

Catheter-related bloodstream infections

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ABSTRACT

Central-venous-catheter-related bloodstream infections (CRBSIs) are an important cause of hospital-acquired infection associated with morbidity, mortality, and cost. Consequences depend on associated organisms, underlying pre-morbid conditions, timeliness, and appropriateness of the treatment/interventions received. We have summarized risk factors, pathogenesis, etiology, diagnosis, and management of CRBSI in this review.

Key Words: Antibiotic lock therapy, *Candida*, catheter related bloodstream infections, Central-venous-catheter, *Staphylococcus*

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INTRODUCTION

Catheter-related bloodstream infection (CRBSI) is defined as the presence of bacteremia originating from an intravenous catheter. It is one of the most frequent, lethal, and costly complications of central venous catheterization and also the most common cause of nosocomial bacteremia. Intravascular catheters are integral to the modern practices and are inserted in critically-ill patients for the administration of fluids, blood products, medication, nutritional solutions, and for hemodynamic monitoring. Central venous catheters (CVCs) pose a greater risk of device-related infections than any other types of medical device and are major causes of morbidity and mortality. They are also the main source of bacteremia and septicemia in hospitalized patients. Majority of CRBSIs are associated with CVCs and in prospective studies, the relative risk for CRBSI is up to 64 times greater with CVCs than with peripheral venous catheters.

Epidemiology of catheter related bloodstream infections

Based on the North American data compiled from the National nosocomial infection surveillance system (NNIS) from October 1986 to December 1990, CRBSI incidence was 2.1 per 1000 catheter days for respiratory Intensive Care Units, 5.1 for medical-surgical ICUs, 5.8 for trauma ICUs, 30.2 for burn units.^[1] More recent data from NNIS from January 1992 through June 2004 showed the median rate of CRBSI in ICUs of all types ranged from 1.8-5.2 per 1000 catheter.^[2] According to Leonardo Lorente *et al.*, (2005) incidence of CRBSI was 2.79 infections per 1000 catheter days, among which CVC were responsible for 2.09% of cases.^[3] According to

S Singh *et al.*, (2010) the overall infection rate for CRBSI was found to be 0.48 per 1000 device days.^[4] According to Ramanathan Parameswaran *et al.*, (2011) the incidence of CRBSI was 8.75 per 1,000 catheter days.^[5] Incidence of CRBSI reported varies from country to country and even hospital to hospitals. Meta-analytical study done at The Johns Hopkins University showed that bloodstream infections (BSIs) were the third leading cause of hospital-acquired infections. These infections have an attributable mortality rate of 12% to 25%.^[6] Individuals counteract 250,000 BSIs each year in the U.S., 60% of CRBSIs were caused by micro-organisms from the patient's skin. CRBSIs often originate in emergency rooms and intensive-care units, where 5.3 bloodstream infections occur per thousand days of central venous catheter insertion.^[7] Intravenous catheters were the devices most frequently used for providing fluids directly into the bloodstream. Although the incidence of local or BSIs associated with these devices is usually low, serious infectious complications produce a considerable number of deaths annually because of the frequency with which such catheters are used.

CRBSI accounts for 10% to 20% of hospital-acquired infections in the UK and is associated with both increased ICU stay and mortality. Rates of CRBSI may be modified by clinical care during insertion and utilization of CVCs.^[8] As such, the incidence of CRBSI has been proposed as a quality indicator. The incidence of CRBSI varies considerably by type of catheter, frequency of catheter manipulation, and patient-related factors, such as underlying disease and severity of illness. Majority of CRBSIs are associated with CVCs, and in prospective studies, the relative risk for CRBSI is up to

