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The importance of blood cultures in the effective management of bloodstream infections

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Abstract

Background: Bloodstream infection (BSI) is a major public health concern due to its severity-related consequences. These infections pose a human health risk, as they can result in human morbidity and mortality over a short period of time. Blood culture remains the gold standard and major tool for the diagnosis of BSI. Blood culture sampling is commonly indicated before administering antimicrobial therapy, whereas the daily therapeutic adjustment to the antibiogram is an effective intervention in management of BSIs. Compliance with the microbiological criteria-based protocols for pathogen identification and antimicrobial susceptibility testing allow treatment correction within 48-72 hours. Interpretation of positive blood cultures may sometimes present a dilemma for clinicians and microbiologists and, therefore, the test findings should be evaluated in the context of the clinical picture.
Conclusions: Over the last decades, we have witnessed an outbreak in the number of BSI studies. The implementation of a standardized algorithm on criteria of a complete blood count sampling, processing and interpretation of the results will help increase the yield rate of BSI pathogens and ultimately improve care management of the patients with BSI. The education and training of medical staff, engaged in BSI patient care is vital in developing good practice, preventing blood culture contamination and obtaining fast and accurate outcomes.
Key words: bloodstream infections, blood cultures, antimicrobials.

Introduction

Bloodstream infection (BSI) has become a subject of medical concern worldwide due to its severity-related consequences. BSI represents a growing public health concern, with an estimated burden of 1.200.000 episodes across Europe and 157.000 deaths annually [1].

The reviewed studies highlight the most common microbial agents involved in the aetiology of BSI, namely: *Escherichia coli, Staphylococcus aureus* and *Streptococcus pneumoniae*, with approximately 35%, 25% and 10% per 100.000 population, respectively. These studies revealed that BSI incidence varies significantly across different geographic regions, and this is largely due to timing of BC specimen collection, demographic population differences and distribution of risk factors within these regions [2].

These infections show high morbidity and mortality rates across the globe and are among the top seven causes of death in North America and Europe [3].

However, accurate data on the incidence of BSI-associated morbidity and mortality in some countries are limited, due to misdiagnosis and insufficient patient follow-up [4-8].

The risk of BSI is due to the immunocompromised human organism that might favor the invasion of various pathogens, which commonly show resistance to a number of antimicrobial groups [9, 10].

BSI diagnosis is based on the detection of bacterial and fungal pathogen isolates from the blood cultures. Over the recent decades, great progress has been made in the development of rapid diagnostic tests based on innovative technologies; BC sampling remains the gold standard for diagnosis of BSIs. This method is one of the most important techniques if any BSI-related suspicions arise. Blood, being normally sterile, has a considerable diagnostic significance in isolating and identifying bacteria or fungi from the blood cultures. It allows establishing the diagnosis for BSI by isolating and rapidly identifying the pathogen (within 2-7 days). Moreover, it guides the physician in choosing the antimicrobial therapy based on the results of Antimicrobial Susceptibility Testing (AST) of pathogen isolates to antimicrobial drugs, thereby contributing to reducing the phenomenon of antibiotic resistance [11].

Most studies have reported variations, from country to country, on recommendations for good blood culture sampling practices [12-14].

At present, there are international guidelines on the collection, processing, interpretation of blood cultures, where-

as this paper will present the rigors stipulated therein [15-18].

Despite the fact that, there are guidelines, methodologies, instructions on BC sampling, however inadequate practices continue to be registered, which exhibit an approximately 3% rate of blood culture contamination [19].

Blood culture contamination produces false-positive results, leading to irrational use of antimicrobial drugs, increased length of hospitalization and higher costs [20].

Furthermore, the authors of the studies highlight the importance of accurate diagnosis for BSI, which requires both laboratory findings on isolation of the microbial agent from blood cultures and presence of compatible clinical signs of the patient. The same studies show that the pathogen, detected as an etiological agent for BSI, should be, preferably, isolated from several blood samples. Moreover, studies recommend identifying the site of primary infection and isolating the same microbial agent from this outbreak [21].

According to some studies, in most cases, only 5 to 13% of blood cultures turn out to be positive with isolation of the microbial agents, and of those, 20–56% represent the contaminating microbial flora, despite the scientific advance in the use of skin antiseptics, which have been successful since 25 years ago, and thus, reducing the risk of contamination by 2.1-6% [22, 23].

Effective management in reducing the overall incidence of BSI is a major reason for indicating BC sampling prior to the administration of antimicrobial therapy, as well as for daily reassessment and appropriate adjustment of this therapy based on definitive pathogen identification and antimicrobial susceptibility testing to antimicrobial preparations. Since BSI patient survival is inversely proportional to time of initiation of appropriate antimicrobial therapy, it is vital to obtain the BC results as soon as possible. Therefore, early diagnosis and appropriate treatment are crucial in the efficient management of BSI. Delays in the initiation of antimicrobial treatment may lower dramatically the survival rate among BSI patients. Patients treated within the first hour of diagnosis may have a survival rate of almost 80%, subsequently, the chances of survival decrease by 7.6% for every hour after. Inappropriate initial antimicrobial treatment is likely to be fatal in these patients [5].

Key terms and definitions

Antiseptic. A substance that inhibits the growth and development of microorganisms [24].

Bloodstream infection. A bacteria or fungi-associated infection [24].

Bacteremia. The presence of bacteria in the blood. It may be transient, intermittent or continuous [24].

Transient bacteremia / fungemia. Transient presence of bacteria or fungi in the blood for a period of several minutes [24].

Intermittent bacteremia. Intermittent BSI is a "recurrent transient infection" that is associated with undrained and intra-abdominal abscesses [24].

Continuous bacteremia. Continuous bacteremia suggests a severe infection that inhibited the host's defense mechanisms. It is a characteristic of BSI, such as infective endocarditis or suppurative thrombophlebitis [24].

Pseudobacteriemia. Pseudobacteremia occurs when blood culture isolates come from outside the patient's bloodstream [24].

SIRS (Systemic Inflammatory Response Syndrome). Systemic inflammatory response syndrome features the early body response to damages of infectious or non-infectious origin [25-27].

Sepsis. Life-threatening organic dysfunction caused by impaired host response to infection [28, 29].

Septic shock. It is defined as a subgroup of sepsis, associated in particular with profound circulatory, cellular metabolism abnormalities, with a higher risk of death than sepsis [30].

