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# Central Line Associated Bloodstream Infection in Adult Intensive Care Unit Population

## —Changes in Epidemiology, Diagnosis, Prevention, and Addition of New Technologies

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## Abstract

**Background:** Intensive care units (ICUs) have an increased risk of Central line associated bloodstream infection (CLABSI) due to the prevalence of invasive procedures, devices, immunosuppression, comorbidity, frailty, and elderly patients. We have seen a successful reduction in Central line associated bloodstream infection related the past decade. In spite of this, Intensive care unit-Catheter related bloodstream infections remain high. The emergence of new pathogens further complicates treatment and threatens patient outcomes in this context. In addition, the SARS-CoV-2 (COVID-19) pandemic served as a reminder that an emerging pathogen poses a challenge for adjusting prevention measures regarding both the risk of exposure to caregivers and maintaining a high level of care. ICU nurses play an important role in the prevention and management of CLABSI as they are involved in basic hygienic care, quality improvement initiatives, microbiological sampling, and aspects of antimicrobial stewardship. Microbiological techniques that are more sensitive and our increased knowledge of the interactions between critically ill patients and their microbiota are forcing us to rethink how we define CLABSIs and how we can diagnose, treat, and prevent them in the ICU. The objective of this multidisciplinary expert review, focused on the ICU setting, is to summarize the recently observed occurrence of CLABSI in ICU, to consider the role of modern microbiological techniques in their diagnosis, to examine clinical and epidemiological definitions, and to redefine several controversial preventive measures including antimicrobial-impregnated catheters, chlorhexidine-gluconate impregnated sponge, and catheter dressings.

## Keywords

Central Venous Catheter, SARS-COV-2, ICU, Bloodstream Infection,

Catheter Colonization, Catheter Insertion

## 1. Introduction

Central venous access entails placing a large bore catheter or a venous access device in a vein in the groin, neck, or upper chest to deliver drugs that cannot be administered via mouth or arm [1]. In addition to antibiotics and chemotherapy, these catheters can be used for the administration of vasoactive drugs, blood products, and intravenous nutrition [2] [3]. Moreover, central venous access is also used in intensive care units to assess venous and cardiac function, or to provide patients with continuous or intermittent renal replacement therapy [4]. However, one of the major issues related to the use of central venous catheters (CVCs) is the possibility of infection caused by microorganisms. However one of the major problems associated with the use of central venous catheters (CVCs) is colonization by micro-organisms that could result in local or systemic infections [4], leading to increased morbidity and mortality rates among patients, as well as increased financial burdens on the community [5]. Two major designations are used to define bloodstream infection due to vascular catheters. Central line associated bloodstream infections (CLABSIs) and catheter related bloodstream infections (CLABSI). Even though they are used interchangeably, they have distinct differences. The term Central Line Associated Bloodstream Infection (CLABSI) refers to infections occurring in the presence of a central venous catheter or within 48 hours after the catheter has been removed and which cannot be attributed to an infection unrelated to a catheter [6]. A catheter related blood stream infection (CLABSI) is a clinical diagnosis attributed to an intravascular catheter that can be confirmed by quantitative culture or by comparing a catheter specimen with peripheral venous blood. According to Maki, catheter colonization is defined as a semi-quantitative culture of >15 colony forming units or a quantitative culture of $10^3$ colony forming units [1], *et al.* CLABSI is one of the most common nosocomial infections and a major cause of bloodstream infections, particularly for patients in intensive care. The majority of CLABSIs are acquired through central venous catheters, and recent studies have found that the risk of acquiring CLABSI via central venous catheters is 64 times greater than that of peripheral catheters [7].

The Centers for Disease Control and Prevention (CDC) estimates that there have been 50% fewer CLABSIs in the US in recent years, but thousands of patients still develop bloodstream infections each year [8] with an average rate of 0 to 2.9 per 1000 CVC days (depending upon the type of unit) and 1 per 1000 CVC days in critical care units. In comparison with the US national health care safety network, a study done by Rupp *et al.* showed that the rate of blood stream infections associated with central lines in western European hospitals is 3.5% (1.7/1000 patient days) with 48.3% associated with central catheters.

China has an estimated CLABSI rate of 4.1 per 1000 CVC days in medical-surgical intensive care units (ICUs). An additional study done in 2015 by Zhang *et al.* in China reported 2631 cases across 7 intensive care units, the estimated CLABSI rate was 7.66/1000 in August 2008 and July 2010 in 4 hospitals [8].

There is a diversity of microorganisms with differing ages, immunity statuses, and disease severity levels. Zhang *et al.* study reported Staphylococcus and streptococcus as the most common microorganisms, but a study from Spain reported that gram-positive cocci and yeasts have been responsible for the majority of CLABSIs and catheter tip colonization. Several recent studies in Europe and China have reported a shift toward gram-negative pathogens associated with CLABSI [8] [9].

A number of studies have shown that risk of developing catheter related bloodstream infections and other complications varied according to the site of insertion. However, the conclusion is controversial, Goetz *et al.* supported the hypothesis that higher incidence of catheter related bloodstream infections was more associated with femoral access site than other central venous sites and concluded that the subclavian site was more preferable access site [4] [10] [11]. Deshpande and his colleagues also assessed the risk of infectious complications associated with central venous catheterization at various insertion sites and reported that there was no risk to catheter related bloodstream infections associated with insertion site [12] [13] [14] [15] [16]. Further-more, recent prospective studies have reported that catheter colonization is lower when subclavian venous access site is used, and rate of colonization for internal jugular venous access and femoral site were of no difference [13] [17], another study demonstrated jugular venous site to be an independent risk factor for catheter colonization [18], Deshpande *et al.* found there was no difference in catheter colonization between subclavian, jugular and femoral venous access site.

## 2. Epidemiology

Central venous catheters are routinely used in critical care units. Patients who are admitted in the ICU are frequently exposed to such devices. The main insertion sites used for CVC insertion are internal jugular, subclavian and femoral veins. Mechanical complications associated with insertion of central venous catheterization include pneumothorax, hemothorax, arterial injury, DVT/PE and the incidence of mechanical complications depends on the choice of insertion site and the number of attempts during insertion which can be reduced by the use of ultrasound.

The episode of catheter related bloodstream infection can be detrimental with a significant mortality and costs [19] [20]. Over 250,000 of bloodstream infections occur annually and central venous catheters is the cause for most of the bloodstream infections. In the US alone, the rate of central line associated bloodstream infection in intensive care units is estimated to be 0.8 per 1000 catheter

days. The International Nosocomial Infection control consortium (INICC) studied the CLABSI rates in 703 medical-surgical ICUs in 50 countries and reported a rate of 4.1 per 1000 catheter days, [21].