64 times greater with CVCs than with peripheral venous catheters. For short-term CVCs (<10 days),^[9] which are most commonly colonized by cutaneous organisms along the external surface of the catheter, the most important preventive systems are those that decrease the extra-luminal contamination. In contrast, with long-term CVCs (>10 days), endo-luminal spread from the hub appears to be the primary mechanism of infection. Technologies that reduce endo-luminal colonization in addition to extra-luminal invasion of the catheter should provide additional protection against CRBSI. The incidence of dialysis-related CRBSI is reported to be 2.5-5.5 cases per 1,000 catheter days, or 0.9-2.0 episodes per patient-year.^[10] The risk of bacteremia is highest in hemodialysis patients using a CVC for vascular access, and increases in a linear fashion with the duration of catheter use.^[11] Most nosocomial BSIs among pediatric patients are related to the use of an intravascular device and in critically-ill neonates, the incidence of CRBSI can be as high as 18 cases per 1000 catheter-days^[12] [Figure 1].

Risk factors

Potential risk factors for CRBSI include underlying disease, method of catheter insertion, site of catheter insertion and duration, and purpose of catheterization. The administration of parenteral nutrition through intravascular catheters increases CRBSI risk. Local risk factors, such as poor personal hygiene, occlusive transparent dressing, moisture around the exit site, *S. aureus* nasal colonization, and contiguous infections support the role of bacterial colonization in the pathogenesis of CRBSI. Other risk factors for dialysis CRBSI include contamination of dialysate or equipment, inadequate water treatment, dialyzer re-use, older age, higher total intravenous iron dose, increased recombinant human erythropoietin dose, lower hemoglobin level, lower serum albumin level, diabetes mellitus, peripheral atherosclerosis, and recent hospitalization or surgery. CRBSI rate varies considerably in different studies.^[13]

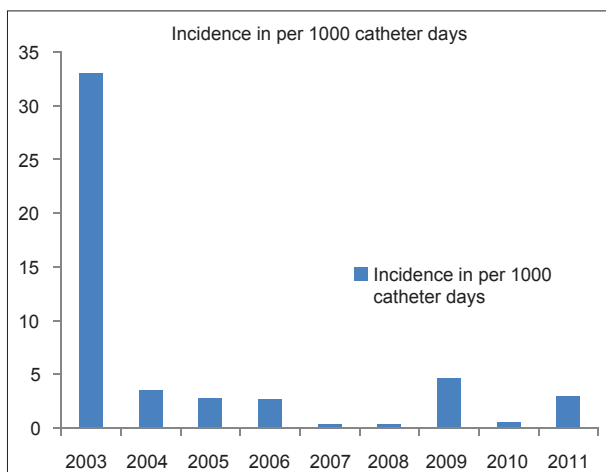


Figure 1: Changing epidemiological trend of CRBSI

Pathogenesis of catheter related bloodstream infections

Several interrelated factors have been proposed to participate in the pathogenesis of CRBSI. The catheter itself can be involved in 4 different pathogenic pathways like colonization of the catheter tip and cutaneous tract with skin flora; colonization of the catheter lumen caused by contamination; hematogenous seeding of the catheter from another infected site; and contamination of the lumen of the catheter with infusate [Figure 2]. Resistance to antibiotic therapy due to biofilm formation also has an important role in development of bacteremia. It is important to know that a negative catheter-related sample rules out CRBSI better than a positive sample indicating one. When the blood culture obtained from the catheter is positive, but the percutaneous blood sample is negative, it indicates colonization of the catheter rather than CRBSI. However, if the organism is *S. aureus* or *Candida*, or if patient has valvular heart disease or neutropenia, close monitoring is required, which includes evaluation for infective endocarditis and metastatic infection.

Catheter related bloodstream infections associated micro-organisms

The organisms associated with CRBSI are usually the normal resident flora of the skin at the insertion site, which may lead to colonization of the catheter inserted. Colonization of the tip of the intravenous catheter is often observed in the ICU practice and can be the source of dangerous bacteremia (CRBSI) and sepsis with multi-organ failure [Figure 3].

