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Narrative review

Contaminants in blood cultures: importance, implications, interpretation and prevention[☆]

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ABSTRACT

Background: Despite the development of new microbiologic technologies, blood cultures (BCs) remain the first-line tool for the diagnosis of bloodstream infections. Their diagnostic value may be affected when a microorganism of questionable evidence is isolated—for example, coagulase-negative staphylococci, *Bacillus* spp., viridans group streptococci, *Corynebacterium* spp., *Propionibacterium* spp. and *Micrococcus* spp. Finally, making a correct diagnosis of pathogenicity (vs. contamination) is challenging.
Aims: To review the current ways of dealing with the problem of BC contaminants (BCCs) and to provide practical suggestions to decrease BCC rates.
Sources: PubMed electronic databases and existing reviews were searched up to December 2017 to retrieve relevant publications related to the topic.
Contents: This review describes the burden of BCC and analyses the main current issues and controversies in interpreting the occurrence of potential BC contaminants. It focuses on the best-described approaches to decide whether BCC is present and discusses the different strategies of prevention in adults.
Implications: Each institution should have an efficient policy to prevent BCC, emphasizing the importance of following guidelines for prescribing and collecting BCs. Training healthcare workers should focus on detrimental influence on patient care and highlight the work and costs due to contaminants. The accurate differentiation of a contaminant from a true pathogen relies on a multidisciplinary approach and the clinical judgement of experienced practitioners. **S. Dargère, Clin Microbiol Infect 2018;24:964**
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Introduction

Blood culture (BC) remains the reference standard for the diagnosis of bloodstream infections (BSIs), but contaminations represent up to 50% of positive BCs [1,2]. A contaminant is defined as a microorganism that is supposed to be introduced into the culture during either specimen collection or processing and that is not pathogenic for the patient. The most frequently isolated microorganisms are coagulase-negative staphylococci (CNS) in 75% to

88% of contaminated BCs, followed by *Bacillus* spp., viridans group streptococci, *Corynebacterium* spp., *Propionibacterium* spp., *Micrococcus* spp. and *Clostridium perfringens* [3,4].

Differentiating a contaminant from a true pathogen is challenging because some of these microorganisms are an increasing source of true bacteraemia, especially in patients with prosthetic devices or catheters. On the basis of prevalence data, it has been recommended that BC contamination (BCC) rates should not exceed 3% of BCs performed, which is considered the standard benchmark [5]. This threshold of 3% is arbitrary and, as described in a recent review, it is possible to further reduce the BCC rate, especially by implementing appropriate blood collection procedures [6].

Here we review the current knowledge dealing with the best ways to distinguish contaminants from true pathogens and to reduce BCCs in order to lower their clinical and financial consequences.

Methods

A comprehensive search on PubMed was conducted up to December 2017, with results limited to English-language reports. The terms in the search used in different combinations were as follows: 'contaminants,' 'blood culture contamination,' 'blood cultures' and 'coagulase negative staphylococci AND bacteraemia.' The studies reviewed were observational studies, case series, smaller trials, randomized trials, cost analyses, guidelines, meta-analyses and literature reviews.

Importance of BCC

Prevalence and factors influencing BCC

The prevalence of BCC varies from 0.6% to 17% of BCs performed [4,7–11]. Such variations may be explained by the sampling conditions and the definition of contamination itself. Factors influencing BCC rates depend on the hospital, the staff and the type of patients. Higher rates were reported in teaching hospitals, especially in emergency departments (EDs) [4,12,13]. Rapid staff turnover, lack of ongoing training and workload may contribute to this phenomenon [12,13]. Age, patient comorbidities and triage level have also been found to be associated with BCC [12–14].

Clinical consequences and financial burden

Patients with contaminated BC need more consultations and more hospital admissions [1,15]. Unnecessary antibiotics are prescribed in 40% to 50% of cases, leading to a 39% increase in charges [1,11,16]. Additional costs associated with unnecessary treatments and additional charges per contaminant in adults were estimated to be $1000 and $8000, respectively [11,17,18]. The annual additional costs reached $2 000 000, and the length of hospital stay was increased from 1 day to 5.4 days [1,17,18]. Lowering BCC rates leads to annual cost savings ranging from $250 000 to $4 100 000 [17,18].

