

Mucosal Barrier Injury Laboratory Confirmed Bloodstream Infections

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Abstract

Purpose of Review To increase the awareness of the new CDC survey definition of Mucosal Barrier Injury Laboratory-Confirmed Bloodstream Infection (MBI-LCBI). We included a comparison of the definition of Central Line-Associated Bloodstream Infection (CLABSI), with a high sensitivity but low specificity and Catheter-Related Bloodstream Infection (CRBSI). There are other parameters like the difference between the size of the inoculum (catheter lumen vs peripheral), that increased specificity and is useful for research and clinical decisions. Also, MBI-LCBI secondary to bacterial translocation in patients who had received myeloablative chemotherapy with severe neutropenia is not related to central venous catheter care.

Recent findings This new survey definition is useful for better classification of nosocomial bloodstream infections among patients receiving myeloablative chemotherapy and has impacted diminishing the incidence of CLABSI, which has probably has been overestimated in patients with hematological malignancies. The concept of MBI-LCBI should not be limited to survey purposes; it is also useful for clinical decisions. We propose to incorporate a second set of blood cultures obtained 48 hours after antibiotic treatment onset, one through the line of the CVC and another one at a peripheral site; if negative, it avoids unnecessary removal of the catheter in patients with severe neutropenia or, on the contrary, if positive blood cultures persist after 48 hours of antimicrobial therapy, there is a clear indication for central venous catheter removal.

Summary The definition of MBI-LCBI avoids over-diagnosis of CLABSI in patients receiving myeloablative chemotherapy with severe neutropenia.

Introduction

The initial worries that infections were produced as a result of health-care workers performing therapeutic or diagnostic procedures started centuries ago. Holmes and Lister described this phenomenon, in which the main point was to identify the event and count it; to achieve this, they needed a definition of the episodes. Semmelweis, Nightingale, Simpson and Meleny compared the occurrence between different groups of the infection events; they included statistical analysis in their observations.

Hospital epidemiology as we know it today, started in 1950s to respond to the pandemic of staphylococcal infections in surgical and pediatric units in Europe and North America. At the end of this decade, bacteremia by Gram-negative bacilli was recognized as a major public health problem [1].

Epidemiological surveillance was developed in order to count the number of cases and, further on, understand the mechanisms that lead to the so-called hospital acquired infections and establish preventive policies to diminished them.

The Centers for Disease Control and Prevention (CDC) provided definitions to standardize the surveillance and try to make the events between institutions comparable, and make possible the evolution of preventive interventions.

Bloodstream infections (BSI) occurring during the care of patients is a major threat to their lives, besides increasing hospital length of stay and healthcare costs. The definitions of the different types of BSI have been modified over time, when the differences in the pathophysiology of the events have been identified. This allows us to understand which of these BSI are really preventable and directly related to the clinical care processes, such as those related to: infusion therapy, hub manipulation, central venous catheter (CVC) installation and care, amongst others.

In 1988, CDC definitions of nosocomial BSIs divided them into two categories [2]: primary and secondary bacteremia.

Primary BSI was defined as the recovery of bacteria from blood without any recognizable focus of infection at the time of positive blood cultures. In 1988, definitions of

bacteremia episodes secondary to intravenous or arterial lines were classified as primary bacteremia.

Secondary BSI was defined as the isolation in blood of the same microorganisms identified at an infection site in another part of the body with an infection. In this classification, septic thrombophlebitis was considered secondary bacteremia to an intravenous line. Contaminated IV infusion was also considered secondary bacteremia.

This classification created confusion, because there were points like "blood cultures obtained through arterial or venous cannula were discouraged because of the risk of obtaining a contaminated culture", and, on the other side, it was stated that "the site to obtain blood-cultures must be carefully chosen and thoroughly cleansed", but at that time, no maximum barrier protection was recommended to obtain blood cultures.

