

# Microbiological and clinical significance of coagulase-negative staphylococci isolated from blood cultures

## Aplicação clínica da interpretação microbiológica de hemoculturas com crescimento de estafilococos coagulase-negativa

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### Abstract

Over the last few years, a gradual change of the microorganisms causing nosocomial infections has been described. Gram-negative bacilli, which were formerly the main microorganisms causing intra-hospital infections, have been replaced by gram-positive cocci, essentially *Staphylococcus aureus* and coagulase-negative staphylococci (CNS). The increasing number of staphylococcal infections, especially those associated with the use of peripheral or central venous catheters, by the increase in parenteral nutrition and by the use of pacemakers and prosthetic materials poses an important challenge to the treating physician. Since most of these infections are associated with bacteremia and septicemia, blood cultures are one of the most valuable complementary methods for a quick diagnosis.

We will review the most useful microbiological parameters that can be applied when interpreting a blood culture isolate (especially if a CNS is isolated). We will also briefly explain the different causes of catheter-related bacteremia and the different rates of contamination and infection associated with the various percutaneous intravascular devices.

**Key words:** Coagulase-negative staphylococci, blood culture, catheter-related infections, bacteremia

### Resumo

Nos últimos anos, tem sido descrita uma progressiva mudança dos microorganismos responsáveis pelas infeções nosocomiais. Os bacilos gram-negativos, que eram os principais microorganismos responsáveis por infeções intrahospitalares, foram substituídos por cocos gram-positivos, essencialmente, *Staphylococcus aureus* e estafilococos coagulase-negativa (ECN). O aumento do número de infeções estafilocócicas, especialmente associadas à utilização de cateteres venosos periféricos ou centrais, ao uso da nutrição parenteral e de pacemakers e materiais protéticos, representa um desafio importante para o médico. Uma vez que a maioria destas infeções está associada com bacteremia e septicemia, as hemoculturas representam um dos mais valiosos métodos complementares para um rápido diagnóstico.

Neste artigo iremos rever os parâmetros microbiológicos mais úteis que podem ser aplicados na interpretação do resultado positivo de uma hemocultura (especialmente se um ECN é identificado). Explicaremos também de forma sucinta as diferentes causas de bacteremia relacionada com cateteres e as diferentes taxas de contaminação e infeção associadas com os vários dispositivos intravasculares percutâneos.

**Palavras chave:** Estafilococos coagulase-negativa, hemocultura, infeções relacionadas a cateteres, bacteremia.

### A INTRODUCTION

Over the past years, a progressive change of the microorganisms responsible for nosocomial infections has been described, a change reported not only in Spanish hospitals, but also in many different hos-

pitals around the world.<sup>1-3</sup> Gram-negative bacilli (*Enterobacteriaceae*, *Pseudomonas* spp and *Acinetobacter* spp), the former principal microorganisms responsible for intrahospital infections, have been progressively replaced by gram-positive cocci, essentially *Staphylococcus aureus* and coagulase-negative staphylococci (CNS), and, in a lesser extent, by alpha-hemolytic *Streptococci* and *Enterococci* spp.<sup>4,5</sup> The EPINE study (Estudio de Prevalencia de las Infecciones Nosocomiales en España) proved that, between 2001 and 2006, gram-positive cocci were responsible for 24% of all nosocomial infections, followed by gram-negative bacilli (10%). In the Uni-

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Recebido para publicação a 22.11.10

Aceite para publicação a 12.12.12

Artigo escrito ao abrigo do novo acordo ortográfico (Resumo)

ted States, 70% of all clinically significant bacteremia were due to gram-positive cocci.<sup>3</sup>

The increase of staphylococcal infections can be explained by the greater life expectancy of severely ill patients (who usually have a peripheral or central venous catheter, an urinary catheter and are, sometimes, being treated with chemo or radiotherapy, immunosuppressive drugs or immunomodulating agents), by the boost of parenteral nutrition and by use of pacemakers and prosthetic materials.<sup>7,8</sup> The greater length of hospital stay, usually associated with these type of patients, is another explanation for the increase of staphylococcal infections.<sup>9-12</sup> These pathogens can be normally found as saprophytic flora of the skin and mucous membranes of the patient itself, and tend to produce bacteremia and septicemia, making blood cultures the most valuable complementary method for diagnosis.

We will review the most useful microbiological parameters that can be applied when interpreting a blood culture isolate (especially if it is a CNS) and will briefly explain the different causes of catheter-related bacteremia and the different rates of contamination and infection that the various percutaneous intravascular devices have.