Bacterial infections

In the study of Ramanathan Parameswaran *et al.*, (2011) 64% of the pathogens causing CRBSI were Gram-positive and 36% were Gram-negative. The commonest pathogen causing CRBSI was *S. aureus* 40%, *Pseudomonas aeruginosa* 16%, coagulase negative staphylococci 8%, *E. coli* 8%, *Klebsiella pneumoniae* 8%, and *Acinetobacter baumannii* 4%.^[5] According to Krishnan *et al.*, (2011) Gram-positive cocci constituted 27% of isolates and gram-negative bacilli were 56%. The proportion of Gram-negative CRBSI was much higher than that reported in western hospitals.^[14] Seifert *et al.*, (2003) showed coagulase-negative staphylococci were present in 50% cases of CRBSI in their study.^[15] In the study of Almuneef *et al.*, (2006) of total 50 CRBSI episodes, 48% were polymicrobial, 32% were due to Gram-negative bacilli, and 10% were due to Gram-positive organisms. The most common organisms isolated were *Klebsiella pneumoniae* 16%, coagulase-negative staphylococci 14%, and *Pseudomonas aeruginosa* 11%.^[16]

Fungal infection

Various studies have showed different rates of fungal infectious agents responsible for CRBSI, these are mainly yeasts, and no filamentous fungus has been reported. In the study of Ramanathan Parameswaran *et al.*, (2011)