There are two definitions used for BSI in patients with CVC for survey of nosocomial BSI: Central line associated bloodstream infection (CLABSI) established by the CDC through the National Healthcare Safety Network (NHSN) in 1996, and a clinical definition for Catheter-related blood stream infection (CRBSI) proposed by the Infectious Diseases Society of America (IDSA) (Table 1) [3,4]. CRBSI is a definition based on clinical and laboratory criteria that is used in research studies and clinical grounds for therapeutic decisions. CRBSI requires a specialized microbiological laboratory, that is not available in all centers, with quantitative or qualitative blood cultures to evaluate inoculum size or the difference in the time to positivity (TTP) between blood cultures obtained through the line of the catheter and from a peripheral vein, a method that has proved useful to identify a catheter as the source of bacteremia [5–11]. In contrast, CLABSI is a simplified definition used to identify bloodstream infections in patients with CVC in whom there is no other known source of bacteremia. This definition is used for surveillance by Infection Prevention Programs to track rates and pathogens over time. The CLABSI definition aimed to be highly sensitive but its disadvantage is that it overestimates the incidence of CRBSI.

Diagnostic consideration of CLABSI vs. CRBSI

Different diagnostic technics had been used over time for the diagnosis of infection in patients with IV lines. The Maki-semiquantitative method for the

Table 1. Bloodstream infection definitions in patients with a central venous catheter

Type		Definition	Objective in Target Population
CRBSI*	IDSA	Clinical signs of sepsis and positive peripheral blood culture in absence of an obvious source other than CVC with 1 of the following: 1. Positive semiquantitative (>15CFU) or quantitative (>10 ³ CFU) culture from the tip of the catheter segment with the same organism isolated peripherally 2. Simultaneous quantitative blood cultures with a ratio of ≥3:1 (CVC vs peripheral) 3. Time to culture positivity difference of more than 2 hrs between CVC and peripheral cultures	Clinical care in patients with CVC
CLABSI €	CDC	Laboratory confirmed bloodstream infection in a patient who had a central line within the 48 hrs period before the date of event	Surveillance in patients with CVC
MBI-LCBI1 €	CDC	Pathogen identified from one or more blood specimens, by a culture or non-culture method, that is not related to an infection at another site with isolation of only intestinal organisms. (e.g., <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Enterococcus faecium</i> , etc.) And patient meets at least one of the following: 1. Is an allogeneic hematopoietic stem cell transplant recipient within the past year with a. Grade III or IV GI GVHD b. ≥1 liter diarrhea in a 24-hour with onset on or within 7 calendar days before the positive blood specimen. 2. Has ANC or total WBC <500 cells/mm ³ for two days within a 7-day time (the day of positive blood specimen, 3 days before and 3 days after)	Surveillance in patients with mucosal barrier injury
MBI-LCBI2 €	CDC	Pathogen identified from one or more blood specimens, by a culture or non-culture method, that is not related to an infection at another site with isolation of only viridans group streptococci. And patient meets at least one of the following: 1. Is an allogeneic hematopoietic stem cell transplant recipient within the past year with a. Grade III or IV GI GVHD b. ≥1 liter diarrhea in a 24-hour with onset on or within 7 calendar days before the positive blood specimen. 2. Has ANC or total WBC <500 cells/mm ³ for two days within a 7-day time (the day of positive blood specimen, 3 days before and 3 days after)	Surveillance in patients with mucosal barrier injury

ANC: Absolute neutrophil count, CDC: Centers of Disease Control and Prevention, CFU: Colony forming units, CVC: Central venous catheter, CLABSI: Central line associated bloodstream infection, CRBSI: Catheter-related bloodstream infection, GI GVHD: Gastrointestinal graft versus host disease, IDSA: Infectious Diseases Society of America, MBI-LCBI: Mucosal barrier injury laboratory confirmed bloodstream infection, WBC: white blood cell count.

*Mermel L, Allon M, Bouza E, et al. Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection: 2009 Update by the Infectious Diseases Society of America. *Clinical Infectious Diseases* 2009;49:1–45.

€ Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central Line Associated Bloodstream Infection) from <https://search.cdc.gov/search/?query=mbi-lcbi&utf8=%E2%9C%93&affiliate=cdc-main>. Accessed February 10th, 2018.

diagnosis of CRBSI has extensively been used in the past, but its great limitation is the loss of the catheter [12, 13]. Other diagnostic strategies were explored including the quantitative blood-culture obtained from a peripheral vein and through-the-line of the catheter; the criterion used for CRBSI has been the differential concentration of microorganisms (size of the inoculum) that is three to five times higher than the peripheral blood culture (catheter/peripheral vein) [5–11, 14–16].