Interpretation of BCC: issues and controversies

Origin of BCC

Contaminations are attributed to the transfer of microorganisms from the immediate environment of the patient or, more rarely, from healthcare workers' hands [19]. The diversity of CNS of the skin flora suggests that they come from several sources (e.g. stratum cornea, contiguous area, clothing and skin of other humans), but after antiseptic treatment, the repopulation of the site occurs with the same strain in favour of a reservoir not reached by topical antiseptics [20]. More than 20% of the skin flora may be beyond the reach of disinfection because microorganisms are located in pilosebaceous units and at other sites where lipids and superficial cornified epithelia protect them [21]. These data suggest that BCC may be due to a defective antisepsis. They also suggest that incompletely sterilized skin fragments are dislodged by venipuncture.

Methods for classification of contaminants

The usual clinical definition of BCC is based on the opinion of skilled physicians and corresponds to the low likelihood that the microorganism isolated would be the cause of infection. Another approach is to define a contamination as a pattern of laboratory results when a microorganism from the skin is isolated. The College of American Pathologists (CAP) defines a BC set as a blood sample collected from a single venipuncture and then inoculated into one aerobic and one anaerobic bottle. The CAP uses the single blood draw definition of BCC as the presence of one or more of the following organisms found in only one BC set and only one of a series of two or three BC sets: CNS, *Micrococcus* spp., viridans group streptococci, *Propionibacterium acnes*, *Corynebacterium* spp. and *Bacillus* spp [22].

Below we present several clues that may help differentiate BCC from true bacteraemia, as well as their reliability in the interpretation of clinical significance of the microorganism.

Identity of microorganism

Predictive multivariate models showed that the identity of microorganism was the most important predictor [1]. Certain microorganisms should almost always represent true pathogens when isolated, while other organisms have been found to represent contaminants. CNS, *Micrococcus* spp., viridans group streptococci, *Propionibacterium acnes* (*Cutibacterium acnes*), *Corynebacterium* spp., *Clostridium perfringens* and *Bacillus* spp. are the organisms most commonly described as contaminants [3,4]. More anecdotally, *Enterococcus* spp., *Abiotrophia/Granulicatella* spp., *Lactobacillus* spp., *Enterobacter* spp. and other Gram-negative bacteria have been reported as contaminants [3,12,16,18]. CNS as well as *Corynebacterium jeikeium* and *Cutibacterium acnes* have emerged as pathogens of healthcare-associated infections [23,24]. They are an increasing source of central venous line–associated infection [24,25], prosthetic joint infection [26], infectious endocarditis involving prosthetic valve or implantable cardiac stimulators [27,28] and other implanted foreign devices (e.g. central nervous system) [24]. The identity of the microorganism is probably the first and most important factor that influences the physician's decision. Nevertheless, it is not possible to diagnose BCC only on the basis of identity of the microorganism, especially when a CNS is isolated.

Number of positive culture sets

In a review of 500 episodes of bacteraemia, when an initial two-bottle set (e.g. one aerobic and one anaerobic bottle) was contaminated, the probability that the subsequent sets would be positive was very low [29]. Even though contaminants were detected in subsequent BCs, they were almost different from those isolated first. A mathematical model has been developed in order to help clinicians to make a decision when a CNS was isolated from BC, taking into account the number of positive two- or three-bottle sets. For samples obtained by venipuncture, the positive predictive value (PPV) was 55% for one positive BC set from one performed, 20% for one positive from two performed and 5% for one positive from three performed [30]. In this study, the PPV was 98% for two positive BC sets from two performed and 90% for two positive from three performed. The number of positive BC sets within a 24-hour period has proved to be a useful aid in interpreting the clinical significance of the isolated microorganism. Such a rule should be used cautiously when appropriate conditions are followed (skin disinfection, adequate volume for each bottle, at least two to four BC sets including aerobic and anaerobic bottles) [31]. Unfortunately, solitary BCs (i.e. only one set) are frequent (ranging from 10% to 30% of BC performed), making this difficult to apply in case of microorganisms of questionable evidence [32–35]. The interpretation of a positive solitary BC as contaminated is facilitated in a few situations (e.g. they have been taken during a febrile episode of spontaneous resolution, the patient had symptoms which were in relation to a focal infection due to other microorganisms or a noninfectious diagnosis has been established), but in cases of patients with foreign devices (e.g. central venous catheter, joint implant or prosthetic heart valve), the task is challenging. Before ruling out true bacteraemia in such patients with a positive solitary BC, special attention should be paid to factors that

may cause doubt about the quality of BC sampling (e.g. previous antibiotic therapy, insufficient blood volume in bottle).