The cost per single CLABSI has been estimated to be $34,508 - $56,000, and the cost of caring for patients per year was estimated to be $2.3 billions. Catheter-related bloodstream infection prolongs hospital stay and affects the number of resources used during hospitalization [22]. Almost 1 out of 4 patients with central line in place stay in hospital for an average of 8 days and is expected to develop catheter colonization and CVC related bacteremia [23]. CLABSI do not only cause life-threatening illnesses, but also could lead to mortality. Mortality attributed to CLABSI is estimated to be 12% - 25% [24] [25].

### 2.1. Anatomic Considerations in Insertion of Central Venous Catheters

Internal Jugular Vein: Venous catheterization most often takes place at the Internal jugular. The advantages are the superficial location, the ease of ultrasonic visualization and the straight path to superior venacava on the right. It is more advantageous to catheterize right Internal jugular vein because its relation to the right superior venacava and is straighter and more direct [26] and increases the likelihood of a successful placement. Catheterizations should be carried out in Trendelenburg position, with active head raising as with Subclavian catheterization. In addition to preventing subclavian pinch-off syndrome as explained by Bannon *et al.*, internal jugular catheterization helps to prevent subclavian stenosis in renal failure patients [27].

The Subclavian Vein: The subclavian vein continues at the lateral border of the first rib and is a continuation of axillary vein. It terminates at the Internal Jugular vein. In addition to the clavicle, there are three muscles surrounding it, namely the subclavius and scalenus anterior muscles. Immediately anterior to it, is the first rib and apical part of the pleura subclavian vein receives external jugular vein at the point of uniting with the with internal jugular vein. Both right and left subclavian veins have bilaterally asymmetrical deep routes. The left subclavian vein contours smoothly when passing through the innominate vein, but the right subclavian vein makes a sharp curve when it joins the internal jugular vein. In most studies, catheter insertion in an infraclavicular percutaneous approach is preferred, however some studies advocate a supraclavicular approach to reduce complications [26]. It is important that the patient be placed in Trendelenburg position during catheter insertion. By doing so, blood can fill the subclavian and prevent air embolism from occurring, [26]. Because the subclavian vein is attached to the tissues surrounding it, the vessel remain patent even in hypovolemic shock. The use of Ultrasound-guided venous puncture has been evaluated as a safe and reliable method to minimize the risk of adventitial arterial puncture [28]. The findings of multiple non-randomized studies indicate that subclavian catheterization may increase the risk of pneumothorax, hemothorax and thrombosis [27]. Despite this, subclavian catheterization remains the norm

in the ICU settings.

Femoral Vein: Femoral vein is the extension of popliteal vein and becomes visible in the anterior thigh. The femoral vein is posterior lateral to the femoral artery in the anterior thigh but close to the inguinal ligament it assumes a more medial position with respect to femoral artery. However 25% of individuals examined by computed tomography, femoral vein appeared to lie posterior to femoral artery [29] thus increasing the chances of arterial puncture during venous catheterization and subsequent risk of chronic arterio-venous fistula as a complication of central venous catheterization. The risk of infectious complications associated with femoral catheters is explained by the proximity of the inguinal region to the anal and urethral orifices. The femoral veins are appropriate sites for placement of cardiac catheters, in addition, femoral venous access may be the only available site for deep venous catheterization in severe extensive burn injury patients [30]. In emergency situations e.g., in hypotensive shock patients' femoral vein is often a site of choice as a part of resuscitation. However, studies have shown that femoral venous catheterization has been associated with higher risks of colonization and catheter related bloodstream infections.

## 2.2. Pathogenesis

As the pathophysiology of central venous central line associated bloodstream infection involves colonization of the catheter, microbes gain access to the patient's bloodstream through two routes: either by the external surface of the catheter (extraluminal) from the skin or by the internal surface (intraluminal) through hubs or ports. Patients' own skin bacteria or exogenous microbes from health care personnel are the most common routes of infection. Infections caused by this mechanism are most frequently seen in short-term central catheters (which are left in place for ten days). The major cause of infection of long-term catheters (catheters in place for more than 30 days) is the handling of the venous line, due to the migration of infectious agents to the catheter's internal lumen (intraluminal). There may be an impact on microbial growth due to the type of fluid administered through the CVC. There is no growth of Gram- positive organisms (*S. aureus*, *S. epidermidis*) in IV fluids but Gram-negative organisms, e.g., *K. pneumoniae*, *Enterobacter*, *and P. aeruginosa*, are sustained in IV fluids. Contamination of catheters can lead to the development of bacterial and fungal biofilm communities which are potent sources of catheter colonization and bloodstream infection, and as such, CLABSI is a biofilm-mediated infection. Infection rates are related to the number of microorganisms present on the catheter tip.

### 2.2.1. Bacterial Biofilm Formation on CVCs

Biofilm formation is best understood when both substratum and cell surfaces are understood in depth. There is a wide range of substratum ranging from highly charged hydrophilic materials, such as glass, to highly hydrophobic material such as latex and silicon. Some materials have antimicrobial coatings, such as

antibiotic-impregnated catheters. There are several factors that can affect the rate at which microorganisms attach to the substratum. Depending on the catheter material, biofilms can form more rapidly on rough, hydrophobic surfaces as opposed to smooth, hydrophilic surfaces. The condition is further complicated when the substratum is placed in a fluid environment, e.g., bloodstream, where it acquires a conditioning film or coating that is made up of protein material. In addition to the properties of the substratum, the cell surface also plays a crucial role. A bacteria's ability to attach may be impacted by flagella, fimbriae or glycocalyx. Researchers found that the presence of flagella facilitated the attachment of gram-negative bacteria to surfaces.

#### 2.2.2. Biofilm Growth

When cells are embedded irreversibly to surfaces, they divide to form microcolonies and make extracellular polymers (EPS) that form a biofilm. Chemical analysis or electron microscopy can be used to examine these polymers. These EPS are the building blocks of the biofilm. Biofilms contain water channels that facilitate the supply of oxygen and nutrients to the cells that are growing in them. In addition to minerals, biofilms can also serve as filters that attract host components, such as fibrin and platelets, such as protein materials. Detachment of cells from a biofilm occurs from cell growth and division or from the removal of the biofilm. When the host factors are favorable, such as low immunity, these detached cells can cause systemic infection.