Neonatal sepsis. Neonatal sepsis is defined as clinically diagnosed SIRS, caused by infection occurring within the first four weeks after birth. The incidence of neonatal sepsis increases with early-onset birth weight decrease and can be divided into two types: early-onset neonatal sepsis (occurs in the first 72 hours of life); late-onset neonatal sepsis (occurs after the first 72 hours of life) [31].

Bloodstream infections in immunocompetent patients include:

Community-acquired infection. Bacteremia and fungemia may often occur in previously healthy individuals, commonly associated with focal infections such as pneumococcal pneumonia. Moreover, bacteria can penetrate into the bloodstream from the patient's own commensal flora or from an undetectable infected site, leading to metastatic infections [31].

Hospital-acquired infection. The increased number of invasive procedures, such as catheterization, immunosuppressive therapy, antibiotic therapy and life support measures, has resulted in higher overall incidence of hospital-acquired bacteremia, candidemia and other fungal infections. These procedures may allow microorganisms to invade into the blood or weaken the host defense system [31].

Health care-associated infections (HCAIs). HCAIs are infections that occur as a result of medical assistance and treatment procedures within outpatient care units, medical offices, healthcare clinics or hospitals [31].

Anaerobic bacteremia. Studies have shown that anaerobic microorganisms make up 1-17% of positive blood cultures. Anaerobic microorganisms are a common cause of bacteremia and, therefore, routine testing should be carried out [31].

Pediatric BSI. The etiology of pediatric bacteremia has changed over the last few years. *Haemophilus influenzae type b* (Hib) infections decreased dramatically after the introduction of national immunization programs, whereas the systemic HCAIs have increased [31].

Catheter-related bloodstream infections. Intravenous catheter (IVC)-related bacteremia or fungemia are difficult to confirm. There is often no evidence of infection at the

catheter insertion site, whereas the involved microorganisms are part of the normal skin flora and common contaminants of BCs [31].

Infective endocarditis (IE). IE is defined as an infection of the endocardium, particularly involving the heart valves, characterized by functional impairment, and termed as an infection of the heart valves and / or other endocardium areas [31].

BSI in immunocompromised patients. Immunocompromised patients are individuals with acquired or drug-induced autoimmune disorders. Defects in phagocytes, complement, antibody response and cell-mediated immunity are often associated with specific disorders or conditions, such as malignancy, HIV infection, organ transplantation, immunosuppressive therapies, and steroid administration. Patients with neutropenia are at highest risk of infection [31].

Recommendations for blood culture sampling

Most of the reviewed studies highlight the importance of doctor's indication for BC sampling in patients exhibiting the following signs: septicemia, septic shock; severe localized infections (meningitis, pneumonia, intra-abdominal abscess); fever or fever history and suspected or detected neutropenia; fever and immunocompromised status; individuals undergoing invasive procedures (catheter, dialysis or surgery); fever and recent trips abroad; suspected bacterial endocarditis; syndromes, suggestive of BSIs with specific germs (enteric fever, brucellosis, leptospirosis), under certain conditions (like pregnancy, cardiac diseases, diabetes, renal failure, hepatic failure, leukocytosis, granulocytopenia) [32, 33].

However, the academic society has not come to a common denominator on the best clinical predictors for BSIs [34, 35].

Key elements and general principles for blood culture sampling

The research underlines the importance of standardization of the blood sampling procedure for microbiological investigations. Therefore, the study outcomes on the implementation of a standardized procedure of BC sampling performed under aseptic conditions , showed a reduction in the contamination rate up to 1.6% ($p < 0.001$), with a previously recorded rate of 3.9% [36]. According to another study by Self et al. (2013) on the development and implementation of a standardized set of sterile tools required for blood sampling , as well as the user's checklist, the contamination rate decreased from 4.3% to 1.7% ($p < 0.001$) [9, 37].

The studies emphasize the importance of timing blood sampling and recommend to be collected soon after the clinical signs appear and before the initiation of antimicrobial therapy. In case if, due to certain circumstances, the patient is already undergoing antimicrobial therapy, blood sampling should be carried out immediately prior to administering the next dose and by inoculating the blood into bottles containing specialized antimicrobial neutralization media. It is not recommended to collect blood through the same needle / lumen through which an antimicrobial drug has been given within the last hour. Information on previously administered antimicrobial preparations should be indicated on the laboratory application form [32, 10].

First, blood samples must be collected from the peripheral vein. Sets withdrawn from either the central or the peripheral vessels must be taken successively or at intervals of 12 hours apart. To obtain reliable BC data, the peripheral blood samples are taken first before other types of investigations [38, 17].

Some authors of the recent studies do not recommend blood sampling through the peripheral intravenous cannula. Moreover, there is also an obvious risk of contamination due to the difficulty of skin disinfection when taking blood from a femoral vein. Therefore, the authors suggest avoiding these sites and, and if no other options for sampling are available, this procedure will be carried out by documenting into the patient's sample accompanying form or clinical record [39, 40].

The study analysis reveals the number and amount of sampling, required to obtain reliable and accurate results. To optimize the yield of bacteria and fungi in the blood, an adequate amount of blood is required. A sufficient volume of blood sampling allows a better detection of small amounts of bacterial or fungal pathogens. It is essential in case if an endovascular infection (such as endocarditis) is suspected. The blood volume obtained for each BC set is the most important variable when isolating microorganisms from patients with BSIs [38].

The blood amount collected from both sampling sites must be sufficient to ensure BC accuracy, e.g. if only 10 ml of blood is obtained from the peripheral vein, additional 10 ml is taken from the central vein. When collecting blood from both central and peripheral veins, the sampling site is clearly indicated on the culture bottle and reference sheet [41].

Researchers demonstrated that blood culture bottles are designed to accommodate the optimal blood- to-broth ratio (1:5 to 1:10) and to allow maximum bacterial and fungal isolation. Commercial continuous monitoring blood culture systems may use a lower blood / broth ratio (<1:5) due to added sodium polyanethol sulfonate or sodium citrate , non-toxic anticoagulants that promote bacterial proliferation by neutralizing the bactericidal activity of human serum and inhibiting the action of some antibiotics [42].

Most studies have reported that adult bacteremia and fungemia in adults commonly develop with a reduced amount of circulating microorganisms, ranging from 1-30 colony-forming units per mL (CFU / mL) of blood. The concentration is over 100 CFU / mL in newborns, babies and older children, therefore the volume of blood sampling differs in both adults and children. For an adult, the recommended blood volume to be obtained per culture is 20 to 30 ml [32, 42, 43].