Number of positive BC bottles within a set

Increasing the number of positive bottles within a set helps to predict the likelihood of true bacteraemia, especially when a CNS is isolated [36,37]. In a prospective study of the single-sampling strategy (SSS), an association between the number of positive bottles within a six-bottle set and the clinical significance of the organism has been demonstrated [38]. Most often, contaminants were isolated from the first (>90%) or second bottles. Considering CNS, the PPV for true bacteraemia was 3.5%, 61%, 78.9% and 100% when one, two, three and four or more bottles were positive respectively. The most difficult cases to interpret were those with two or three positive bottles, which represented only 5% of patients. The number of positive BC bottles within a set may be useful to interpret the clinical significance of microorganisms in institutions where the SSS is implemented. So when a CNS or another possible contaminant is isolated from one or two bottles within a four- or six-bottle set, it is likely that it should be considered as a contaminant. Like the multisampling strategy (MSS), the sensitivity of this technique depends on the volume of blood cultured, and it is important to underline that it needs to be validated for the diagnosis of infectious endocarditis [31].

Time to growth

It makes sense to think that the bacterial inoculum in a true bacteraemia is higher than in a BCC and grows faster. When a CNS is isolated, a growth time more than 20 hours is usually considered in favour of a contaminant [39,40]. Prior administration of antibiotics, volume of blood sample, delay of sample transfer and interval of BC review are factors that reduce the reliability of this parameter. Moreover, growth times between contaminants and true pathogens overlap [39,40]. Nowadays, even though it may be affected by blood volume inoculated into BC bottle, the increasing performance of incubator systems reduces the time to detection. Although the time to detection of CNS is still longer than that of other microorganisms (e.g. Enterobacteriaceae, Staphylococcus aureus, viridans group streptococci), the threshold of 20 hours to consider a CNS as a contaminant should be revised [41]. Moreover, the development of new technologies for detection of microorganisms in whole blood makes this clue obsolete.

Phenotyping, genotyping profile and new microbiologic technologies

Comparing the susceptibility testing of CNS isolated from different BCs has been shown to be highly predictive of strain relatedness; conversely, microorganisms are frequently genetically unrelated in contaminations [42]. Pulsed-field gel electrophoresis is a powerful tool to distinguish contaminant from pathogen CNS, and genotyping diversity has been described in BCC [43,44]. Despite this, molecular typing correlated poorly with clinical criteria of BSI, and this technique is not realistic in routine practice [45]. Identifying virulence markers of Staphylococcus epidermidis isolated from BCs to predict its clinical significance was unsuccessful [46]. More recently, it has been shown that despite the same antibiotype there were different CNS genotypes, indicating that only rapid molecular methods can provide proof [47]. Although highly effective in distinguishing between strains of CNS isolated from BCs, this method is still expensive and time consuming.

Over the last few decades. several molecular methods have been developed for the detection of microorganisms in whole blood. Using specific targets (i.e. SeptiFast, VYOO and Magicplex) or universal/conserved targets (i.e. SepsiTest, PCR with ESI-MS mass spectrometry) for the detection of a broad range of microorganisms, these PCR-based methods circumvent the culture step and

reduce the turnaround time of microbial diagnosis [48]. However, the limited correlation between identification obtained by these molecular methods and BC-based methods, the sensitivity of these new technologies to contamination and the lack of interventional study do not allow an estimation of their impact on the classification of a microorganism isolated from blood as a contaminant.

Few reports investigated the effect of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) on the management of BCs positive for CNS [49,50]. Compared to the conventional processing, MALDI-TOF MS resulted in a decreased duration of inappropriate antimicrobial therapy but did not decrease the mean time to identify a BC as contaminated [50]. Moreover, these new technologies were always evaluated in association with an antimicrobial stewardship program; the role of MALDI-TOF MS itself in decreasing the duration of inappropriate antimicrobial therapy remains to be proved.