#### MICROBIOLOGICAL AND CLINICAL SIGNIFICANCE OF COAGULASE-NEGATIVE STAPHYLOCOCCI ISOLATED FROM BLOOD CULTURES

The bloodstream is sterile, although transitory bacteremia can be found, usually without any clinical relevance in a healthy person with a normal immune system.

Nevertheless, a blood culture is usually performed in a patient with signs and symptoms of infection, in occasions, critically ill patients. A positive blood culture can represent the opportunity of obtaining a definitive diagnosis and initiate a specific and effective antimicrobial therapy, which will improve the prognosis of our patient.<sup>13</sup>

As any other complementary method for diagnosis, blood cultures can lead to erroneous results. As an example, one can obtain false-positive results due to contamination, because of a badly antiseptic technique at the moment of extracting blood or at the moment of processing the “blood bottle” in the laboratory, or false-negative results, mainly because of the difficulty of isolating a microorganism with a demanding and/or slow growth rate. CNS

**Table 1**

#### Patient-related risk factors for device-associated bacteremia

**Age < 1 year, > 60 years**  
**Granulocytopenia**  
**Immunosuppressive chemotherapy**  
**Loss of skin integrity (e.g., burns, psoriasis)**  
**Severity of underlying illness**  
**Presence of distant infection**

From: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Chapter 279: Bacteremia due to Percutaneous Intravascular Devices. Churchill Livingstone. Third edition.

are non-demanding bacteria with a rapid growth rate (18-24 hours after starting incubation at 37°C and with 5% CO<sub>2</sub> in aerobiosis, in a standard nutrient plate), making false-positive results, due to contamination, the most common erroneous result.

Since there is no clinical or microbiological definitive method which confirms that the CNS isolated in the blood culture of a patient with signs and symptoms of infection is actually responsible for the disease, several laboratory parameters have been proposed and are currently used:

- **Microorganism identification:** it is one of the most important parameters in order to correlate a positive blood culture with a true bacteremia. A blood culture isolate of a gram-negative bacilli, *S. aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Listeria monocitogenes*, *Neisseria meningitidis*, *Neisseria gonorrhoeae* and *Bacteroides fragilis* group bacteria should be considered as the cause of true bacteremia. Although CNS are the third most frequent cause of bacteremia, only 12% of all CNS blood culture isolates will be related with a true bacteremia, making it important to know if the same bacteria has been isolated in the prosthetic material or in the primary infection site of the patient (left untreated, CNS bacteremia can have dismal results).<sup>14</sup> Since molecular biology techniques for the diagnosis of cellular clones are not available in the majority of clinical microbiology laboratories, in order to identify two bacterial colonies as of the same strain, one should use its principal phenotypes: gender, specie, colony morphology and antimicrobial susceptibility.<sup>15</sup>

Table 2

**Additional factors associated with increased risk for device-associated infection**

Alteration in patient's cutaneous microflora  
 Health care provider hygiene (hand washing)  
 Contaminated ointment or cream  
 Catheter composition/construction  
     Flexibility/stiffness  
     Thrombogenicity  
     Microbial adherence properties  
 Size of catheter  
 Number of catheter lumens  
 Distant infection (hematogenous seeding)  
 Catheter function/use  
 Catheter management: entry into the system

From: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Chapter 279: Bacteremia due to Percutaneous Intravascular Devices. Churchill Livingstone. Third edition.

- **Number of positive sets:** since bacteremia is usually intermittent, blood should be extracted in two or three different occasions. Each extraction should be injected into two "blood bottles", one aerobic and the other anaerobic (these two bottles constitute one blood culture set). The complete and final sample, that is currently recommended, is four to six aerobic and anaerobic "blood bottles", divided into two or three respectively blood culture sets. Although the number of positive sets could be a useful tool, it is not used to differentiate a true bacteremia from a contamination.<sup>16</sup> CNS are aerobic and anaerobic facultative bacteria and are able to grow in the two types of "blood bottles". This makes the total number of positive "blood bottles" a more value and important tool.
- **Number of positive "blood bottles":** it is the most useful parameter when confirming a true bacteremia.<sup>10-12,16,17</sup> CNS growth in one or two "blood bottles" usually indicates contamination, but the growth of the same bacteria in more than half of the bottles is highly indicative of a true bacteremia. A large study performed by Schifman et al.<sup>18</sup>, called CAP Q-probes Study, proved that 77% of the 640 interviewed microbiology laboratories considered this parameter as "very important" when validating a blood culture isolate as a true bacteremia. In the same study, 11167 CNS blood culture isolates were examined, concluding that