The standard indicates that BC set should include two bottles (for aerobic and anaerobic microorganisms), and about 10 ml of blood should be collected per each in adults. This volume is required to optimize pathogen isolation

when the amount of bacteria or fungi is less than 1 UFC / mL of blood. Two or three bottle sets (two bottles per set) are recommended to be used for each septic episode, viz. in adults, 40-60 mL of blood is collected for 4-6 bottles, 10 mL per each bottle [44].

Few studies have been carried out on the optimum blood volume taken from infants and children, however, the available data indicate that the yield of pathogens also increases in direct proportion to the volume of blood cultured and inoculated. Also, the recommended blood volume to be collected should depend on the patient's body weight, and only one aerobic bottle is used, if no anaerobic infection is suspected. In this context, in children under 2 years, specifically designed bottles to maintain the blood-to-broth ratio (1:5 to 1:10) are used, with smaller blood volumes [32, 45].

The researchers have shown that, as bacteria and fungi are not always present in the bloodstream; the sensitivity of a single BC set might be compromised.

The study results on the cumulative sensitivity of blood cultures, using continuous-monitoring blood culture systems for 24 hours demonstrated that four blood cultures might be needed to achieve a detection rate of > 99% in BSIs. Thus, the authors observed that the cumulative yield of pathogens from three blood culture sets (2 bottles per set) with a 20 mL blood volume in each set (10 mL per bottle) was 73.1% for the first set, 89.7% – the first two sets and 98.3% – the first three sets [46].

Most studies emphasize that, it is not generally recommended for adult patients to collect a single bottle or a single blood culture sample set since this practice will result in insufficient BC volume and failure to detect the causative agent in a considerable number of bacteremias [43].

Furthermore, international guidelines recommend collecting 2, or preferably 3 blood culture sample sets for each septic episode in order to differentiate BC contamination during sampling of true bacteremia. In case of BC contamination, the microbial flora will be present in only one bottle or a set of blood culture bottles, unlike true BSI, in which multiple bottles or sets will be positive. In case of 2-3 blood culture sets sampling, followed by a 24-48 hour incubation period, the results are negative and the patient is still septic, 2-3 additional BCs should be taken [15, 22, 42].

A number of studies have described the variety and usefulness of inoculation of blood culture media. Various BSI-causing microorganisms (aerobic and anaerobic pathogens, fungi, fastidious microorganisms, etc.) require specific growth factors and incubation conditions. In cases when a patient is administered antimicrobial therapy, specialized media with antibiotic neutralization factors should be used. Some studies have shown that media, containing antibiotic inhibitors, increase the degree of isolation and identification of pathogens in a shorter time compared to standard media [47-50].

An essential element in blood culture sampling is the sequence of bottles inoculation. Therefore, when using vacuum blood-sampling system, the blood is first transferred into the aerobic bottle to prevent transfer of air from the sampling device to the anaerobic bottle. When using a needle or syringe, the anaerobic bottle is first inoculated to avoid air ingress. If the taken blood volume is less than the recommended one, then 10 ml of blood is first inoculated into the aerobic bottle, as most bacterial cases are caused by aerobic and facultatively anaerobic bacteria. In addition, pathogenic fungi and strictly aerobic bacteria (e.g. Pseudomonas spp.) are almost exclusively isolated from aerobic bottles. Any remaining blood amount is recommended to be inoculated into the anaerobic bottle [11].

The study analysis reported that the time interval between taking two blood samples is not considered a critical factor, since the yield of diagnosis remains the same [51].

At the same time, international guidelines recommend that the first two / three blood culture sets (two bottles / set) should be obtained over a short period of time (e.g. within one hour) or as a single sample taken at one time. Blood sampling at long intervals, such as 1-2 hour intervals, is recommended when monitoring continuous bacteremia/ fungemia in patients with suspected infective endocarditis or other endovascular infections [32, 43].

In severe infections or to increase detection sensitivity (e.g. pyelonephritis), two or three additional blood culture sets are collected, in case if the first 2-3 hemocultures are negative after 24-48 hours of incubation. Moreover, the time interval depends on the suspected BSI-causing agents: the sensitivity is relatively good for such microorganisms as *Escherichia coli* or *Staphylococcus aureus*, and lower for *Pseudomonas aeruginosa, streptococci or fungi* [52].

Methods and techniques for the processing and interpretation of blood culture results

Most microbiology laboratories use incubation, automated continuous monitoring, shaking, and automated blood culture systems. Many manufacturers provide such devices with almost similar performance characteristics [53-56].

Automated systems place the BC bottles for a predetermined incubation period, giving a visual or warning signal if increase is detected. Each automated blood culture system produces its own media, which should be carefully assessed and selected by the user. The blood culture bottles typically contain culture medium approved mixtures, anticoagulants and, in many cases, resins or coal mixtures to neutralize antimicrobial and other toxic compounds. Commonly, the mixture of different substances is complementary to each other and is chosen to improve the range of bacterial life, including the fastidious microorganisms. Blood culture media formulas allow the detection of aerobes (including fungi), anaerobes and mycobacteria [51, 57, 22].

Other studies, comparing the performance of media with and without the addition of antimicrobial neutralizing agents (resins and / or coal compounds), have repeatedly demonstrated that these substances are obviously superior in the recovery of microorganisms, particularly the fastidious ones and levuriform mycetes [58-60].

Studies in the field examined the requirements for blood

culture media and highlight the most essential rule to be followed. Thus, media must be sufficiently sensitive to yield a wide range of clinically relevant microorganisms, even the most fastidious ones (e.g. .*Neisseria spp., Haemophilus spp.*) or that require lower amount of CO2 (e.g., *Brucella spp., Acinetobacter spp*.) [57, 61].

Blood cultures are usually incubated for 5 days via automated systems. Multiple studies have proven that this is an appropriate incubation period for detection of most pathogens, including the bacterial strains like *Haemophilus, Actinobacillus, Cardiobacterium, Eikinella and Kingella* (HACEK) group, whereas the incubation period over 5 days increases the number of contaminant isolates [62, 63].

However, studies emphasize that a longer incubation period is required in case of suspected fungemia or bacteremia caused by *Legionella, Brucella, Bartonella or Nocardia spp*. *Mycobacterial* and blood culture should be incubated for 4 weeks [64, 65].

Bloodstream infections of suspected fungal etiology do not require special culture media since most fungi grow on conventional aerobic media within 2 to 3 days. *Candida glabrata* and *Cryptococcus neoformans* are exceptions to this rule that usually require 3 to 5 days of incubation. *Fusarium* and *Paecilomyces* can be isolated in the conventional blood culture broth, while other filamentous fungi are not detected [61, 66].