Algorithms and clinical judgement

On the basis of the identity of microorganism and the number of positive BCs, acceptable laboratory-based algorithms have been provided [51]. Because the interpretation of BCs positive for CNS (and other potential contaminants) is challenging, the most recent algorithms have tried to identify key points that may help in clinical practice: (a) when suspecting a false-positive BC, the microbiologist should communicate personalized information to the clinician and should avoid providing antimicrobial susceptibility testing in order to limit unnecessary antimicrobial therapy [51]; (b) the microbiologist and the clinician have to take into account the clinical status of the patient at the moment of the microbiologic diagnosis, clinical evidence of infection and the presence of foreign device (e.g. central line, prosthetic joint, implantable cardiac device) [51—53]; and (c) additional blood samples positive for the same organism in a 5- to 7-day period are an additional argument in favour of a true bacteraemia [52,53].

These algorithms were studied in heterogeneous populations, and even though they had an acceptable specificity, their PPV and negative predictive value should be assessed in specific populations [52,53].

The clinical judgement that varies with the experience of the physician is important. For example, in a recent study the clinical decision about significance of BCs positive for CNS differed significantly from the criteria of BSI recommended by the US Centers for Disease Control and Prevention, as clinicians considered patients with comorbidities, foreign devices, recent operation, at least two positive culture sets, more than two positive bottles within a set and lower time to growth, to have a true bacteraemia [54]. The recognition of a potential contaminant isolated from a BC as a contaminant is easier when the microorganism causing the sepsis is different and already identified when there is an evident focus and when the patient recovers despite not receiving specific treatment.

Prevention

There are several steps in the process of decreasing BCC.

Blood sample

Antisepsis

The literature review identified many studies focusing on the skin antisepsis, but few studies were randomized. In a meta-analysis of six clinical trials, alcoholic solutions were more effective than nonalcoholic solutions, and 2% alcoholic chlorhexidine gluconate (CHG) was found to be more effective than nonalcoholic povidone-iodine (PVI). Iodine tincture was not superior to PVI, alcoholic iodine

was not different from nonalcoholic iodine, alcohol alone was not inferior to any iodine products and the difference between CHG and iodine compounds was not conclusive [55]. More recently, a randomized trial comparing the effectiveness of three skin antiseptics (10% aqueous PVI, 2% iodine tincture and 2% alcoholic CHG) found that the choice of the product did not affect the BCC rate when phlebotomists collected blood samples for culture [56]. The low basal rate of contamination (0.76%) and the use of phlebotomy carts may have biased the results. Other authors did not find any significant difference between the BCC rates comparing CHG to 2% iodine tincture [57] or alcohol alone to 2% alcoholic CHG [58]. It is difficult to make a recommendation because some of these studies lacked power, and compliance with BC sampling guidelines was not evaluated. Alcoholic solutions appear to be better than nonalcoholic products as skin antiseptics in preventing BCC. Guidelines most often recommend using 2% alcoholic CHG solution, respecting the drying time (30 seconds) and disinfecting the top of the bottle with the same product [59–61].

Hand hygiene with alcohol-based sanitizer is recommended, and nonsterile gloves must be worn [62].

Venipuncture vs. catheter draw

In EDs, before care is provided, an intravenous catheter is often placed, and thereafter blood samples are drawn for culture. A meta-analysis including nine studies showed that the contamination rate was lower when blood samples were taken via venipuncture compared to a catheter [63]. A recent study confirmed that the relative risk of contamination for culture in samples collected via a catheter compared with venipuncture was increased [64]. The difference between the two procedures decreases when blood collection is performed through a newly inserted catheter [65].

Commercial kits

In a meta-analysis, Snyder et al. [63] were not able to make recommendations for or against prepackaged kits. Self et al. [66,67] demonstrated that when sterile kits were used, BCC rates were reduced from 4.3% with usual care to 1.7%, with an estimated annual net saving of $483 219, which is difficult to extrapolate elsewhere in the world.

Phlebotomy team

In the United States, BC is not considered a routine procedure, and it has been shown that BCC is lower when phlebotomists collect blood samples compared to other healthcare workers [56,63,67]. In a recent study with the intervention of phlebotomists, the annual savings were approximately $290 000 [67]. Phlebotomists are not available everywhere, but it has been demonstrated that specifically educated or motivated nurses could also have low BCC rates [68].

