in Malaysia, especially in East-coast of Malaysia (A hospital based study done in Malaysia:-UKM Medical Centre, Kuala Lumpur from 2008 to 2009 by Anita et al. (Sulong *et al.*, 2011) and a study of incidence and risk factors of CRBSI in ICU of Hospital Sultanah Aminah in 2005 by Tan *et al.* (Tan *et al.*, 2007).

Therefore the aim of this study was to study the impact of implementation of CVC Care Bundle in Hospital USM for prevention of CRBSI. The CVC kit was created and introduced to enhance the compliance of practicing this bundle. The incidence rate of CRBSI following the implementation of this bundle was analysed and their causative microbial agents were described. This intervention was intended for health care personnel who inserted and cared for intravascular catheters and who were responsible for the surveillance, prevention, and control of infections in all health care settings. Hence, intervention aimed at improving outcomes related to CVCs should be seriously considered.

This study could establish a benchmark for comparison with future study in Malaysia and for maintenance of CRBSI bundle that was implemented. Apart of that, this could monitor performance improvement by documenting and reporting rates of compliance with all components of the bundles as benchmark for quality assurance and performance improvement. This study would benefit and evoke healthcare workers so that they would be more alert to the prevention of CRBSI. We learned that implementation of a CVC Care Bundle required not only education, but also engagement of staff and changes in staff behaviour. The ultimate goal was to fully integrate the new behaviour into everyday practice, which would take some time to implement completely.

1.15 Objectives

1.15.1 General Objectives

To determine the incidence rate of CRBSI in Hospital USM before and after the implementation of CVC Care Bundle.

1.15.2 Specific Objectives

1. To compare the incidence rate of CRBSI in Hospital USM before and after the implementation of CVC Care Bundle.
2. To identify the etiological agent and its sensitivity pattern of patient with CRBSI.
3. To describe the CVC Care Bundle compliance rates.

CHAPTER 2

METHODOLOGY

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2.1 Study design

This was a cohort study.

2.2 Study period

The study was carried out from April 2016 to December 2017.

2.3 Study location

The sample was from medical wards, surgical wards and intensive care units in Hospital USM.

2.4 Reference population

The reference population was all patients with CVC insertion admitted to Hospital USM.

2.5 Source population

The source population of this study was defined as patients who fulfil the CRBSI criteria.

2.6 Study participants

Patient with CVC inserted on them with various indication that were eligible for data record in ward of Hospital USM from April 2017 to December 2017 were recruited in the study.

2.7 Inclusion and exclusion criteria

- Inclusion criteria

1. Age≥ 18years old
2. Newly admitted patient for various indication of catheterization

- Exclusion criteria

1. Have other central venous access devices

2.8 Sample size calculation

Single proportion calculation based on incidence density of CRBSI

(The prevalence of CRBSI in Malaysia is around 3.2-9.43 per 1000 catheter days)

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

$= (1.96/0.05)^2 \times 9.43 \, (1-9.43)$

Therefore number of patient involves estimated to be 147.

2.9 Sampling method

All patients suspected with CRBSI were recruited.

2.10 List of variable factors/ Ascertainment (Outcome & Independent variables)

- Age
- Sex
- Site of CVC
- Length of hospital stay
- Length of catheter days
- Duration of CVC

2.11 Research measurement tool

CVC Care Bundle checklist included compliance (established checklist by KKM)

2.12 Case definition

A CVC was defined as an intravascular catheter terminating at or close to the heart or in a great vessel and used for infusion, withdrawal of blood, or hemodynamic monitoring (Horan *et al.*, 2008).

CRBSI was defined according to Centers for Disease Control and Prevention/National Healthcare Safety Network surveillance criteria as bacteremia/fungemia in a patient with an intravascular catheter (the line was in use during the 48-hour period before the development of the bloodstream infection) with positive blood culture (central and peripheral fulfilled requirement based on time to positivity), clinical manifestations of infection (ie, fever, chills, and/or hypotension), and no apparent source for the bloodstream infection except the catheter (Dimick *et al.*, 2001; Horan, 2004b; Horan *et al.*, 2008; O'grady *et al.*, 2011).

Incidence refers to the occurrence, rate or frequency of disease during a specific period in a given specified population (Shields and Twycross, 2003). Incidence of CRBSI is estimated by the number of cases per 1000 days of implanted CVCs (Horan, 2004a).

$$\frac{\text{Total no. of CRBSI cases}}{\text{Total no. of catheter days}} \times 1000 \text{ catheter days}$$

CRBSI rate also can be calculated using denominator of cases per 100 admission-days. (Control and Prevention, 2017)

$$\frac{\text{Total no. of admission days of CRBSI cases}}{\text{Total no. of admission days of all patients}} \times 100 \text{ admission days}$$

2.13 Pre-intervention

Pre-intervention study was done from April 2016 to December 2016. Record tracings of confirmed cases of CRBSI were done. Patient's clinical data including demographic, co-morbid illness, clinical manifestations, CVC's information and clinical outcomes were obtained from clinical notes. The data were analysed and interpreted according to the objectives.