Furthermore, there are no sufficient data on dimorphic fungi growth, such as *Histoplasma* and *Blastomyces,* which grow in blood culture broth requiring more than 2-week incubation period. Therefore, some studies recommend that slow growth of fungi and fastidious bacteria should be carried out via more specialized systems such as the lysis centrifugation system [67].

BSI-diseased patients, under certain circumstances, are often administered antimicrobials prior to sampling, thus suppressing the bacterial and fungal growth. Therefore, manufacturers of blood culture systems might complement their own media formulations with antibiotic binding resins or absorbent carbon. The analysis of these compounds characteristics has shown significant outcomes in the absorption of antibacterial and antifungal preparations, thus increasing bacterial and fungal yield rates and reducing the detection time of positive cultures [58, 68-70].

The identification of BSI causative agents can be performed by both manual technique and automated systems. This technique is initiated by taking a Gram stain, which is absolutely necessary for the management of these samples. A positive Gram stain with gram positive or negative microbial flora identification is immediately reported to the clinician in order to provide prompt antimicrobial therapy and measures of controlling these infections. Subcultures are performed later on, to allow identification and susceptibility testing to be carried out normally within the next 24–48 hours. Laboratories should have a standardized protocol to guide the lab staff activity on blood sampling in order to optimize the use of resources for complete organism identification and organism-specific susceptibility testing of clinically important organisms that are probably the contaminating flora [71, 72].

Interpretation of positive blood culture results is often simple, but sometimes presents a dilemma for both clinicians and microbiologists. Therefore, laboratory data must be evaluated in the context of clinical symptoms to achieve an accurate interpretation. A true positive blood culture result is obtained when most or all of the blood culture sets, withdrawn by independent venipuncture, are positive for the same microorganism. Thus, the probability that the isolated microorganism represents the BSI-causing agent is very high, regardless of the organism's identity [52].

The identification of microorganisms isolated from positive blood cultures is also significant, namely: *Staphylococcus aureus, Streptococcus pneumoniae, Enterobacteriaceae, Pseudomonas aeruginosa* and *Candida albicans* are almost always predictive of true BSI. However, *Corynebacterium spp.* and *Propionibacterium spp*. often represent the contaminating flora. Isolation of viridans group streptococci, coagulase-negative staphylococci (CoNS) and enterococci is more difficult to interpret, as some studies have reported that they cause BSIs in 38%, 15% and 78%, respectively. Coagulase-negative staphylococci are particularly the most common blood culture contaminants. Moreover, a number of studies have reported that these microorganisms have an obvious clinical importance in BSI etiology among patients with implanted medical devices and localized catheters. Therefore, the accurate result interpretation can be achieved, when a few sets of blood cultures are positive with the same CoNS species. Under these circumstances, the probability of these microorganisms to represent the true cause of bacteremia is much higher [73].

Rapid methods for identification and susceptibility testing of blood culture isolates responsible for BSI are crucial and may guide clinicians in decision-making on therapeutic interventions. Blood cultures incubated in modern systems commonly signal a positive result in a mean time of 12-36 hours, whereas the positive time from sampling to detection is longer for some fastidious microorganisms, anaerobes and fungi [55, 56].

According to the microbilogical protocols on blood culture sampling, even from the initial steps, the gram stained smear provides immediate useful information to the clinician, who might determine both the importance of the positive result and / or the initial antimicrobial therapy. Compliance with standard microbiological protocols, based on the biochemical identification of microorganisms and antimicrobial susceptibility testing, allow the adjustment of antimicrobial therapy after 48-72 hours. However, microorganisms that are difficult to be identified biochemically or slowly grow "in vitro", may require a longer period. Therefore, the prolonged result delivery (3-5 days from the blood culture collection to final identification and testing of antimicrobial susceptibility) is one of the main challenges encountered within the microbiology laboratory. In this context, the researchers highlight the continuous interest to reduce this time by developing rapid methods. For example,

the coagulase test, traditionally used to distinguish CoNS isolates from coagulase-positive isolates, can be conducted directly on positive blood culture broths, containing Gram-positive cocci on Gram staining [74].

This approach allows a rapid distinction between CoNS and coagulase-positive staphylococci (for example, *S. aureus*) and may influence clinicians' ability to interpret the clinical significance of a positive blood culture result and initiate an appropriate antimicrobial therapy. Clearly, this is not a complete solution as it does not definitively detect the micro-organism and does not provide data on susceptibility. Similarly, it is possible to couple direct coagulase testing with the use of chromogenic media, which allows identification of methicillin-resistant S. aureus isolates within 18-24 hours [75].

Some studies come with stronger evidence and approach to improve the laboratory diagnosis of BSIs by using new and rapid methods. Molecular methods, including nucleic acid amplification assays (NAATs) and DNA sequencing approaches have emerged as highly useful tools for identifying microorganisms and, in some cases, predicting antimicrobial susceptibility for selected antibiotics [76-79] .

Furthermore, a series of studies have proven that novel phenotypic approaches reduce the time for identification and antimicrobial susceptibility testing for selected microorganisms [80].

Researchers also describe another rapid method, such as Mass Spectrometry, which is widely used within clinical microbiology laboratories as a routine method for rapid identification of microorganisms directly from positive blood culture broth [81, 82].

This method provides much more specific results within a limited time, regarding the microorganism identification and the present resistance mechanisms, compared to traditional methodology. Clinicians should get familiar with the criteria for interpreting these results, as well as the initial antimicrobial treatment schemes and subsequent adjustment of therapy on the basis of final outcomes [83, 67].

Therefore, these methods can only be used as additional assessment to the already existing standard protocols on BSI patient management. Many infections show similar clinical picture, whereas the laboratory diagnosis of infectious diseases is limited to testing, as only the most common pathogens are associated with clinical syndrome. Thus, it results in a number of undiagnosed infections, requiring additional sampling, patient dissatisfaction and a compromised health care. The syndrome-related approach to diagnosing infectious diseases might change this situation. This might become a symptom-based diagnostic method that might assess multiple common pathogens using a single rapid test (multiplex PCR). This method allows physicians to quickly choose the right test and improve treatment management for a number of infections. Hospital-related mortality rate among septic patients ranges from 10% to 50%. Inappropriate antimicrobial therapy for septic shock occurs in approximately 20% of patients and is associated with a fivefold reduction in patient survival rate. Rapid diagnosis and targeted treatment might prevent up to 80% of sepsis-related deaths [84, 85].