#### 2.2.3. Biofilm's Formation In Relation to Antimicrobial Resistance

According to Ceri *et al.*, the formation of a biofilm reduces the pathogen's susceptibility to antimicrobial treatment [31]. It is this property that allows biofilms to persist in a hostile environment. Biofilms can withstand 100 - 1000 times higher concentrations of antimicrobials and biocides than planktonic cells. Williams *et al.* showed that *S. aureus* biofilms require > 10 times the maximum binding capacity (MBC) of vancomycin for a reduction of 3-logs [32] [33]. Antimicrobial tolerance of bacterial and fungal biofilms is mediated by numerous mechanisms. These may be intrinsic (related to biofilm mode of growth) or acquired (resulting from the acquisition of resistant plasmids). Biofilms exhibit intrinsic antimicrobial resistance for at least three reasons. An antimicrobial agent must first diffuse through the EPS matrix to reach and inactivate microorganisms within a biofilm. EPS slows the diffusion of antimicrobial molecule either by chemically reacting with them or by impeding their penetration. The study Anderson *et al.* conducted revealed that EPS pseudomonas aeruginosa is capable of binding tobramycin [34]. Additionally, biofilm-associated organisms have a reduced growth rate, minimizing the rate at which anti-infective agents are absorbed into the cells. Duguid *et al.* found Staphylococcus epidermidis biofilms were more susceptible to infection when they exhibited rapid growth rate [35]. Furthermore, the biofilm may act as a protective environment for the organism it contains.

Plasmids can be exchanged in biofilms under favorable conditions, resulting

in acquired resistance. A plasmid is an extrachromosomal DNA circle that encodes resistance to antimicrobials. It may encode resistance to b-lactams, tetracycline, aminoglycosides, or sulphonamides. It has been demonstrated that several bacteria can transfer plasmids to other bacteria.

Biofilms provide a means by which pathogens evade the host's immune system. The immune system of the host is less likely to recognize microorganisms in biofilms *in vitro*. *A. baumanii*, for instance, can thrive in desiccation for number of weeks, making it possible for infection to spread within the health care setting. The inability to control biofilm formation and growth in central venous catheters necessitates the use of treatments that inhibit biofilm formation. Using antimicrobial coated CVCs to prevent biofilm growth is a novel method of preventing biofilm growth. In addition, if CVC is necessary, its duration must be reduced in order to avoid unnecessary catheterization.

## 3. Associated Pathogens with Central Line Associated Bloodstream Infection

The microorganisms associated with catheter related-bloodstream infections are usually resident flora of the skin at the site of insertion which migrate to the catheter during catheter placement and cause catheter colonization. Catheter tip colonization is mostly observed in critically-ill patients in the ICU and is the major cause of BSI, sepsis and septic shock, and multi-organ dysfunction MODS [36].

### 3.1. Bacterial Infection

A study done in China by Yu He *et al.*, to identify common pathogens associated with the development of CLABSI, showed that the gram-negative bacteria were the predominant among the isolated bacteria (44%), the gram-negative bacteria were *A. baumanii* (19.8%), *and pseudomonas aeruginosa* (9.8% (**Figure 1**)). Other gram-negative microorganisms isolated were *K. pneumoniae*, *and Enterobacter.* Colonization of CVCs by *Acinetobacter* is the most common microorganisms in China and it may be related to larger proportions of patients with CVCs in ICU. The common Gram-positive bacteria isolated on CVCs were *S. epidermidis* (11.3%), and *S. haemolyticus* (9.2%) [37].

### 3.2. Fungal Infection

A China scan study done by Bo Hu *et al.* found that 9.86% of candidemia in ICU was due to CLABSI, and *candida parapilosis* was responsible for high proportion of Central line associated bloodstream infection (33.3%), followed by *Candida albicans* (28.6%) [38].

### 3.3. Viral and Parasitic Infection

SARS-COV-2 pandemic has interrupted routine practice and may have contributed to an increase in CLABSI-rates through 1) diversion of ordinary efforts to