Table 3

**Hospital-related risk factors for catheter-acquired infection**

Type of catheter (plastic > steel)  
 Location of catheter (central > peripheral, femoral > jugular/subclavian)  
 Type of placement (cutdown > percutaneous)  
 Duration of placement (at least 72 hr > less than 72 hr)  
 Emergent placement > elective  
 Skill of venipuncturist (others > iv team)  
 Type/Use of catheter (the balloon tipped or flow-directed catheter > percutaneous or central venous catheter > tunneled central venous catheter)

From: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Chapter 279: Bacteremia due to Percutaneous Intravascular Devices. Churchill Livingstone. Third edition.

<sup>1</sup>O acrónimo para Coagulase-negativa staphylococci é CoNS, para evitar confusão com sistema nervoso central CNS

- the percentage of false-positive results was correlated with the number of positive "blood bottles": 27.8% when the microorganism was isolated in four "blood bottles" and 75.2% when it grew in only two bottles.
- **Growth rate:** based on the hypothesis that a positive blood culture from a bacteremia would have a higher inoculum that one of a contamination and that the detection system would identify it in a lesser amount of time. This parameter has been investigated by many authors,<sup>19-23</sup> who consider that a growth detected in the first three days of incubation is highly suggestive of true bacteremia. The same hypothesis could be applied to the pediatric sample, which normally has only one "blood bottle". In this case, when growth is detected in the first 15 hours of incubation, the positive predictive value for the diagnosis of true bacteremia reaches up to 84%.<sup>21</sup> Nevertheless, many authors do not consider growth rate as a good parameter<sup>24-28</sup> and it is not frequently used in clinical microbiology.<sup>18</sup>
- **"Blood bottle" quantitative colony count:** this method, successfully used to differentiate colonization from infection in the case of sputum samples of patients with pneumonia, urine cultures in patients with lower urinary tract infections and in the case of catheter tip cultures when determining the source of a bacteremia, cannot be applied to

blood cultures. St Geme III et al.<sup>29</sup> have performed a study comparing the clinical symptoms of patients with the colony count obtained after processing the “blood bottles” in a standard system, and did not find any correlation between them. Growth variability of the different staphylococcal species and different characteristics of the patients explained the lack of correlation between both variables. Nowadays, this parameter is not used.

### BACTEREMIA DUE TO PERCUTANEOUS INTRAVASCULAR DEVICES

Technological and medical advances have led to many different types of devices that allow an accurate diagnosis and treatment, such as catheters and probes. Its manipulation and prolonged use have led to several complications, such as catheter contamination, followed by infection and bacteremia. Primary bacteremia appears in one of every four cases, but catheter-related bacteremia are diagnosed in 40% of all cases.<sup>30,31</sup> Although staphylococci of the patient itself are the most frequent bacteria associated with catheter contamination, it is also important to mention that these devices can function as entry ports for other microorganisms through parenteral nutrition or intravenous medication.<sup>32</sup>

#### CONTAMINATION SITES

- **Contamination of an intravenous infusate:** although both infusate manufacture and in-use contamination are two causes of catheter-related sepsis,<sup>30,32</sup> gram-negative bacilli and yeast are the most frequent microorganisms isolated in these cases. CNS contamination is less frequent, except in the case of casein-hydrolyzed preparations or lipid emulsions.<sup>33</sup>
- **Catheter hub contamination:** the hub of the different catheters is an important area of CNS contamination or colonization, and bacteremia can be related to an intraluminal colonization or an external contamination, which is more important when the hub is not completely sealed.<sup>34,35</sup> Salzman et al.<sup>36</sup> have found that cleaning the lumen of the catheter hub–infusion tubing junction, before sealing the hubs, with an impregnated swab with ethanol 70% or chlorhexidine (for better safety of the patient) can significantly reduce hub contamination by these microorganisms.