Rapid multiplex PCR systems used in positive blood culture sampling detect over 20 types of microorganisms, including antibiotic-resistant genes (carbapenemases, MRSA, VRE), which provide fast and reliable results within several hours for rapid clinical decision-making. Ease of sample collection, rapidity and ability to cover a wide range of pathogens, including the antibiotic- resistant genes, provide excellent laboratory opportunities for delivering data for further positive care assistance among patients with BSIs [86, 87].

Unlike the traditional blood culture method, the multiplex PCR system rapidly reduces the time required for identification of microorganisms in positive BC bottles, viz. from 26.5 hours to less than 3 hours. The mean time required to identify the potential antibiotic resistance mechanisms was 2.2 hours, whereas the results of bacterial antibiotic sensitivity testing (phenotypic) were available within 33.3 hours on average. The multiplex PCR system test accurately identified the presence or absence of antibiotic resistance mechanisms in all 70 bacteria detected within the study (35 samples with *S. aureus*, 6 – *Enterococcus spp*., 29 – *Enterobacteriaceae* and *P. aeruginosa*). These study results allowed clinicians to adjust an empirical combined treatment in 22 out of 112 patients [88].

Most studies emphasize the importance of implementation of rapid diagnostic solutions along with manual method of BC sampling, in order to identify and differentiate the underlying pathogens of BSI etiology. The implementation of these rapid diagnostic methods (multiplex PCR) is crucial in urgent therapeutic management and patient follow-up, which helps reduce the intervention time and targeted treatment, as well as additional sampling and length of hospitalization [88].

Overall considerations on blood culture contamination

Inappropriate practices result in blood culture contamination with skin commensals on the venipuncture site. Blood culture contamination during the sampling process may lead to false positive results, which may have a negative impact on the patient condition. A false positive result is defined as an increase of bacteria in the blood culture bottle that are not normally present in patient's blood , which might have been introduced during blood sampling. Contamination may originate from a number of sources: the patient's skin, the equipment used for sampling, the hands of the person taking the blood sample or the environment [61, 81].

Taking uncontaminated blood specimens is essential in providing a blood culture result that has a clinical value. Certain microorganisms such as coagulase-negative staphylococci and streptococci from the group of *Viridans, Bacillus spp, Propionibacterium spp., Difteroides, Micrococcus spp* may rarely cause severe bacterial infections or BSIs. These microorganisms are common skin contaminants and, al-

though they are able to cause severe infections, under appropriate conditions, their detection in a single, blood culture set can be reasonably identified as a possible contaminant with no clinical significance. However, coagulase-negative staphylococci are considered the primary cause of catheter-associated infections and may exhibit clinical significance in up to 20% of cases [19].

The most difficult challenge for physicians is to interpret whether the microorganism isolated from a blood culture is a BSI-causing pathogen or a contaminant. If it is a contaminant, the antibiotic therapy in patients is unnecessary or inappropriate, resulting in life-threatening condition and additional costs for the health care assistance. The microbial isolate should be distinguished as a real etiological factor from the contaminant one, based on venipuncture blood sampling or via an intra-vascular device and multiple isolation of the same species of microorganisms. Therefore, it is highly important to include information regarding the site of blood culture sampling in the application form before sending the sample to the laboratory [32].

Prevention of blood culture contamination

The most effective way to reduce contamination rate is to strictly comply with the rules of hand hygiene, as well as follow the best practices in blood sampling, skin processing, venipuncture and blood transfer in BC bottles. However, although the best blood sampling protocols have been carried out, it is impossible to reduce the contamination rate below 2% [37, 61, 89].

The American Society for Microbiology (ASM) and CLSI recommend that the contamination rates should not exceed 3% of the total of collected sets [32].

The study outcomes on the analysis of contamination sources showed a good understanding of blood culture sampling time but described a variety of methods and equipment used. Subsequently, the study authors suggested measures on rationalization and standardization of blood sampling equipment and techniques, as well as personnel training regarding their compliance. This project operated for 12 months within an Emergency Department and successfully reduced local contamination rates up to 2.0% [90].

Blood culture contamination of skin microbiota is an important issue regarding the patient outcome and management, and might lead to inappropriate use of antibiotics, additional laboratory and radiological tests, antimicrobial side effects and increased length of hospitalization [91].

Personnel training in sampling, processing and interpretation of blood cultures

Education and professional training of medical staff (doctors, nurses, phlebotomists or technicians), engaged in caring of patients with BSIs is paramount in developing best clinical practices and preventing blood culture contamination [22, 92-94].

Over the last decades, a number of studies have focused on the study of causes and measures to prevent blood culture contamination. Thus, according to some authors, training of the staff on the proper sampling techniques, monitoring of blood culture contamination rates and getting familiar with these data might reduce the contamination rate [95, 22].

Other studies have reported that continuous training and their efficiency assessment have been associated with lower rates of blood culture contamination (from 2.59% to 2.23%). Moreover, the decrease in the contamination rates from 5.7% to 1.95% due to personnel training was registered in other studies, as well [96].

Studies that described the use of combined interactive learning methods (video materials, simulations for developing practical skills), and determined their impact on blood culture contamination rates were performed. The study revealed that contamination rates remained the same, except for the experienced staff (from 4.1% to 2.7%), hence theoretical education is considered inefficient without coherent practices [95, 96].

A group of researchers demonstrated a decrease of 44% in the contamination rate (from 1.82% to 1.01%) as a result of personal training and counseling. Considerable results (from 11.8% to 7.4%) were recorded when using the same mechanisms (individual training and counseling) but with more frequent sessions, e.g. twice a month [22, 96].

Another approach in staff training on good practices, in terms of preventing blood culture contamination, was conducted by another group of researchers, who introduced theoretical education along with proper using of blood culture sampling containers, hence reporting a decrease of 42% in the contamination rate [95].

Thus, the reviewed studies presented evidence-based data on the importance of staff training in sampling, processing and interpretation of blood cultures, using various interactive methods, as well as counseling sessions in terms blood culture sampling.

In order to increase the yield of BSI-causing pathogens, as well as to obtain fast and reliable outcomes, prevent blood culture contamination and improve patient management of BSIs, it is paramount to implement a standardized algorithm for the sampling, processing and interpretation of blood cultures.

Conclusions

1. Bloodstream infections represent a serious medical issue for public health care worldwide, as well as a challenge in their diagnosis and management.

2. Data collection on BSI etiology and microorganism resistance at a regional level provides a rational basis for optimizing further potential preventive strategies such as immunization, environmental hygiene and chronic disease management.

3. Implementation and compliance to a standardized algorithm, blood culture identification by the clinician, and proper sampling procedure will help increase the pathogen isolation rate of BSIs.