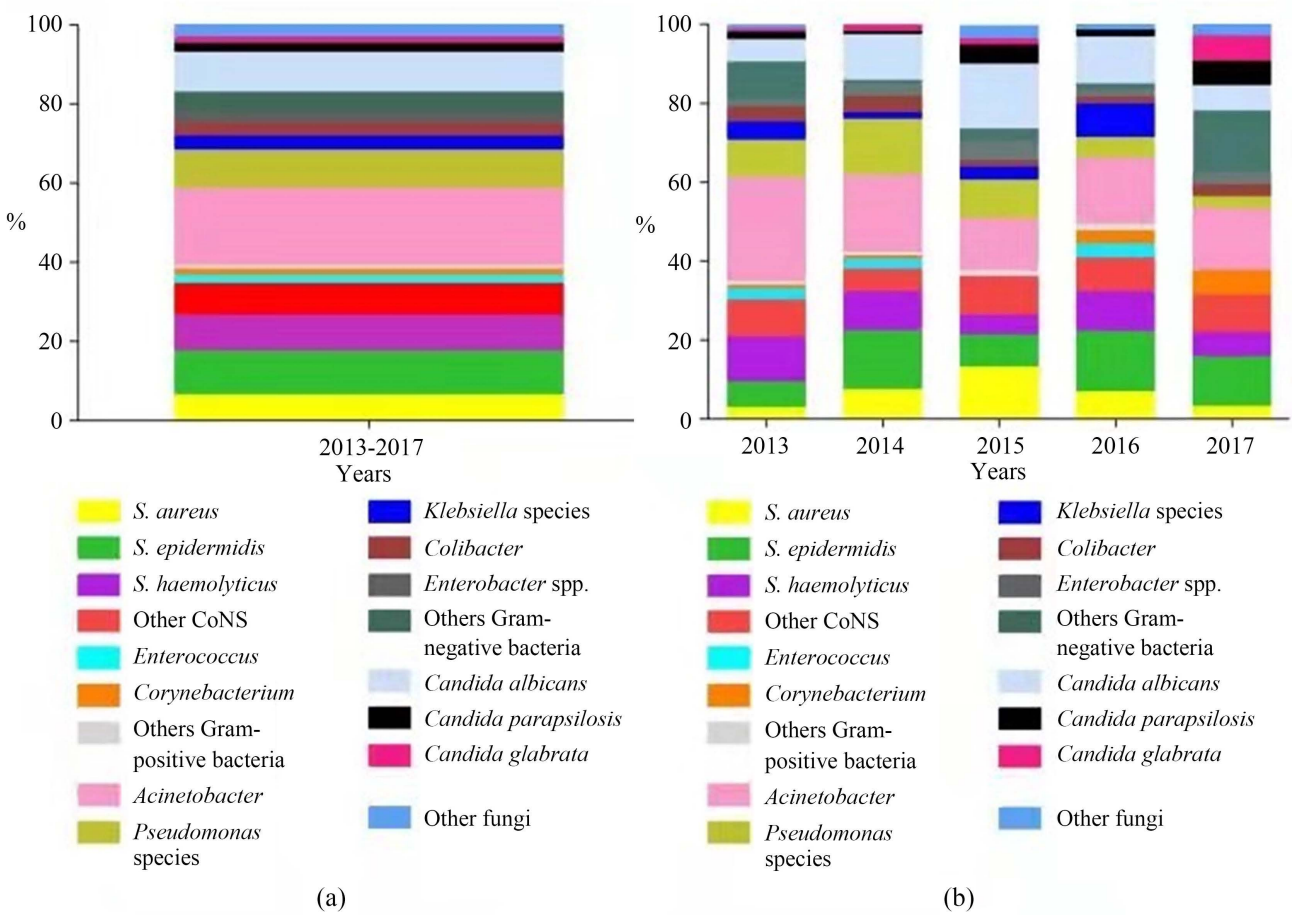


**Figure 1.** Changing epidemiology of CLABSI: bacteria and fungi isolated between 2013-2017 in China [37].

monitor and prevent CLABSI to treat COVID-19, 2) increased utilization of PPE may have led to reduced focus CLABSI prevention strategies. SARS-COV-2 (COVID-19) serves as a reminder an emerging pathogen poses a challenge for adjusting prevention measures regarding both the risk of exposure to health care workers and maintaining high level of care.

## 4. Risk Factors Associated with the Development of CLABSI

The risk of CLABSI in the ICU depends on numerous factors. Many are related to patient diagnosis and underlying health conditions; other factors are related to elective decisions made by health care professionals. Some of the common risk factors are listed below.

### 4.1. The Insertion Site

Non-tunneled CVCs are inserted in the Internal Jugular, Subclavian, and Femoral Veins. Insertion sites influence the odds of CLABSI. Studies have shown that catheters inserted in the femoral vein have a higher risk of developing CLABSI and colonization than those inserted at the subclavian site [13] [14] and most recent prospective observational studies have reported similar findings.

### 4.2. Number of Catheter Lumens

The number of lumens attached to CVCs may influence the risk of CLABSI and colonization. Gupta *et al.* compared the risks of infection between a double lumen catheter and a single lumen catheter and found the double lumen catheter to be less risky [39].

### 4.3. Concurrent CVC Use

In a study by William Dube and colleagues, patients with concurrent CVC (2 or more CVCs) were at 62% increased risk of developing CLABSI compared to patients without concurrent CVC use or with less concurrent CVC use [40].

### 4.4. Central Line Days

Studies have shown that patients with CLABSI have more central line days than those without infection [40]. Pepin *et al.* found that patients with CLABSI had a median of 5.5 central line days, while those without CLABSI had a median of 4 central line days. Patients with CLABSI spent an average of 25.3 days in the ICU, while those without infection spent an average of 8.8 days in the ICU [41].

### 4.5. Charlson Comorbidity Index Score

Patients with CLABSI had CCI > 3, while patients without CLABSI had CCI of 2, according to the study done by Pepin *et al.*, indicating that CLABSI patients have more comorbid conditions as compared to patients without CLABSI. Moreover, patients with liver disease, renal disease and cerebral vascular disease were more likely to develop CLABSI as compared to patients with no underlying diseases [41].

### 4.6. Catheter Choice/Material

Studies have shown that uncoated catheters made of Teflon or polyurethane material have been linked to fewer infectious complications compared to catheters made of polyvinyl chloride or polyethylene [42]. A recent meta-analysis done by Casey *et al.* indicated that silver coated, silver impregnated and silver-iontophoretic CVCs were associated with catheter tip colonization and CLABSI [43].

### 4.7. COVID-19 Infection

COVID-19 pandemic has increased the rates of CLABSI in the ICU by 71.0% from 0.68 to 1.16 per 1000 catheter days and by 90.7% from 2.95 to 5.63 per 10,000 patient days [44]. The result of COVID-19 is acute respiratory distress syndrome with profound hypoxia and a long duration of mechanical ventilation, both factors that contribute to the risk of CLABSI. As a result of numerous factors, including a less rigorous adherence to standard prevention strategies, disease- and therapy-related immune impairment, and prolonged mechanical ventilation and sedation periods, COVID-19 increases the risk of CLABSI. Central

line associated bloodstream infection prevention programs may have been less effective because of overcrowding in ICUs and the use of suboptimal trained health care personnel.

### 4.8. Medical Personnel Behavior and Education Intervention

It has been observed that catheter placement by less experienced health care professionals is associated with higher risk of catheter colonization and BSI [42]. Moreover lack of compliance with practices known to reduce/prevent CLABSI is also a risk factor, Coopersmith *et al.* performed an audit on the compliance in their surgical ICU with the best practice principles to prevent CLABSI and found that hand hygiene practice before catheter insertion was poor, only 13% of doctors and nurses washed their hands prior catheter placement procedure, moreover, a sterile drape was used only in 50% of catheter placement [45].

## 5. Diagnosis of CLABSI

### 5.1. Clinical Presentation

Local symptoms: include exit site infection. They may present with signs of *inflammation*, *purulence* and *Frank induration*/*erythema* > 0.5 *cm* at the insertion site [46]. The vast majority of CLABSI occur without local signs and the absence of those signs is no reassurance against diagnosis of CLABSI in a febrile patient.

### 5.2. Systemic Symptoms

The clinical presentation of CLABSI includes, 1) Fever, 2) Chills [47] [48], 3) unstable hemodynamics where the systolic BP < 90 mmhg or decrease of SBP by 40 mmhg from baseline or mean BP of 65 mmHg in the absence of no other cause of hypotension.

### 5.3. Laboratory Examination of CLABSI

1) Procalcitonin: The parathyroid gland produces this polypeptide of calcitonin, which is responsible for calcium homeostasis. PCT has effects on a variety of inflammatory conditions, such as burns, trauma, and infection. It has recently been recognized as a biomarker for infections caused by various microorganisms [49]. Human PCT is usually low in healthy individuals, but it tends to increase in severe infections, such as sepsis. PCT has shown to be able to differentiate between bloodstream infections and systemic inflammatory syndrome in pediatric patients [50]; however, it is unable to distinguish bloodstream infections from non-infectious causes of systemic inflammatory syndrome in critically ill patients [49]. PCT is one of the most crucial biomarkers for BSI [51], recent studies have shown that it was used as a rapid diagnostic marker for children with catheter-related bloodstream infection [49].