Educational intervention

A significant decline in BCC rates has been noted after implementation of educational interventions to reach medical and nursing staffs [66–72]. It is recommended to focus on the detrimental influence of contaminants on care; to highlight the work and costs created by contaminants; and to establish protocols for appropriate BC sampling, proposing clinical skills tests, workshops, posters, video demonstrations and simulation practice.

Initial specimen diversion technique

Needle changing showed significant reduction in BCC, although healthcare workers are at risk of needle injury. Vacuum-activated transfer devices are now available, and guidelines recommend that blood samples for culture be drawn separately from other blood collection tubes, or that blood for culture inoculation be drawn first [73]. Assuming that the contamination may be due to colonized skin fragments that are dislodged by venipuncture, a few studies have demonstrated a reduction of 30% to 50% in contaminants when the first few millilitres (0.5–2 mL) of blood are discarded in a tube before BC collection [74,75]. Specific marketed devices for the initial specimen diversion technique have shown that they may contribute to a decrease in BCC rates in the ED [76]. This study, which was supported by the manufacturer of the device, compared this technique to phlebotomy via syringe and subsequent transfer of blood to culture vials, which may increase the contamination rate. This interesting strategy to reduce BCC needs to be evaluated in a large randomized study.

Ordering BCs

Another step to decrease BCC is to avoid opportunities to isolate a contaminant. Physicians frequently overestimate the likelihood of bacteraemia [77]. The Infectious Diseases Society of America has provided recommendations for BC collections in several infections, but many guidelines do not [73]. Many models for predicting bacteraemia have been developed in specific populations or for specific settings, but it is hard to implement them in clinical practice [78].

Sampling strategy

Sampling an adequate volume of blood is the most important parameter for the detection of BSI. It can be achieved either by increasing the number of venipunctures (MSS) or by collecting a large volume through the SSS [31]. As specified above and despite the recommendations, the MSS is associated with a high proportion of solitary BCs, mainly in the ED. This situation makes it difficult to interpret the isolation of certain microorganisms. We have to improve the ordering process of the MSS or use an alternative strategy, such as SSS. A forcing function in the computerized BC ordering process combined with an education intervention has demonstrated that solitary BC rates were decreased from 41% to 11.6% [35]. In this study, two sets of labels were systematically printed out when BCs were ordered and served as a reminder to draw one additional BC set. Despite this, each venipuncture required from the MSS remains an opportunity for contamination.

By inoculating a single sample of 40 mL (i.e. one venipuncture of four bottles) of blood instead of 30 mL, Arendrup et al. [79] showed that the increased yield of true bacteraemia was 4.2%. When they analysed BCs positive for CNS and the number of positive bottles within a set, most cases of contaminants were isolated from one or two bottles of the four-bottle set. Using a probabilistic approach, Lamy et al. [80] confirmed that the best strategy for BC sampling is one venipuncture of a six-bottle set with a specificity of 97.5% and a very good sensitivity. Considering the numbers of pathogens missed and contaminants, Dargère et al. [81], in a prospective multicentre study, demonstrated that the SSS was superior to the MSS. When the process yielded a contaminant, it was isolated from one or two bottles of the four-bottle set in 92% of cases. Clinical studies demonstrated that there was a positive correlation between the number of positive culture bottles and the recovery of a clinically significant microorganism [79,81], but large prospective studies are needed to validate the ability of the SSS to decrease the BCC rate as well as increase the yield in true bacteraemia. Moreover, comparing the SSS vs. MSS should take into account the impact of new molecular microbiologic detection methods.

Conclusion

There is growing evidence that BCC is responsible for unnecessary and costly treatment or investigations. Several studies have

tried to address two main issues: identifying BCC among positive BCs and reducing the risk of contaminating the blood sample for culture. This review shows that there is no single solution to these problems. The development of rapid molecular methods will permit earlier identification but will need to be weighed against a careful clinical analysis of the conditions of sampling, the search for an alternative diagnosis and the patient's risk factor by poorly pathogenic bacteria. The antibiotic stewardship and educational programs may provide such analyses, thereby decreasing the additional costs associated with contaminants. To reduce the risk of contamination at the time of blood sampling, a rigorous implementation of guidelines should be combined with strategies to avoid unnecessary venipuncture. A bundle of measures that take all these parameters into account might be helpful and should be prospectively investigated in order to reach BCC rates below 3%.

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Transparency declaration

All authors report no conflicts of interest relevant to this article.

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