4. The epidemiological surveillance of these infections is a continuous and permanent multidisciplinary activity of healthcare professionals.

5. Standardization of blood culture sampling methods, blood volume optimization, using of a checklist, using effective antiseptics and staff training, lead to the development of good practices for collecting blood culture samples and thus reducing their contamination at the lowest possible rate, not more than 2%.

6. Education of medical staff, trained in the sampling, processing and interpretation of blood cultures is vital for improving patient care and management in case of BSIs.

7. The study calls attention to insufficient data on patient evolution with BSI due to misdiagnosis, resulting in irrational microbial administration and uncontrolled spread of MDR microorganisms that generally occur within the hospital and community.

References

1. Goto M, Al-Hasan MN. Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. Clin Microb Infect. 2013;19(6):501-9.
2. Laupland KB. Incidence of bloodstream infection: a review of population-based studies. Clin Microbiol Infect. 2013;19(6):492-500.
3. Fleischmann-Struzek C, Goldfarb DM, Schlattmann P, et al. The global burden of paediatric and neonatal sepsis: a systematic review. Lancet Respir Med. 2018;6(3):168-70.
4. Fleischmann C, Scherag A, Adhikari NKJ, et al. Assessment of global incidence and mortality of hospital-treated sepsis current estimates and limitations. Am J Respir Crit Care Med. 2016;193(3):259-72.
5. Kumar A, Ellis P, Arabi Y, et al. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. Chest. 2009;136(5):1237-484.
6. Otu A, Elston J, Nsutebu E. Sepsis in Africa: practical steps to stem the tide. Pan Afr Med J. 2015;21:323.
7. Petti CA, Polage CR, Quinn TC, et al. Laboratory medicine in Africa: a barrier to effective health care. Clin Infect Dis. 2006;42(3):377-82.
8. Vincent JL, Marshall JC, Ñamendys-Silva SA, et al. Assessment of the worldwide burden of critical illness: the Intensive Care Over Nations (ICON) audit. Lancet Respir Med. 2014;2:380-6.
9. Bassetti M, Righi E, Carnelutti A. Bloodstream infections in the Intensive Care Unit. Virulence. 2016;7:267-279.
10. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. Am J Med. 1994;96(3):200-9.
11. Garey KW, Rege M, Pai MP, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. Clin Infect Dis. 2006;43(1):25-31.
12. Reimer LG, Wilson ML, Weinstein MP. Update on detection of bacteremia and fungemia. Clin Microbiol Rev. 1997;10(3):444-465.
13. Washington JA 2nd, Ilstrup DM. Blood cultures: issues and controversies. Rev Infect Dis. 1986;8(5):792-802.
14. Weinstein MP. Current blood culture methods and systems: clinical concepts, technology, and interpretation of results. Clin Infect Dis. 1996;23(1):40-46.
15. Clinical Practice Guideline: Prevention of Blood Culture Contamination. J Emerg Nurs. 2018;44(3):285.e1-285.e24.
16. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62(4):e1-e50.
17. Towns ML, Jarvis WR, Hsueh PR. Guidelines on blood cultures. J Microbiol Immunol Infect. 2010;43(4):347-9.
18. Woods-Hill CZ, Fackler J, Nelson McMillan K, et al. Association of a clinical practice guideline with blood culture use in critically ill children. JAMA Pediatr. 2017;171(2):157-164.
19. Hall KK, Lyman JA. Updated review of blood culture contamination. Clin Microbiol Rev. 2006;19(4):788-802.
20. Souvenir D, Anderson DE Jr, Palpant S, et al. Blood cultures positive for coagulase-negative staphylococci: antisepsis, pseudobacteremia, and therapy of patients. J Clin Microbiol. 1998;36(7):1923-1926.
21. Clinical and Laboratory Standards Institute (CLSI). Principles and procedures for Blood Cultures. Approved Guideline, CLSI document M47-A. Wayne, PA: CLSI; 2007. 13 p.
22. Dargere S, Parienti JJ, Roupie E, et al. Unique blood culture for diagnosis of bloodstream infections in emergency departments: A prospective multicentre study. Clin Microbiol Infect. 2014;20:920-927.
23. Garcia R, Spitzer ED, Beaudry J, et al. Multidisciplinary team review of best practices for collection and handling of blood cultures to determine effective interventions for increasing the yield of true-positive bacteremias, reducing contamination, and eliminating false-positive central line-associated bloodstream infections. Am J Infect Control. 2015;43(11):1222-37.
24. Wilson ML. Blood cultures: introduction. Clin Lab Med. 1994;14(1):1-7.
25. Bone RC, Balk RA, Cerra FB, et al. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med. 1992;20(6):864-874.
26. Levy MM, Fink MP, Marshall JC, et al. 2001SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med. 2003;29(4):530-538.
27. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med. 1992;20:864-874.
28. Mervyn S, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801-810.
29. Vincent JL, de Mendonça A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organdysfunction/failure in intensive care units: results of a multicenter, prospective study. Working Group on "Sepsis-Related Problems" of the European Society of Intensive Care Medicine. Crit Care Med.1998;26(11):1793-1800.
30. Lamy B, Dargère S, Arendrup MC, et al. How to optimize the use of blood cultures for the diagnosis of bloodstream infections? A state-of-the art. Front Microbiol. 2016;7:697.
31. UK Standards for Microbiology Investigations (UK SMI): general information [Internet]. London: Public Health England; 2014 [cited 2019 Mar 9]. Available from: https://www.gov.uk/guidance/uk-standards-for-microbiology-investigations-smi-quality-and-consistency-in-clinical-laboratories.
32. Baron EJ, Miller JM, Weinstein MP, et al. A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2013 recommendations by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM)(a). Clin Infect Dis. 2013;57(4):e22-e121.
33. Kumar PJ, Srinivasan NM, Thakkar JM, Mathew S. A prospective observational study of the outcome of central venous catheterization in 100 patients. Anesth Essays Res. 2013 Jan-Apr;7(1):71-5.
34. Brown JD, Chapman S, Ferguson PE. Blood cultures and bacteraemia in an Australian emergency department: evaluating a predictive rule to guide collection and their clinical impact. Emerg Med Australas. 2017;29:56-62.
35. Eliakim-Raz N, Bates DW, Leibovici L. Predicting bacteraemia in validated models – a systematic review. Clin Microbiol Infect. 2015;21:295-301.
36. Hall RT, Domenico HJ, Self WH, et al. Reducing the blood culture contamination rate in a pediatric emergency department and subsequent cost savings. Pediatrics. 2013;131(1):e292-e297.
37. Hodgson LE, Dragolea N, Venn R, et al. An external validation study of a clinical prediction rule for medical patients with suspected bacteraemia. Emerg Med J. 2016;33:124-9.
38. Bouza E, Sousa D, Rodríguez-Créixems M, et al. Is the volume of blood cultured still a significant factor in the diagnosis of bloodstream infections? J Clin Microbiol. 2007;45:2765-9.