2) C-reactive protein: It is a liver-derived acute phase protein secreted after IL-6 secretion. Immediately after inflammation occurs, CRP levels rise rapidly and peak after six hours. After 48 hours, CRP levels are at their highest. In addi-

tion to contributing to the complement system, CRP plays a role in bacterial opsonization as well as phagocytosis. Its drawback is that CRP can rise in non-inflammatory states such as post-acute myocardial infarction and diseases with rheumatic origin.

3) Interleukin-6: It is released by T cells and macrophages in response to a pathogen or injury as an inflammatory cytokine. It has been used to predict severity and clinical outcomes in cases of bloodstream infection [52] [53]. The cytokine is not a specific biomarker for bloodstream infections since it can also be elevated in other conditions.

4) Full blood picture to check the levels of WBC.

5) Serum Lactate levels.

6) Traditional Culture methods for the diagnosis of CLABSI.

In the event of suspicion of CLABSI arises patients should have peripheral and central venous blood collected where 20 - 30 ml of peripheral venous blood and 10 - 20 ml of central blood are taken within 10 minutes apart and inoculated into the aerobic and anaerobic blood culture bottles then incubated as soon as possible (within 4 hours).

Incubation typically lasts five days for most microbes. In order to determine whether isolated microorganisms are different from each other or indistinguishable, they must be characterized using standard laboratory techniques.

CLABSI can be diagnosed using paired qualitative (measured using differential time to positivity, DTP) and/or using paired quantitative (measured using pour plates) blood cultures from peripheral vein and from the catheter.

For DTP (paired qualitative method), this is the time difference between the positive result of blood cultures collected simultaneously from the CVC and peripheral blood [50]. The culture bottle is injected with 10 ml of venous blood under aseptic conditions. In order to perform this test, a minimum of four samples are required, two from central venous catheters and two from peripheral veins. The samples are loaded into the blood culture machine according to the machine's instructions. The blood culture system records the time of loading and positivity for each bottle in accordance with the programmed positivity parameters. CLABSI is diagnosed when the blood collected from the CVC is at least two hours (120 minutes) earlier than the blood collected from the peripheral vein at the same time. The DTP method is also accurate in diagnosing CLABSI in patients who have long-term catheters. If the CVC is the source of bacteremia, blood cultures from the CVC will have a higher inoculum than blood taken from the periphery. As a result, they should show evidence of microbial growth sooner. There are several advantages to this method, including its sensitivity of 86% - 92% and its specificity of 79% - 87% in diagnosing CLABSI, so it is more accurate compared to the quantitative method therefore it is more accurate in diagnosing CLABSI than the quantitative method [50] [54]. Additionally, this method is cost-effective, as most microbiology laboratories are capable of determining DTP. One disadvantage of this method is its incapability to distinguish

CRBSI from non-CRBSI in patients who have been initiated on antibiotics [55]. Secondly, DTP is controversial when it comes to diagnosis of Central line associated bloodstream-candidemia. Previous studies showed that DTP is 85% sensitive and 82% specific for the diagnosis of CLABSI (50). However, other studies were found to have poor specificity (40%) for the diagnosis of CVC-candidemia [56].

The pour plate method (paired quantitative methods) involves injecting 1 ml of venous blood into 3 mL of 1% liquid containing brain heart infusion broth, preparing the Columbia agar base, cooling it to 55˚C, mixing gently, and pouring it into a petri dish, where it is then aerobically incubated for five days at 35 - 37 degrees Celsius., and colony growth is observed, for five days [57]. If the same organism is isolated from blood sampled from the catheter hub as well as blood sampled from the peripheral vein, and the colony count in the CVC collection is three times higher than in the peripheral blood sample collected percutaneously, CLABSI has been diagnosed [48]. To diagnose CLABSI with a CVC *in-situ*, expats recommend obtaining blood cultures from both the CVC and peripheral blood in order to compare before initiating antibiotics. Among the advantages of this method is its specificity of 98% - 100% and sensitivity of 74% - 84% when diagnosing CLABSI in patients with long term catheters [54]. Therefore, it has the best diagnostic accuracy and is recommended internationally. Its disadvantage is that it uses a small volume of blood to test for CLABSI, so it cannot replace conventional blood cultures as part of the work-up for fever of unknown origin.

Blood culture methods have several disadvantages, including: 1) small blood volume; this limit diagnostic yields, studies have shown that the rate of isolation increases with the volume of blood collected. This is especially important for pediatric patients, where it is not possible to collect enough blood for a culture. 2) To reduce the chance of false negative samples caused by delaying the incubation of samples, ideally blood cultures should be loaded onto the continuous monitoring instrument as soon as possible. 3) Fastidious microorganisms and antibiotic therapy; blood cultures are not sensitive enough to detect slow-growing, fastidious microorganisms and uncultivable microbes, these includes mycobacteria, nocardia etc. 4) Turnaround time; the turnaround time for pathogen identification is usually long.

7) Molecular testing techniques to diagnose CLABSI.

PCR and electrophoresis: VYOO: The test is based on PCR multiplexing. The system consists of nucleic acid extraction from clinical specimens, high order multiplex PCR, and post-PCR curve analysis. When a positive blood culture result is obtained in the culture system, 100 ul of broth from a positive blood culture is diluted with 500 ul of dilution buffer, then 300 ul is injected into a film array for analysis. A minimum of 30 different types of bacteria can be detected with this technique. Furthermore, it can identify at least five antibiotic resistance markers. It has a sensitivity of 3 - 10 CFU/ml for detecting microorganisms. A

turnaround time of eight hours is required [58]

- Advantage of this technique: it can identify 35 bacterial species including *S. aureus*, *S. pyogens*, *S. pneumoniae*, *E. fecalis*, *E. cloacum*, *K. pneumoniae*, *proteus mirabillis*, *H. influenza*, *S. martophilia*, *N. meningitidis*, *B. fragilis*, *Burkhoderiacepacia*, etc., it can also identify six fungal species *including C. albicans*, *C. parapilosis*, *C. tropicalis*, *C. gibrata*, *C. krusei*, *Aspegillusfumigatu*s, can also identify five antibiotic resistant markers. This method removes > 90% of human DNA and therefore increases the sensitivity of detecting pathogens. This method also has an 8-hour turnaround time.
- Disadvantage: This method is not effective at detecting microorganisms from blood culture bottles that have polymicrobial growth [59].