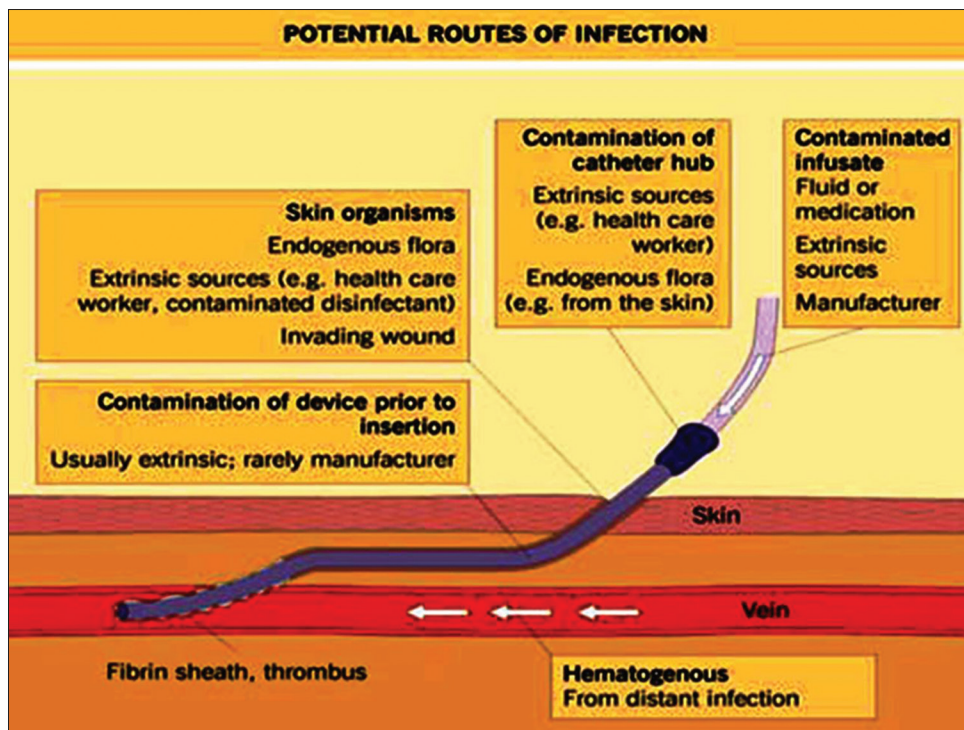


Figure 2: Potential routes of infections causing CRBSI

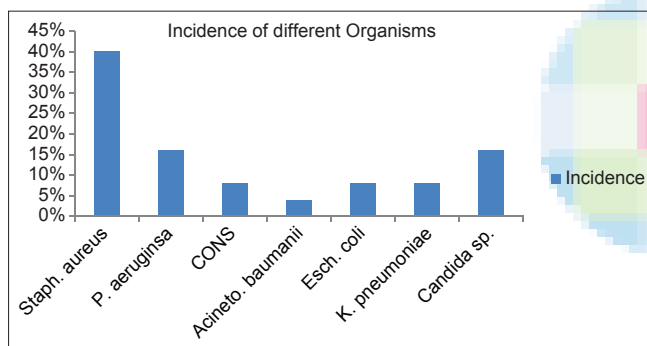


Figure 3: Causative organisms of CRBSI

16% of infectious agents were *Candida sp.*,^[5] according to Pawar *et al.*, (2008) fungal pathogen isolated from CVC was *Candida* 11.7%,^[17] and Chopdekar *et al.* (2011) showed non-albicans *Candida spp.* in one case.^[18]

Viral and Parasitic infections

The CRBSI organisms are usually skin flora, which is mainly bacteria and yeasts, very less is known about normal viral and parasitic skin flora, and no study has shown any viral or parasitic cause of CRBSI.

Catheter related bloodstream infections detection

Detection of CRBSI includes both clinical as well as laboratory examination.

CLINICAL PRESENTATION

The diagnosis of CRBSI is often suspected clinically in a patient using a CVC who presents with fever or chills, unexplained hypotension, and no other localizing

sign.^[19,20] Mild symptoms include malaise and nausea, and severe symptoms include high fever with rigors, hypotension, vomiting, and changes in mental status in the setting of a normal catheter exit site or tunnel, on physical examination.^[21] Exit-site infection is indicated by the presence of erythema, swelling, tenderness, and purulent drainage around the catheter exit and the part of the tunnel external to the cuff. Severe sepsis and metastatic infectious complications, such as infective endocarditis, septic arthritis, osteomyelitis, spinal epidural abscess and septic emboli, can prolong the course of CRBSI^[22] and should be considered in patients who do not respond appropriately to treatment. Infective endocarditis should be suspected in those patients with onset of new cardiac murmur, repeatedly positive blood cultures, and other features of the modified Duke criteria. A clinical diagnosis can be made after exclusion of alternative sources of infection.^[19]

Laboratory diagnosis of catheter related bloodstream infections

The diagnosis of CRBSI requires a positive culture of blood from a peripheral vein and clear evidence that the catheter is the source. CRBSI means a patient with an intravascular catheter has at least one positive blood culture obtained from a peripheral vein, clinical manifestations of infections (i.e., fever, chills, and/or hypotension), and no apparent source for the BSI, except the catheter. In addition, one of the following is also present: A positive semi-quantitative (>15 CFU/catheter segment)^[23] or quantitative (>10³ CFU/catheter segment)^[24]

catheter tip culture also, the same organism (species and anti-biogram) is isolated from the catheter segment and peripheral blood culture. Simultaneous quantitative paired blood cultures with a >5:1 ratio CVC versus peripheral, or differential time to positivity, whereby a non-quantitative blood culture drawn from the CVC that becomes positive at least 2 hr earlier than the peripheral blood culture, is a new method for the diagnosis of CRBSI without removing the catheter^[15] [Table 1].

Quantitative paired blood culture

CRBSI is defined as a quantitative blood culture ratio of >5:1 (CVC versus peripheral) with proven identity of isolates from positive peripheral and CVC blood cultures confirmed by pulsed-field gel electrophoresis. CRBSI can be diagnosed when colony counts are at least 3-fold higher in cultures of blood obtained via the CVC than in cultures of blood taken from a peripheral vein. The fold difference between the CVC and peripheral blood varies in the literature with suggested cut offs from 3-fold to 10-fold. To diagnose CRBSI with the CVC *in situ*, most experts recommend comparative blood cultures obtained via the CVC and a peripheral vein prior to initiating antibiotics. Cultures should be obtained from all lumens of the CVC, it is the most specific method of diagnosing CRBSI. If a blood sample cannot be drawn from a peripheral vein, it is recommended that 2 blood samples should be drawn through different catheter lumens, and the colony count for the blood sample drawn through one lumen is at least 3-fold greater than the colony count for the blood sample obtained from the second lumen should be considered to indicate possible CRBSI.