39. Homerton University Hospital NHS Foundation Trust [Internet]. London: Homerton NHS Trust; c2014 [cited 2019 Mar 9]. Available from: http://www.homerton.nhs.uk/
40. Medicine Joint Prescribing Guidelines 2.3.: Blood Cultures & when & how to take them.
41. Mermel LA, Maki DG. Detection of bacteremia in adults: consequences of culturing an inadequate volume of blood. Ann Intern Med. 1993;119(4):270-272.
42. Lamy B, Roy P, Carret G, et al. What is the relevance of obtaining multiple blood samples for culture? A comprehensive model to optimize the strategy for diagnosing bacteremia. Clin Infect Dis. 2002;35(7):842-850.
43. World Sepsis Day – 13 September. WSD fact sheet 2013 [Internet]. Geneva: World Federation of Pediatric Intensive and Critical Care Societies; c2019. [cited 2019 Mar 13]. Available from: http://www.wfpiccs.org/projects/sepsis-initiative/world-sepsis-day-13-september/.
44. Cockerill FR 3rd, Wilson JW, Vetter EA, et al. Optimal testing parameters for blood cultures. Clin Infect Dis. 2004;38:1724-1730.
45. Freedman SB, Roosevelt GE. Utility of anaerobic blood cultures in a pediatric emergency department. Pediatr Emerg Care. 2004;20(7): 433-6.
46. Lee A, Mirrett S, Reller LB, Weinstein MP. Detection of bloodstream infections in adults: how many blood cultures are needed? J Clin Microbiol. 2007;45(11):3546-3548.
47. Amarsy-Guerle R, Mougari F, Jacquier H, et al. High medical impact of implementing the new polymeric bead-based BacT/ALERT® FA Plus and FN Plus blood culture bottles in standard care. Eur J Clin Microbiol Dis. 2015;34(5):1031-1037.
48. Doern C, Mirrett S, Halstead D, et al. Controlled clinical comparison of new pediatric medium with adsorbent polymeric beads (PF Plus) versus charcoal-containing PF medium in the BacT/ALERT blood culture system. J Clin Microbiol. 2014;52(6):1898-1900.
49. Kirn TJ, Mirrett S, Reller LB, et al. Controlled clinical comparison of BacT/ ALERT FA plus and FN plus blood culture media with BacT/ALERT FA and FN blood culture media. J Clin Microbiol. 2014;52(3):839-843.
50. Lee DH, Kim SC, Bae IG, et al. Clinical evaluation of BacT/ALERT FA plus and FN plus bottles compared with standard bottles. J Clin Microbiol. 2013;51(12):4150-4155.
51. Ntusi N, Aubin L, Oliver S, et al. Guideline for the optimal use of blood cultures. S Afr Med J. 2010;100(12):839-843.
52. Weinstein MP, Murphy JR, Reller LB, et al. The clinical significance of positive blood cultures: a comprehensive analysis of 500 episodes of bacteremia and fungemia in adults. II. Clinical observations, with special reference to factors influencing prognosis. Rev Infect Dis. 1983;5(1):54-70.
53. Kirn TJ, Weinstein MP. Update on blood cultures: how to obtain, process, report, and interpret. Clin Microbiol Infect. 2013;19(6):513-20.
54. Magadia RR, Weinstein MP. Laboratory diagnosis of bacteremia and fungemia. Infect Dis Clin North Am. 2001;15(4):1009-1024.
55. Mirrett S, Reller LB, Petti CA, et al. Controlled clinical comparison of bact/alert standard aerobic medium with bactec standard aerobic medium for culturing blood. J Clin Microbiol. 2003;41(6):2391-2394.
56. Wilson ML, Mirrett S, Meredith FT, et al. Controlled comparison of BacT/Alert FAN aerobic medium and BACTEC fungal blood culture medium for detection of fungemia. J Clin Microbiol. 2001;39(2): 622-624.
57. Opota O, Croxatto A, Prod'hom G, et al. Blood culture-based diagnosis of bacteraemia: state of the art. Clin Microbiol Infect. 2015;21(4):313-22.
58. Flayhart D, Borek AP, Wakefield T, Dick J, Carroll KC. Comparison of BACTEC Plus blood culture media to BacT/Alert FA blood culture media for detection of bacterial pathogens in samples containing therapeutic levels of antibiotics. J Clin Microbiol. 2007;45:816-821.
59. Pohlman JK, Kirkley BA, Easley KA, et al. Controlled clinical evaluation of BACTEC Plus Aerobic/F and BacT/ Alert aerobic FAN bottles for detection of bloodstream infections. J Clin Microbiol. 1995;33(11):2856-2858.
60. Wilson ML, Mirrett S, Meredith FT, et al. Controlled clinical comparison of BACTEC Plus Anaerobic/F to standard Anaerobic/F as the anaerobic companion bottle to plus Aerobic/F medium for culturing blood from adults. J Clin Microbiol. 2001.39(3):983-989.
61. Gilligan PH. Blood culture contamination: a clinical and financial burden. Infect Control Hosp Epidemiol. 2013;34(1)22-23.
62. Baron EJ, Scot JD, Tompkins LS. Prolonged incubation and extensive subculturing do not increase recovery of clinically significant microorganisms from standard automated blood cultures. Clin Infect Dis. 2005;41:1677-1680.
63. Petti CA, Bhally HS, Weinstein MP, et al. Utility of extended blood culture incubation for isolation of Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella organisms: a retrospective multicenter evaluation. J Clin Microbiol. 2006;44:257-259.
64. Brenner SA, Rooney JA, Manzewitsch P, Regnery RL. Isolation of Bartonella (Rochalimaea) henselae: effects of methods of blood collection and handling. J Clin Microbiol. 1997;35:544-547.
65. Lyon R, Woods G. Comparison of the BacT/Alert and Isolator blood culture systems for recovery of fungi. Am J Clin Pathol. 1995;103(5):660-662.
66. Viscoli C. Bloodstream Infections: the peak of the iceberg. Virulence. 2016;7(3):248-251.
67. Murray PR, Masur H, et al. Current approaches to the diagnosis of xacterial and fungal bloodstream infections for the intensive care unit. Crit Care Med. 2012;40(12):3277-3282.
68. Miller NS, Rogan D, Orr BL, et al. Comparison of BD Bactec Plus blood culture media to VersaTREK Redox blood culture media for detection of bacterial pathogens in simulated adult blood cultures containing therapeutic concentrations of antibiotics. J Clin Microbiol. 2011;49(4):1624-1627.
69. Riedel S, Eisinger SW, Dam L, et al. Comparison of BD Bactec Plus Aerobic/F medium to VersaTREK Redox 1 blood culture medium for detection of Candida spp. in seeded blood culture specimens containing therapeutic levels of antifungal agents. J Clin Microbiol. 2011;49(4):1524-1529.
70. Vigano EF, Vasconi E, Agrappi C, et al. Use of simulated blood cultures for antibiotic effect on time to detection of the two blood culture systems BacT/ALERT and BACTEC 9240. New Microbiol. 2004;27(3):235-248.
71. Richter SS, Beekmann SE, Croco JL, et al. Minimizing the workup of blood culture contaminants: Implementation and evaluation of a laboratory-based algorithm. J Clin Microbiol. 2002;40(7):2437-2444.
72. Weinstein MP. Blood culture contamination: persisting problems and partial progress. J Clin Microbiol. 2003;41(6):2275-2278.
73. Weinstein MP, Mirrett S, Van Pelt L, et al. Clinical importance of identifying coagulase-negative staphylococci isolated from blood cultures: evaluation of microscan rapid and dried overnight gram-positive panels versus a conventional reference method. J Clin Microbiol. 1998;36(7):2089-2092.
74. Qian Q, Eichelberger K, Kirby JE. Rapid identification of Staphylococcus aureus in blood cultures by use of the direct tube coagulase test. J Clin Microbiol. 2007;45(7):2267-2269.
75. Pape J, Wadlin J, Nachamkin I. Use of BBL Chromagar MRSA medium for identification of methicillin-resistant Staphylococcus aureus directly from blood cultures. J Clin Microbiol. 2006;44(7):2575-2576.
76. Jordan JA, Jones-Laughner J, Durso MB. Utility of pyrosequencing in identifying bacteria directly from positive blood culture bottles. J Clin Microbiol. 2009;47(2):368-372.
77. Shepard JR, Addison RM, Alexander BD, et al. Multicenter evaluation of the Candida albicans/Candida glabrata peptide nucleic acid fluorescent in situ hybridization method for simultaneous dual-color identification of *C.* albicans and C. glabrata directly from blood culture bottles. J Clin. Microbiol. 2008;46(1):50-55.
78. Son JS, Song JH, Ko KS, et al. Bloodstream infections and clinical significance of healthcare-associated bacteremia: a multicenter surveillance study in Korean hospitals. J Korean Med Sci. 2010;25(7):992-998.
79. Wolk DM, Picton E, Johnson D, et al. Multicenter evaluation of the Cepheid XPERT Methicillin-Resistant Staphylococcus aureus (MRSA)