PCR and sequencing: In this PCR machine, the target is a conserved region of a pathogen's genome, specifically the 16S rRNA gene of bacteria and the 18S rRNA gene of fungi. It can detect bacterial or fungal infections in four hours by sequencing their rRNA genes (16S or 18S) [58].

- Advantages: This method has superior sensitivity to traditional blood culture to detect bacteremia and fungemia by 88.5% and 83.5% respectively [60]. It can identify cultivatable and non-cultivatable species and non -viable bacteria from patients who are already on antibiotics
- Disadvantage: This method is more sensitive when used in conjunction with culture methods, especially in the case of polymicrobial growth [60].

Real-time PCR: This PCR machine can detect 25 different types of bacteria, including staphylococcus aureus and coagulase negative staphylococci [58]. Using dual fluorescence resonance energy transfer probes, the assay targets DNA regions specific for each species.

- Advantages: Quick turnaround time (4 - 6 hours). Reduces contamination due to its real-time format.
- Disadvantage: Extremely expensive and unable to detect mild bacteremia [61].

High throughput sequencing: Using high throughput DNA sequencing technologies, metagenomics is a novel field that examines large amounts of data. They are studies that are culture independent of the set of pathogenic genomes found in consortia that can exist in all kinds of environments. Microbials that weren't detected in blood cultures can now be detected with this method [58].

- Advantages: Can detect polymicrobial infections and diverse microbes without having to isolate and culture microbes.
- Disadvantages: It is highly expensive, requires bioinformatics skills, and requires extensive knowledge of biostatistics analysis, currently only used by research laboratories.

8) Sample type

Peripheral blood: Peripheral blood cultures should be obtained if CVC-tip cultures are positive for *S. aureus* [62]. It has been shown that a positive culture of the tip of a central venous catheter for *Staphylococcus* is often accompanied with subsequent positive blood cultures. Bacteremia caused by *S. aureus* is often associated with the development of septic complications [36] [63]. In most cases,

catheter colonization with *Staphylococcus aureus* is generally associated with bacteremia that may occur between 24 and 48 hours after removal of the CVC [36]

Blood pooling from Multiple lumen catheters: IDSA's current guidelines do not recommend culture of more than one lumen of CVCs. It is nevertheless possible to miss as many as 37.5% of CLABSIs if only one lumen of a multi-lumen catheter is cultured [64]. Furthermore, one third of CLABSI could be missed if all lumens of a multi-lumen catheter are not cultured [65]. In order to save costs and avoid missing the diagnosis of CLABSI [62], blood from all lumens could be gathered into a single culture bottle [66].

Catheter-tip segment: IDSA guidelines recommend catheter cultures to be performed only when there's suspicion for CLABSI. For short term CVC only the 5-cm tip of the catheter segment should be cultured by roll-plate technique [67]. When the catheter infection is suspected and there's catheter exit site exudate, expats recommend the drainage should be swabbed and collected for culture and Gram staining. Growth of >15 colony forming unit (CFU) form a 5cm segment of the catheter tip by roll plate (semiquantitative) or growth of $>10^3$ colony forming unit from a catheter tip by quantitative broth culture, diagnosis of catheter colonization is confirmed [68].

Venous subcutaneous ports for long-term catheters: Exit site exudate: If catheter related infection is suspected and there's exit site exudate, swab the drainage to obtain sample for gram staining, culture and sensitivity

9) Imaging.

Ct scan examination: Experts suggest the use of Ct-scan in the presence of bacteremia or fungal infection due to CLABSI that lasts longer than 3 days even after initiation of antibiotic/anti-fungal treatment. CLABSI can lead to local and systemic infections which include skin and soft tissue infection, suppuration at the CVC access site, septic emboli to the pulmonary arteries and endocarditis if *S. aureus* is involved [68] [69].

Transesophageal echocardiography: Patients who have persistent bacteremia due *S. aureus* that lasts longer than 3 days even after initiation of antibiotics, have high risk of infective endocarditis and septic emboli, transesophageal echocardiography is recommended in these patients. Other conditions are patients who are in hemodialysis, patients with implantable ports, prosthetic devices, IVD users, and patients with VHD.

A definitive diagnosis of CLABSI, as preferred by Infectious Disease Society of America (IDSA), requires one of the following criteria: growth of the same pathogen from a quantitative blood culture drawn from a CVC and from a peripheral vein, with a single bacterial colony count of at least 3-fold in the sample from the central line as compared from that of a peripheral vein or the same pathogen isolated from percutaneous blood culture and from quantitative (>15 colony forming units) culture of the catheter tip or a shorter time to positivity (DTP) of >2 hours earlier in the CVC sample than peripheral sample

[48].

A definitive diagnosis of CLABSI, as preferred by Center for Disease control (CDC)-isolation of a pathogen from a blood culture (a single blood culture for organisms which is not a skin commensal, and two or more blood cultures for organisms which are skin commensals) in a patient who had CVC at a time of infection or within 48 hours before the onset of infection. The infection cannot be associated to any other infection the patient might have, and must not have been present when the patient was admitted in the facility [70]. Most often in ICU, Prompt removal of CVC is done if the patient develops fever of unknown etiology. Moreover, when a physician makes a decision to remove a CVC based on clinical grounds, he/she is often wrong. Establishing a diagnosis of CLABSI based on clinical symptoms and findings is extremely difficult, especially in an intensive care unit where the presence of unexplained fever in critically-ill patients is a daily challenge. A study was done in Belgium by Rijnders *et al.* where they developed a clinical guideline to limit unnecessary removal of CVC for suspected CLABSI. It was discovered that watchful waiting may reduce unnecessary catheter removal by 62%, and removing the catheter was only necessary when the patient becomes hemodynamically unstable, develops bacteremia, or after 5 days of observation [71]. Infectious Disease Society of America (IDSA) guidelines proposed that non-tunneled CVCs should not be removed in patients with moderately to severe disease [48].

Catheter colonization is the growth of >15 colony forming unit from a 5 cm segment of a catheter tip by semiquantitative (roll plate), or growth of $>10^3$ colony forming unit from a catheter by quantitative (sonication) broth culture [55]. Semiquantitative methods of catheter culture are preferred for short term catheters. In long term catheters, growth of <15 colony forming units/plate of the same microorganism from insertion site culture and catheter hub culture suggests that the catheter is not the source of bloodstream infection.

Catheter colonization can be diagnosed by either *semi quantitative* (*roll plate*) method or *quantitative method* (vortex or sonication).