Differential time to positivity

CRBSI is suggested when blood from the CVC demonstrates microbial growth at least 2 h earlier than growth is detected in blood collected simultaneously from a peripheral vein. Most currently used automated blood culture systems can readily provide this information, and it is likely that this will become a standard diagnostic test.

Short-term catheters, including arterial catheters

For short-term catheter tip cultures, the roll plate technique is recommended for routine clinical microbiological analysis.^[25] For suspected pulmonary artery catheter infection, the introducer tip is cultured.^[26]

Long-term catheters

Semi-quantitative growth of 15 cfu/catheter segment of the same microbe from both the insertion site culture, and the catheter hub culture strongly suggests that the catheter is the source of a bloodstream infection. A venous access subcutaneous port is removed for suspected CRBSI, and the port is sent to the microbiology laboratory for qualitative culture of the port reservoir contents, in addition to the catheter tip.^[27]

Management of catheter related bloodstream infections

Regular ICU rounds by clinical microbiologists and bed-side discussion with intensivists regarding infection management. Prompt communication of urgent microbiology results.

Assessment of infection

This constitutes the central objective of the clinical microbiology round in ICU so that diagnostic, therapeutic,

Table 1: Different microbiological methods to detect CRBSI

Method	Diagnostic criteria	Advantages	Disadvantages	Sensitivity (%)	Specificity (%)
Simultaneous quantitative blood cultures	Blood culture via catheter yields CFU $\geq 3 \times$ higher than CFU via peripheral vein	Recommended by the IDSA Defines CLA-BSI Does not require catheter removal	Very labor intensive Costly	93	97-100
Differential time to positivity of blood culture via catheter versus peripheral vein	Blood culture via catheter turns positive ≥ 2 h before simultaneous culture from peripheral vein	Recommended by IDSA Defines CLA-BSI Does not require catheter removal Data currently available with most automated blood culture systems	Use of antibiotics via catheter (or use of lock) may impair interpretation	89-90	72-87
Quantitative blood culture via catheter	Blood culture via catheter is ≥ 100 CFU/mL	Does not require catheter removal	Unable to differentiate between CLA-BSI and high grade bacteremia	81-86	85-96
Acridine orange leukocyte cytospin	Presence of any organisms	Does not require catheter removal	Limited data of utility	87	94
Endoluminal brush	Quantitative culture > 100 CFU/mL	Does not require catheter removal	Limited data of utility May precipitate arrhythmia, embolization May cause bacteremia	95	84
Semiquantitative culture of catheter tip	≥ 15 CFU/mL from 5-cm segment of catheter tip (reflects catheter colonization)	Recommended by IDSA Defines catheter colonization (same organism isolated from peripheral vein defines CLA-BSI) Available in most hospital labs	Requires catheter removal Most obtain Semi-quantitative catheter segment aseptically Does not allow culture of intra-luminal organisms	45-84	85

CRBSI: Catheter-related bloodstream infection, CFU: Colony Forming Unit, IDSA: Infectious Disease Society of America, CLA-BSI: Central Line Associated Blood Stream Infection **Source:** (1) Raad I, Hanna H, Maki D. Intravascular catheter-related infections: Advances in diagnosis, prevention, and management. *Lancet Infect Dis* 2007;7:645-57. (2) Eggimann P. Diagnosis of intravascular catheter infection. *Curr Opin Infect Dis* 2007;3:53-9. (3) Mermel LA, Alon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Disease Society of America. *Clin Infect Dis* 2009;49:1-45.

and infection control interventions can be initiated at the earliest. Assessment of infection has to be a broad-based approach relying on an entire gamut of historical, epidemiological, clinical, diagnostic parameters (physical examination, hematological, biochemical, radiological) along with microbiology results.