2.14 Intervention

Intervention study was done from January 2017 to March 2017. The intervention consists of:

1. Implementation of CVC care bundle (insertion and maintenance)
2. Introduction of CVC kit.
3. Education and practical session of CRBSI care bundle.
4. Introduction of CVC care module (video and posters)
5. Strengthened the audit surveillance for CRBSI based on adopted form by KKM.

During this intervention period, CVC care bundle based on IDSA guideline 2009 and CDC 2011 was implemented (Mermel *et al.*, 2009; O'grady *et al.*, 2011). CVC Care Bundle which consists of CVC Insertion Bundle and CVC Maintenance Bundle was introduced. The components for CVC Insertion Bundle include proper hand hygiene, maximal barrier precautions upon insertion including full body drape, 2% chlorhexidine in 70% alcohol solution for skin antisepsis before CVC insertion and daily review of line necessity with prompt removal of unnecessary lines. Whereas the components for CVC Maintenance Bundle were hand hygiene when accessing, repairing, dressing or any manipulation of the IV system, dressing change, scrub the hub with alcohol wipes for 15 seconds and daily CVC need assessment.

CVC kit was created and used to enhanced compliance and adherence to the insertion bundle. The kit consist of a box which contain of material needed for CVC insertion; CVC checklist form, surgical face mask, cap, sterile glove, sterile preparation of 2%

chlorhexidine with 70% alcohol, blade, suture, 3 way connector, gauze (op-site), catheter lumen, syringe, needle and sterile gown.

Education regarding this bundle was given. This program involved two days' workshop in two separate occasions. Each workshop was attended by 40-50 participants. The participant was healthcare-workers of Hospital USM including medical officers, house officers and staff nurses of different wards. The workshops focused on providing knowledge on CRBSI and its preventive measures. The education was given in the form of 2 hours lectures by clinical microbiologist and followed by practical session on insertion and maintenance bundle. The demonstration and practical session on CVC care base on CDC guideline in 2009 using mannequin. The staffs were also emphasized on the use of checklist as a tool to remind the healthcare-workers of the right thing to do at the right time. The education session was given periodically (twice) to teach the nurses and doctors who were inserting and taking care of the catheters.

An educational module was created to aid in implementation of CVC care bundle. This module was adopted by MOH based on international Institute for Healthcare improvement (Improvement, 2012). The content of the modules includes introduction and epidemiology of the subject matter, the surveillance form of insertion and maintenance bundle, and the checklist form. Audio visual educational demonstration, manual book module and posters were provided for the intervention.

CVC Insertion Bundle Compliance Checklist Form and CVC Maintenance Bundle Compliance Checklist Form were introduced to record the activity. Upon completion of CVC insertion, the attending personnel should fill the CVC Insertion Bundle Compliance Checklist Form. The attending doctor should review the necessity of continued CVC placement for every day. Nurses on duty should chart the indication for continued CVC placement whether no longer required in the CVC Maintenance Bundle Compliance

Checklist Form. The completed form were send to Unit Kawalan Jangkitan & Epidemilogi Hospital USM (UKJEH).

2.14.1 Application of CVC insertion bundle

1. Hand hygiene- Hands are decontaminated immediately before and after each episode of patient contact using the correct hand hygiene technique. An organized approach "5 Moments of Hand Hygiene" will be use.

2. Use of full barrier precautions/PPE- Maximal sterile barriers and aseptic technique, including a sterile gown, sterile gloves, and a large sterile drape, will be use for the insertion of a central venous access device.

3. Chlorhexidine skin antisepsis- A solution of 2% chlorhexidine gluconate in 70% isopropyl alcohol is used and allowed to dry for at least 30 seconds. If a patient is sensitive to this agent, povidone-iodine application may be used. Aseptic technique is maintained throughout insertion of CVCs.

4. Dressing - A sterile dressing will be apply (gauze and transparent dressing)

2.14.2 Application of CVC maintenance bundle

1. Daily review of line necessity with prompt removal of unnecessary CVCs and documentation will be conducted. Daily review of the need for CVCs will be done in the following ways:

i. During multidisciplinary patient care rounds or

ii. By using reminders- stickers on patient records and reminder by staff nurse assisting doctor during daily ward round.

2. Details of removal of CVC will be documented in the records (including date, name and signature of the operator undertaking removal)