- **Contamination of the insertion site:** it is the place more frequently accepted for contamination of the catheter’s surface.<sup>32</sup> Numerous factors influence the risk of a catheter-associated bacteremia (*Tables 1, 2 and 3*). Of all, number 2 deserves a more detailed insight:
- **Change of the patient’s cutaneous flora:** it could be a result of antimicrobial treatment or colonization by a hospital endemic microorganism, mainly transmitted by the hands of the sanitary personnel. This situation is specifically important in the intensive care units.<sup>37,38</sup>
- **Device manipulation:** contamination normally occurs when obtaining a microbiological sample. The flow-directed or the balloon tipped pulmonary artery catheters have a greater risk of contamination since they are most often used in critically ill patients in order to obtain different vital parameters.<sup>39</sup>
- **Catheter composition:** catheters that cause inflammation of the vascular intima are more thrombogenic and, thus, have a greater risk of producing an infection.<sup>40</sup> Silicone elastomer and polyurethane catheters have a significantly lesser risk of producing thrombosis than polyvinylchloride catheters,<sup>41</sup> which have been progressively abandoned.<sup>32</sup> Furthermore, CNS have a greater ability of adhering to these type of catheters than the ones made of Teflon.<sup>42</sup> The size is also important since a bigger catheter tends to create a greater defect in our patient’s skin at the entry site. It is unknown if the use of triple lumen catheters bears a greater risk of infection than the ones with only a single lumen.<sup>43-46</sup>

#### SPECIAL CHARACTERISTICS OF EACH TYPE OF CATHETER

- **Peripheral venous catheter:** generally, these catheters have a lesser risk of infection than the central ones. Stainless steel needles have also a lesser infection rate than the plastic catheters, but can produce more complications, such as extravasation. Catheters placed in the lower extremities, especially in the femoral veins, usually are associated with a higher risk of any type of complication.<sup>47,48</sup> Percutaneous catheters have a lesser risk of infection than the ones placed by cutdown.<sup>49</sup> Other risk factors which are important to mention are its use for more than 72 hours

and being placed in an emergent situation (normally the rules of disinfection and manipulation are broken). Catheters placed by members of an intravenous therapy team are associated with lower complication rates than are those placed by other health care professionals.<sup>32</sup> Several studies have compared the intervals of the intravenous administration sets replacements at 24, 48 and 72-hours, but failed to prove a decrease of the risk of catheter-associated infection between them.<sup>50,51</sup>

- **Central venous catheter:** these catheters have a higher rate of contamination and infection since they normally remain in place for a longer time. Infective endocarditis and suppurative thrombophlebitis are also more frequent.<sup>32</sup> Studies have proven that intraluminal or extraluminal fibrin is not an infectious risk factor related with these catheters.<sup>40,52</sup> Catheter exchange over a guidewire is controversial. Maher et al.<sup>53</sup> have used this technique in order to change catheters in situations when the risk of infection was low, with good results, but Bach et al.<sup>54</sup> and Cobb et al.<sup>55</sup> have demonstrated that it is not useful when changing an infected catheter for a new one. The use of ointment with antiseptics and antibiotics in the entry site has not demonstrated to decrease the risk of infection, both in central as in peripheral intravenous catheters, but the use of a subcutaneous sleeve around the catheter impregnated with silver sulfadiazine, cephazolin or penicillin has proven its efficacy.<sup>32</sup>
- **Tunneled central venous catheters:** in 1973, Broviac and colleagues developed a chronic indwelling right atrial catheter for long-term parenteral nutrition, publishing an infection rate in non-neutropenic patients of 1 infection per 5.5 patient years.<sup>56</sup> Hickman et al. modified the Broviac catheter so that it could be used in stem cell transplanted patients. Nowadays, this catheter is used for intensive chemotherapy, transfusions or phlebotomies and liquid administration, with an overall risk of infection around 0.14 – 0.41 infections per 100 catheter-days<sup>57,58</sup> and a bacteremia rate of 0.26 infections per 100 catheter-days.

### KEY LEARNING POINTS

- a) Nowadays, one of the microorganisms most frequently isolated in blood cultures are CNS.
- b) The growth of the same bacteria in more than half

of the “blood bottles” is highly indicative of a true bacteremia by CNS.

- c) Although both peripheral and central venous catheters are the principal sources of CNS bacteremia, central catheters pose a greater risk of infection.
- d) Microbial colonization around the catheter insertion site is considered to be the most significant risk factor for catheter-associated infection.
- e) Whenever a blood culture is positive for CNS, an evaluation of the patient’s catheter is obliged, especially if inflammation signs in the entry site are seen.
- f) A combined evaluation of blood culture isolates between the microbiologist and an infectious diseases expert is sometimes mandatory in order to reach a correct interpretation of the results of blood cultures.

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