Infection prevention and control

This consists of microbiology result interpretation and feedback to intensive care unit team regarding anti-microbial resistance, audit and policy implementation, rational utilization of diagnostic, therapeutic and infection prevention/control resources.

General Management

Catheters should be removed from patients with CRBSI associated with any local or systemic inflammation or immunocompromised condition. Antibiotic therapy for catheter-related infection is often initiated empirically. The initial choice of antibiotics will depend on the severity of the patient's clinical disease, the risk factors for infection, and the likely pathogens associated with the specific intravascular device. There are no compelling data to support specific recommendations for the duration of therapy for device-related infection. Vancomycin is recommended for empirical therapy for methicillin-resistant *Staphylococcus aureus*; for vancomycin minimum inhibitory concentration values $>2 \mu\text{g/mL}$, alternative agents, such as daptomycin, should be used. Linezolid should not be used for empirical.^[28] Empirical coverage for Gram-negative bacilli should be based on local anti-microbial susceptibility data and the severity of disease (e.g., a fourth-generation cephalosporin, carbapenem, or β -lactam/ β -lactamase combination, with or without an aminoglycoside). In addition to coverage for Gram-positive pathogens, empirical therapy for suspected CRBSI involving femoral catheters in critically-ill patients should include coverage for Gram-negative bacilli and *Candida* species.^[29] For empirical treatment of suspected catheter-related candidemia, echinocandin is used or, in selected patients, fluconazole.^[30] Antibiotic lock therapy should be used for catheter salvage; however, if antibiotic lock therapy cannot be used in this situation, systemic antibiotics should be administered through the colonized catheter.^[31]

Antibiotic lock therapy and its use to treat patients with catheter-related infection

Recurrent bacteremia after parenteral therapy is more likely to occur if that therapy is administered through a retained catheter than if the catheter is removed.^[32] This likely reflects the inability of most antibiotics to achieve therapeutic concentrations needed to kill microbes growing in a biofilm. Because the majority of infections involving long-term catheters or totally implanted catheters are intra-luminal, eradication of such infections is attempted by filling the catheter lumen

with supra-therapeutic concentrations of antibiotics and leaving them indwelling for hours or days, thereby creating an antibiotic lock. Antibiotic lock therapy for CRBSI is used in conjunction with systemic antibiotic therapy and involves installing a high concentration of an antibiotic, to which the causative microbe is susceptible in the catheter lumen. The likelihood of success varies with the site of infection (e.g., tunnel or pocket infection are unresponsive to salvage) and with the microbe causing the infection (e.g., coagulase-negative staphylococci are likely to respond; *S. aureus* is not).

CONCLUSION

Catheter-related bloodstream infection (CRBSI) is the commonest cause of nosocomial bacteremia. CRBSI is one of the most frequent, lethal, and costly complications of central venous catheterization. CVCs are commonly associated with hospital-acquired bloodstream infections and lead to both increased ICU stay and mortality. Early diagnosis and treatment are vital to reduce the morbidity and mortality involved. National guidelines exist on the prevention of CRBSI, these should be followed, and central venous catheter must be reviewed daily. Different measures have been implemented to reduce the risk for CRBSI, including use of maximal barrier, precautions during catheter insertion, effective cutaneous anti-sepsis, and preventive strategies based on inhibiting micro-organisms originating from the skin or catheter hub from adhering to the catheter. Institution of continuous quality improvement programs, education, and training of health care workers, and adherence to standardized protocols for insertion and maintenance of intravascular catheters significantly reduced the incidence of catheter-related infections and represent the most important preventive measures. New technologies for prevention of infections directed at CVCs, which have been shown to reduce the risk of CRBSI, including catheters and dressings impregnated with antiseptics or antibiotics, new hub models and antibiotic lock solutions, are in use.

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