The roll plate method or semi quantitative: Method requires catheter removal, and the tip or 5-cm segment is aseptically cut, then rolled back and forth in blood agar plate for 4-time, then the plate is incubated for up to 48 hours and colony forming units are counted. Growth of >15 CFU is considered catheter tip culture positive, the advantages of this method is that it is fast and easy to perform therefore it a famous technique for catheter cultures, the disadvantage of this method is that it only cultures the organisms that are present on the external surface of the catheter, therefore it is possible to miss out the microorganisms that are present within the lumen of the catheter.

Quantitative culture of the catheter segment: This method requires flushing the catheter segment with broth, or centrifuging or sonicating or vortexing with broth followed by serial dilutions and surface plating on blood agar [72]. The process of sonication and flushing of the lumen increases diagnostic accuracy

[73]. Growth of $>10^2$ CFU is considered significant. The predictive value of semiquantitative or quantitative methods of catheter culture depends on the catheter insertion site, culture methodology used and the source of catheter colonization [74], e.g., a catheter inserted < 1 week is likely to be colonized by skin commensals therefore the roll plate method will be sensitive in identifying such colonization. As the use of antibiotic coated catheters become more prevalent, the existing definition of catheter colonization and catheter related bloodstream infection may need to be modified since such coatings may lead to false negative results [75].

## 6. Management of CLABSI

When CVC-bacteremia is suspected or fungaemia, empiric antibiotics should be initiated after obtaining appropriate cultures. The choice of antibiotics is based on patient's demographics, known or suspected microorganism causing colonization and bloodstream infection, the local epidemiology and distribution patterns. Use **Figure 2** below.

## 7. Prevention of CVC-Related Infection

The CDC identifies catheter-related complications as one of its safety healthcare challenges [76]. There are several existing guidelines and recommendations

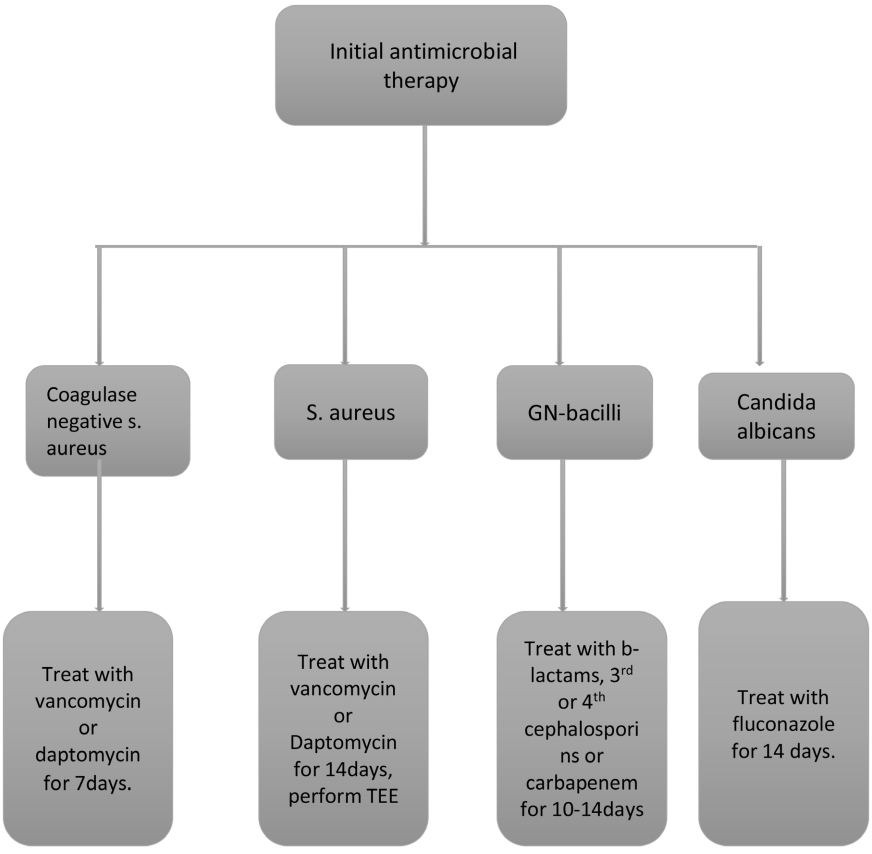


**Figure 2.** Treatment algorithms for CLABSI associated with short term CVCs.

on the prevention of Central line associated bloodstream infections. This chapter has summarized the basic principles for prevention of CLABSI into three groups: before CVC insertion, during the CVC insertion and after the CVC insertion.

### 7.1. Before the CVC Insertion

Implementing a checklist of indications and contraindications for CVC use will reduce unnecessary central venous catheterization [77].

A comprehensive educational program to educate health care providers about catheter insertion, maintenance, and care, and to ensure all health care providers involved in catheter care attend and complete the program on what can be done to lower the risk of CLABSI, and to establish competence before putting the catheter in place independently [78] [79] [80]. Experience and competency of the physician are important factors, as studies show that the risk of CLABSI is inversely proportional to the skills of the physician [43]. Furthermore, simulation training for proper catheter placement during residency is highly beneficial [81].

### 7.2. During the CVC Insertion

ICUs must have a protocol to ensure adherence to infection prevention best practices at the time of catheter placement, e.g. a checklist [82]. The use of checklists has been suggested in various guidelines and studies for ensuring safe insertion practices. It is recommended to ensure that aseptic techniques are maintained by the supervision of a nurse/physician who has been trained on prevention strategies to reduce CLABSI [82]. In the case of failure to observe aseptic techniques during catheter insertion, the nurse or physician supervisor has the authority to stop the procedure, except in emergency situations [82] [83].

Hand hygiene with alcohol-based hand rubs or antimicrobial soaps (containing antiseptics) and water before catheter placement or manipulation is recommended [84].

Solutions/hand rubs containing alcohol are effective against gram-positive and gram-negative bacteria as well as certain pathogens, such as MDR Staphylococcus aureus, MTB, and certain viruses, such as HIV virus encapsulated viruses. Furthermore, alcohol has been proven to reduce bacterial counts on hands [84].

It is not recommended to catheterize the femoral vein in obese adult patients when the procedure is elective [85] [86].

There are controversies regarding the infectious and noninfectious complications between the different access points for CVCs, There have been varying results between studies [16] [86]. CVC insertion must be weighed against these risks and benefits, e.g., inserting the CVC in the jugular venous access may increase the risk of infectious complications if a tracheostomy is present [87].