test as a rapid screening method for detection of MRSA in hares. J Clin Microbiol. 2009;47(3):758-764.
80. Kirn TJ, Weinstein MP. Update on blood cultures: how to obtain, process, report, and interpret. Clin Microbiol Infect. 2013;19(6):513-520.
81. Riley JA, Heiter BJ, Bourbeau PP. Comparison of recovery of blood culture isolates from two BacT/ALERT FAN aerobic blood culture bottles with recovery from one FAN aerobic bottle and one FAN anaerobic bottle. J Clin Microbiol. 2003;41(1):213-217.
82. Savage RD, Fowler RA, Rishu AH, et al. The effect of inadequate initial empiric antimicrobial treatment on mortality in critically ill patients with bloodstream infections: a multi-centre retrospective cohort study. PLoS ONE. 2016;11(5):e0154944.
83. Lagace-Wiens PR, Adam HJ, Karlowsky JA, et al. Identification of blood culture isolates directly from positive blood cultures by use of matrix-assisted laser desorption ionization-time of flight mass spectrometry and a commercial extraction system: Analysis of performance, cost, and turnaround time. J Clin Microbiol. 2012;50:3324-3328.
84. Gaieski D, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the United States. Crit Care Med. 2013;41(5):1167-74.
85. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006 Jun;34(6):1589-96.
86. Banerjee R, Teng CB, Cunningham SA, et al. Randomized trial of rapid multiplex polymerase chain reaction-based blood culture identification and susceptibility testing. Clin Infect Dis. 2015;61(7):1071-1080.
87. Fiori B, D'Inzeo T, Giaquinto A, et al. Optimized use of the MALDI BioTyper system and the FilmArray BCID panel for direct identification of microbial pathogens from positive blood cultures. J Clin Microbiol. 2016;54(3):576-584.
88. Payne M, Champagne S, Lowe C, et al. Evaluation of the FilmArray blood culture identification panel compared to direct MALDI-TOF identification for rapid identification of pathogens. J Med Microbiol. 2018;67(9):1253-56.
89. Tissari P, Zumla A, Tarkka E, et al. Accurate and rapid identification of bacterial species from positive blood cultures with a DNA-based microarray platform: an observational study. Lancet. 2010;375:224-230.
90. Bentley J, Thakore S, Muir L, et al. A change of culture: reducing blood culture contamination rates in an Emergency Department. BMJ Qual Improv Rep. 2016;5(1). pii: u206760.w2754.
91. Van der Heijden YF, Miller G, Wright PW, et al. Clinical impact of blood cultures contaminated with coagulase-negative staphylococci at an Academic Medical Center. Infect Control Hosp Epidemiol. 2011 Jun;32(6):623-5.
92. Li J, Plorde JJ, Carlson LG. Effects of volume and periodicity on blood cultures. J Clin Microbiol. 1994;32(11):2829-2831.
93. Nair A, Elliott SP, Al Mohajer M. Knowledge, attitude, and practice of blood culture contamination: A multicenter study. Am J Infect Control. 2017;45(5):547-548.
94. Weinbaum FI, Lavie S, Danek M, et al. Doing it right the first time: quality improvement and the contaminant blood culture. J Clin Microbiol. 1997;35(3):563-565.
95. Arif Al-Hamad, Al-Ibrahim M, Alhajhouj E, et al. Nurses'competency in drawing blood cultures and educational intervention to reduce the contamination rate. J Infect Public Health. 2016;9(1)66-74.
96. Van Ingen J, Hilt N, Bosboom R. Education of phlebotomy teams improves blood volume in blood culture bottles. J Clin Microbiol. 2013;51(3):1020-1021.