The introduction of automatized qualitative blood-cultures in the early 1990s became a major diagnostic tool, as quantitative blood-cultures (Isolator) once considered the most reliable method, was a costly and time consuming process. The time to positivity obtained during incubation of the bottles is inversely correlated to the inoculum size, and could be compared depending the site from which the blood cultures were obtained. Although the usefulness of blood cultures obtained through-the-line of the catheter, has been questioned, in order to evaluate a possible false positive result of these samples, it is important to know the care taken in obtaining the specimen.

The survey of CLABSI at the Instituto Nacional de Cancerologia (INCan) in Mexico City, (a referral oncological center for adult patients) with an intravenous therapy team working with trained nurses and standardized catheter care procedures [17–19] incorporated a modified CRBSI *definition to standardize surveillance and maximize sensitivity*.

The diagnostic criteria for CRBSI are divided accordingly if the patients are ambulatory or hospitalized. We have been using qualitative blood cultures and, as a standard, we use a maximum barrier to obtain them. The site and order on how they were taken, with the time and the date of the procedure should be correctly labeled on each bottle. TTP is recorded for each bottle.

For ambulatory patients with a long-indwelling line, besides the above, at least one of the following four criteria should be met:

- 1) A positive blood culture from the catheter and the first peripheral culture negative, or positive peripheral blood cultures with the same bacteria but with a difference TTP >2 h longer than through the catheter.
- 2) Clinical signs of bacteremia (shivers and / or fever) developed after manipulation of the catheter during or after heparin or fluids flushing.
- 3) Outpatients with CRBSI can complain of fever or shivering after catheter use (heparin flushing, after starting IV infusion) without other sites of infection.
- 4) Semi-quantitative catheter tip culture with the same bacteria isolated from blood.
- 5) Same microorganism isolated from insertion catheter site and from blood.

In hospitalized patients they should have at least one of the other four criteria using the standard criteria described before:

- 1) A positive blood culture from the catheter and the first peripheral culture negative, or positive peripheral blood cultures with the same bacteria but with a difference TTP >2 h longer than through the catheter.
- 2) No other source of infection in a patient with a central venous catheter.
- 3) Semi-quantitative catheter tip culture with the same bacteria isolated from blood.
- 4) Resolution of symptoms after removing the catheter.

- 5) Same microorganism isolated from insertion site and from blood.
- 6) In neutropenic patients, if new blood cultures at 48 hours remain positive and the same microorganism persists in patients receiving antibiotics for whom the bacteria is susceptible, it is considered to be a CLABSI.

Mucosal Barrier Injury Laboratory-Confirmed Bloodstream Infection

Pitter stated in the early 1990s that medical therapy can have unexpected adverse effects on patients, mentioning that some agents could be toxic to mucosal cells lining the gastrointestinal tract, causing a disruption in mechanical barriers, which in turn, allows bacterial invasion [20].

Oral mucositis was recognized as a significant complication in patients receiving therapy for cancer; the injury to oral mucosa secondary to decrease cell renewal, epithelial thinning leading to ulceration, and secondary infection in parallel to reduced myeloproliferation, and neutropenia, were leading to infection [21]. Further on, mucositis affecting the entire gastrointestinal mucosa was recognized as an inevitable side-effect of the intensive conditioning therapy used for hematologic stem cell transplantation. In 2000 Blijevens [22••] presented an overview of the pathobiology of mucosa barrier injury, in both the oral and the gastrointestinal tract. This model has four successive phases: (1) inflammatory, followed by (2) an epithelial phase, leading to (3) an ulcerative/bacteriological phase, and ultimately (4) a healing phase. The onset and duration of mucositis mirrors the course of neutropenia [23].

In the first phase, radiation and/or cytotoxic drugs induce systemic release of pro-inflammatory cytokines that increase the expression of histocompatibility (HLA) antigens and critical adhesion molecules that amplify local injury. Villous blunting, apoptosis and brush border loss are manifestations of intestinal damage.

In the epithelial phase, rapid dividing of mucosa cells (the entire epithelium is renewed in 4 to 6 days) is interfered with by cytotoxic drugs and/or radiation, leading to mucosal atrophy, thinning and necrosis.

In the ulcerative-bacteriological phase, the normal microbiota that habitually contributes to maintain the integrity of the integument and prevents pathogenic bacteria from gaining a foothold, is lost. Once the mucosa is damaged, bacteria can invade the submucosa, and translocation can occur. The rate of translocation of enterobacteria like *Escherichia coli* and other Gram-negative bacilli such as *Pseudomonas aeruginosa* is strongly associated with the degree of neutropenia [24].