A catheter kit must be available and easy to access in ICUs and other units that use CVCs, including the use of all materials necessary for aseptic catheter placement [82].

Point-of-care ultrasounds (POCUS) have been advocated in recent studies to

confirm catheter placement and to evaluate post catheterization complications [88].

Placement of central venous catheters under ultrasound guidance has been shown to reduce risks of infectious and non-infectious complications [89] [90] [91]. Studies have shown that ultrasound guidance reduces the risk of pneumothorax and arterial injuries, deep venous thrombosis and pulmonary embolism. Using USS to locate the vein reduces failure rate and saves time.

Maximum barrier precautions: Use maximum barrier precautions when placing a catheter, which include a mask, a cap, sterile drape, sterile gown, and sterile gloves. There is evidence that using maximum barrier precaution methods reduces CLABSI rates in acute care settings [80] [92].

Skin antisepsis with an alcoholic chlorohexidine solution [84] [93].

The major predisposing factor for catheter-related BSI is the density of pathogens at the site of catheter insertion. Preparation of the skin with chlorohexidine is one of the prevention methods [94]. There is evidence that chlorohexidine solution reduces catheter-related infections [95]. According to a randomized trial comparing 10% povidone-iodine, 70% alcohol, and 2% chlorohexidine solution, chlorohexidine was superior in preventing catheter related infections [73] [96].

Application of chlorohexidine solution containing 0.5% chlorohexidine gluconate at the skin insertion site is advised [97]. A synergistic effect between chlorohexidine and alcohol is responsible for its efficacy [97]. Povidone-iodine also showed synergistic effects in a RCT comparing 10% aqueous povidone-iodine solution with 5% povidone iodine solution 70% ethanol for skin antisepsis. The incidence rates of catheter colonization were significantly low in the alcohol povidone-iodine combination than in the povidone iodine alone [98]. Chlorohexidine aqueous solution appears to be superior to povidone-iodine in reducing infectious complication rates and should therefore be used as a first-line antisepsis for central venous catheter care, although more clinical trials are needed to confirm these results. Antimicrobial/antisepsis coated CVCs should not offer benefits in prevention of CLABSI in adult patients [94].

Among the measures proposed to reduce CLABSI rates, is the utilization of antiseptic (chlorohexidine-silver sulphadiazine) coated CVCs or antimicrobial (minocycline-rifampin) coated CVCs [94]. However, some studies suggest that the use of antimicrobial/antiseptic CVC may have no benefit in reducing CLABSI rates [99]. A RCT done to compare antimicrobial coated CVCs with standard CVCs, showed no reduction in risk of CLABSI expressed per 1000 catheter days regardless of the use of antimicrobial-coated CVCs, no reduction in the risk of catheter related local infections regardless of antimicrobial coated CVCs use [100].

### 7.3. After Catheter Insertion

To ensure adequate number of nurse-to-patient ratio and avoid the use of float nurses.

Reduction of nurses below the critical level has shown to contribute to the increase in incidence rates of CLABSI [101] [102] [103] [104].

Studies proposed that there should be a ratio of 1 to 2 nurses in ICUs where nurses are managing patients with central venous catheters and that the number of float nurses should be kept minimal.

To disinfect catheter hubs, connectors, and injection ports prior to catheter assessment [105].

Aseptic procedures are very important during catheter assessment. Catheter tubing or catheter manipulation must be done only after washing hands with alcohol hand-rub. Hubs and ports should be disinfected with chlorohexidine solutions prior assessments [106]. Prolonged catheterization increases the risk of catheter related infection from frequent assessment of catheter hubs rather than catheter insertion site. Frequent manipulations of the central line catheters especially in aseptic conditions increase the risks of CLABSI.

Non-essential catheters should be removed [107].

Daily assessment of continued need of the catheter should be done and once the catheter is no longer required for medical management, it's removal should be considered.

Chlorhexidine impregnated dressing should be used to prevent central venous catheter related bloodstream infections.

A randomized control trial which included 1636 adults found that the application of chlorhexidine dressing placed over central venous catheters reduced the risk of central venous catheter related bloodstream infections from 1.3 infections per 1000 catheter days to 0.5 infections per 1000 catheter days [108], another study conducted by the same team on 1879 patients found that the application of chlorhexidine gel impregnated dressing placed on central venous catheters reduced the risk of central venous catheter related bloodstream infections from 1.3 infections per 1000 catheter days to 0.5 infections per 1000 catheter days [109].

A Meta-analysis that combined four studies also showed that the application of chlorhexidine impregnated sponge placed on central venous catheters reduced risk of central venous catheter-bacteremia (OR 0.51; 95% CI [0.33 - 0.78]) and catheter colonization (OR 0.58; 95% CI [0.47 - 0.73]) [110].

To perform surveillance in an intensive care unit settings and non-ICU settings [111].

Surveillance networks have been associated with the decrease rates of infection [112]. There are several examples that have been published in literature that on setting up prevention programs [82] [113].

Catheter lock prophylaxis for preventing infectious and thrombotic events.

This is a technique by which central venous catheters lumens are flushed with antibiotics solution, over a certain period of time in order to achieve high antimicrobial concentrations, therefore preventing or treating catheter related infections. This procedure is done in patients with long term catheters, or patients with previous history of catheter related bloodstream infections. Antibiotics that

have been used for these procedures include vancomycin, gentamycin, minocycline, these antibiotic solutions are in combination with anticoagulants e.g., heparin thus preventing long term infections [114] [115]. In a recent meta-analysis done by Zachariodakis *et al.* conducted on twenty-three studies on adult patients, pediatric and cancer patients who were receiving TPN, it was found that the application of antibiotic lock prophylaxis was associated with 69% reduction in CLABSI rates and infection on the catheter exit site [116]. The use of antibiotic lock solutions on short-term catheters is questionable because studies that have been conducted to assess the efficacy of this technique on short-term catheters are lacking [117].

## 8. Conclusion

CLABSI is the commonest among HAI. It is one of the most frequent, fatal and costly complications of central CVC insertion in the ICU settings, CLABSI lead to increased morbidity and mortality among critically-ill patients. A timely diagnosis and treatment are essential for reducing mortality and morbidity. The prevention of CLABSI is guided by national guidelines, and central lines should be checked daily. Technologies for diagnosing and preventing infections directed at CVCs, which have been shown to reduce CRBSI incidence, are discussed in this paper, including antiseptic and antibiotic-impregnated catheters and dressings, new hub models, and antibiotic lock solutions.

## Conflicts of Interest

Authors declare that there's no conflict of interest

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