In the healing phase, the repair of mucosal barrier injury depends on the severity of the damage and parallels the hematologic recovery of peripheral blood cells count.

All chemotherapeutic regimens cause significant mucosal barrier dysfunction, in part through tight junction proteolysis, although Idarubicin has been identified as the agent that produces a more pronounced and prolonged dysfunction [25–27].

CLABSI and the impact on healthcare reimbursement

The National Healthcare Safety Network (NHSN) receives the reports of CLABSI. This data is public, and it is used as a measure of health care quality,

but also to determine reimbursement through Medicaid and Medicare services. It was increasingly recognized that in certain populations, CLABSI definition lacked specificity, particularly among patients receiving chemotherapy that produce mucosal barrier injury [28, 29].

Cancer patients are a special population with frequent use of CVC and decreased immunity due to the underlying disease and/or the use of myeloablative chemotherapy. CLABSI reports are likely to differ in oncological and non-oncological hospitals [30]. Higher CLABSI rates in cancer can result from more frequent use of central lines and from a population at higher risk of infection, but also because the definition overestimates the real CVC related infections [30, 31].

A modification of the NHSN BSI definition, proposed a new type of BSI: Mucosal Barrier Injury Laboratory-Confirmed Bloodstream Infections (MBI-LCBI), Table 1 [32].

MBI-LCBIs are those BSI that meet the NHSN definition for CLABSI but are not associated with central venous catheter care, and are integrated into primary BSI for surveillance.

The MBI-LCBI definition includes: (1) A microorganism known to be commensal of the oral cavity or gastrointestinal tract. The microorganisms included in this definition are *Bacteroides spp.*, *Candida spp.*, *Clostridium spp.*, *Enterococcus spp.*, *Fusobacterium spp.*, *Pepto streptococcus spp.*, *Prevotella spp.*, *Veillonella spp.*, or *Enterobacteriaceae* and, (2) occurred in a patient with signs and symptoms compatible with mucosal barrier injury. (Table 1)

In a field test of this new NNHS definition, 282 CLABSI, 103 (36.5%) met MBI-LCBI criteria. *Enterococcus faecium* (16%), *E. coli* (14.9%), *Klebsiella spp.* (7.4%), and *viridans Streptococci* (7.4 %), were the most frequent microorganisms isolated; only 9% occurred in patients with allo-HSCT in the previous year. Ninety-four (91%) met the neutropenia criteria, 77% of them with single ANC of less than 100 cells/mm³ [33••]

This definition, developed for surveillance purposes, needs additional criteria to increase its usefulness in clinical practice in order to avoid the removal of a central line that it is usually of great value for the patient.

At the INCan we are performing prospectively a diagnostic tool to improve therapeutic decisions for patients that meet the MBI-LCBI definition. This consists in those febrile neutropenic patients that have a central venous line with positive blood cultures taken before starting an empirical antimicrobial therapy, a second set of blood cultures through the CVC line (each lumen of the catheter), and a peripheral vein are taken 48 hours later. If the second blood cultures are negative, the catheter is not removed. If control blood cultures persist as positive with the same microorganism, when the antimicrobial treatment used has been reported susceptible to the identified bacteria, the catheter is removed and considered CLABSI.

What is the impact of MBI-LCBI in bloodstream surveillance?

The inclusion of the MBI-LCBI definition in oncological centers, particularly in the hematologic services, has diminished the incidence rate of CLABSI in the population that receives myeloablative chemotherapeutic regimes [34].

In a retrospective study analysis, when the MBI-LCBI definition was applied to CLABSI cases in a group of cancer patients, 71% were reclassified as MBI-LCBI [35•]. In this study, the incidence of CLABSI not meeting the MBI-LCBI definition decreased after a targeted intervention was introduced to improve central line care and maintenance, but not for those classified as MBI-LCBI.

At INCan we performed a retrospective analysis of nosocomial bloodstream infections (NBSI) from 2013 to 2015, to evaluate how many of these episodes fulfilled the MBI-LCBI definition. There were 338 episodes of NBSI identified by regular surveillance. Thirty-one (9.2%) were classified as secondary bacteremia, 134 (39.6%) as CLABSI, and 163 (48%) as primary bacteremia; of the latter, 116 (34%) fulfilled MBI-LCBI criteria, which represents 71% of all primary bacteremia. In this series, 107 (92.2%) patients had a hematologic malignancy, 63% had acute leukemia; and only five cases had an allo-HSCT. Eight percent had a solid tumor, with germinal nonseminoma (3.5%) the most frequent. The chemotherapy regimens that preceded the episode of BSI were: 25.9% Hyper-CAVD (Course A: cyclophosphamide, vincristine, doxorubicin (also known by its trade name, Adriamycin), and dexamethasone. Course B consists of methotrexate and cytarabine); 8.6% 7+3; 14.7%, FLAG-IDA (idarubicin, fludarabine, cytarabine, G-CSF); 5.2% R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone), and 4.3% HiDAC (High dose intermittent ARA-C). This shows that highly myeloablative chemotherapy impacts in the occurrence of BSI in this population. We propose that the incidence of MBI-LCBI should be reported per type of chemotherapy, particularly for highly myeloablative regimens. Many of these episodes do not occurred while the patients were hospitalized, but a high percentage of patients presents at the Emergency Room because of fever, days after hospital discharge; so the real occurrence of MBI-LCBI can be underestimated.

What is the microbiology of MBI-LCBI?

The microbiology of MBI-LCBI is different from that of CLABSI, in the study by See [33••] *E. faecium* and *E. coli* were the most frequent microorganisms isolated (16% and 12.6% respectively), in patients that fulfilled the MBI-LCBI definition; compared to CLABSI not meeting the MBI-LCBI definition, where coagulase-negative staphylococci (18%), *Staphylococcus aureus* (10%), *Candida species non-albicans* (9.4) and *Candida albicans* (9.4%) were the most frequent. In the retrospective study at INCan we found that *E. coli* was isolated in 50.4% of the cases, *K. pneumoniae* in 6.5% and *E. faecium* in 5.7%. These microbiology findings are consistent with the findings reported in a study from the MD Anderson Cancer Center and in Japan [36]. The pattern of resistance of these isolates showed that 56% of *E. coli* and 12% of the *K. pneumoniae*, were extended spectrum beta-lactamase producers (ESBL). In a study of an outbreak of *E. faecium* BSI at an hemato-oncological ward, [37•] 72% of the 58 of the cases fulfilled the MBI-LCBI definition, not different from *E. faecium* vancomycin resistant (*VREfm*) and vancomycin susceptible strains. The rate of *VREfm* bacteremia per ten chemotherapy cycles was 1.01 for FLAG-IDA and 0.04 for Hyper-CVAD, and the one-year mortality of the whole group was 79%,

reflecting a group of patients with advanced disease exposed to therapeutic interventions, with major adverse events and high mortality risk.

Conclusions

The incorporation of the MBI-LCBI definition is important in BSI surveillance to decrease over-diagnosis of CLABSI [38•], particularly in patients with cancer, but it is also a diagnostic definition useful to the clinician when dealing with a febrile neutropenic patient with a CVC, that helps to avoid unnecessary removal or, on the contrary, a clear indication to remove a catheter.

The occurrence of MBI-LCBI, which is a serious adverse event, needs further study to evaluate its impact in health-care costs, hospital stay, morbidity and mortality among the different myeloablative regimes and their short- and long-term outcomes.

BSI is a dynamic process, in patients with cancer receiving myeloablative chemotherapy, the event can start as an MBI-LCBI, but in certain circumstances that favors persistence of bacterial translocation and continuous bacteremia, facilitating the adhesion of microorganisms to the catheter and predisposing the patient to finally develop a CLABSI; such is not related to catheter care, and, thus, it should not be taken as a measure of quality of care, this fact needs further investigation.

Compliance with Ethical Standards

Conflict of Interest

Patricia Volkow, Pamela Alatorre, Victor Hugo Lozano and Patricia Cornejo-Juarez have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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This study describes an outbreak of resistant polyclonal *Enterococcus faecium* vancomycin. Most of the cases fulfilled the MBI-LCBI definition. This outbreak was not related to nosocomial transmission but to the use of highly myeloablative chemotherapy producing long periods or prolonged neutropenia, in patients exposed to antimicrobials, significantly associated with vancomycin use

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This study shows that the introduction of MBI-LCBI decreased the incidence of CLABSI mainly in hemato-oncological patients receiving chemotherapy