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Patricia Muñoz[1,2,3,4*]
María Guembe[1,2*]
María Jesús Pérez-Granda[1,2,3,5]
José Luís del Pozo[6]
Luis Eduardo López-Cortés[7]
Mauro Pittiruti[8]
María Cruz Martín-Delgado[9]
Emilio Bouza[1,2,3,4]

Vascular catheter-related infections: an endemic disease in healthcare institutions. An opinion paper of the Spanish Society of Cardiovascular Infections (SEICAV)

[1]Clinical Microbiology and Infectious Diseases Department, Hospital General Universitario Gregorio Marañón. Dr. Esquerdo, 46 28007, Madrid, Spain.
[2]Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain.
[3]CIBER de Enfermedades Respiratorias-CIBERES (CB06/06/0058), Madrid, Spain.
[4]Medicine Department, School of Medicine, Universidad Complutense de Madrid, Madrid, Spain
[5]Department of Nursing, School of Nursing, Physiotherapy and Podiatry, Universidad Complutense de Madrid.
[6]Infectious Disease Division, Laboratory of Microbial Biofilms, Clínica Universidad de Navarra, Navarra, Spain.
[7]Infectious Diseases Department. Hospital Universitario Virgen Macarena, Sevilla, Spain.
[8]Department of Surgery. Catholic University Hospital 'A.Gemelli', Rome, Italy.
[9]Department of Intensive Care, Hospital Universitario de Torrejón, Torrejón de Ardoz, Madrid, Spain.

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ABSTRACT

Catheter-related infections (CRI) are a serious healthcare problem due to their potential to cause serious complications, including bacteraemia or infective endocarditis, and to increase patient morbidity and mortality. In addition, these infections significantly prolong hospital stay and cost. Preventing CRI is crucial and is considered a criterion for quality and safety in healthcare.

For these reasons, the Spanish Society of Cardiovascular Infections (SEICAV) has considered it pertinent to review this topic, with experts in different areas including clinical microbiologists, infectious disease specialists, surgeons and nurses. The data were presented at a session held at the Ramón Areces Foundation, which was organised in the form of specific questions grouped into three round tables. The first panel analysed the scale of the problem including epidemiological, clinical and diagnostic aspects; the second panel addressed advances in the treatment of CRI; and the third panel reviewed developments in the prevention of CRI. The recorded session is available on the Areces Foundation website and we believe it may be of interest not only to health professionals, but also to any non-expert citizen interested in the subject.

Keywords: vascular catheter; infection; bacteremia; consequences; safety of healthcare.

Correspondence:
Patricia Muñoz, MD, PhD
Clinical Microbiology and Infectious Diseases Department, Hospital General Universitario Gregorio Marañón.
Dr. Esquerdo, 46 28007 Madrid, Spain
E-mail: pmunoz@hggm.es
*Both authors contributed equally to this work.

Infecciones relacionadas con catéteres vasculares: un mal endémico en las instituciones sanitarias. Un artículo de opinión de la Sociedad Española de Infecciones Cardiovasculares (SEICAV)

RESUMEN

Las infecciones asociadas a catéter (IRC) son un grave problema sanitario debido a su potencial para causar complicaciones graves, incluyendo bacteriemia o endocarditis infecciosa, y aumentar la morbilidad y mortalidad de los pacientes. Además, estas infecciones prolongan significativamente la estancia hospitalaria y el coste de la asistencia. Prevenir las IRC es crucial y se considera un criterio de calidad y seguridad de la atención sanitaria.

Por estos motivos, la Sociedad Española de Infecciones Cardiovasculares (SEICAV) ha considerado pertinente revisar este tema, contando con expertos en diferentes áreas que incluyen microbiólogos clínicos, infectólogos, cirujanos y enfermeras. Los datos se presentaron en una sesión celebrada en la Fundación Ramón Areces, que se organizó en forma de preguntas concretas agrupadas en tres mesas redondas. La primera mesa analizó la dimensión del problema incluyendo aspectos epidemiológicos, clínicos y diagnósticos; la segunda mesa abordó los avances en el tratamiento de las IRC; y en la tercera mesa se revisaron las novedades en la prevención de estas infecciones. La sesión grabada está disponible en la página de la Fundación Areces y creemos puede resultar de interés, no sólo para los profesionales de la salud, si no para cualquier ciudadano no experto interesado en el tema.

Palabras clave: catéter vascular; infección; bacteriemia; nosocomial; consecuencias; seguridad del paciente.

DIMENSION OF THE PROBLEM

Question 1: Which endovascular catheters are most frequently implanted in hospitals?

Though a precise estimate is not possible, indirect data suggest that approximately 20-22 million peripheral venous access devices (VAD) are inserted in Italian hospitals each year [1-3]. According to the World Congress on Vascular Access (WoCoVA) classification, peripheral venous access devices are classified as short peripheral cannulas, long peripheral cannulas, and midline catheters (see the ERPIUP consensus). The vast majority of peripheral VADs used in Italian hospitals are short peripheral cannulas. The rate of infections related to peripheral VADs is currently unknown, though it is considered not as negligible as once assumed, probably around 0.2-0.5 episodes per 1,000 VAD days.

In recent years, the use of midline catheters has increased progressively. The main advantage over peripheral venous accesses is their greater durability, which avoids having to perform multiple cannulations of peripheral accesses during the patient's admission, and they can also have more than one lumen for simultaneous perfusions.

The number of central VADs inserted each year in Italian hospitals is almost one million, which includes 900,000 external central venous catheters (CVCs) (of which, about 200,000 are peripherally inserted central catheters [PICCs]), either tunneled or non-tunneled, plus approximately 50 thousand ports (of which, about 10 thousand are PICC-ports). The incidence of catheter-related bloodstream infection (C-RBSI) is extremely variable, depending on the device and on the clinical setting, and ranges between 0.1-0.2 episodes per 1,000 catheter days for chest-ports and PICC-ports, vs. 0.5-3.0 episodes for 1,000 catheter days for non-tunneled CVCs. The incidence of C-RBSI is higher for CVCs used for parenteral nutrition; also, CVCs with exit site at the neck or at the groin have higher risk of C-RBSI than CVCs with the exit site in the infra-clavicular area or at mid-arm.

The use of some new types of VADs is increasing very rapidly in Italy, which include (a) long peripheral catheters (also called mini-midline, 6-15 cm in length), (b) PICC-ports (brachial ports inserted with PICC technology), and femorally Inserted Central Catheters (FICCs) introduced into the superficial femoral vein, with exit site at mid-thigh. Current clinical studies suggest that mini-midlines may have the same risk of infection than other peripheral VADs, and that PICC-ports have the same infection risk of chest-ports. On the contrary, FICCs inserted by ultrasound guided cannulation of the superficial femoral vein, with exit site at mid-thigh, appear to have lower infection risk than FICCs inserted into the common femoral vein, with exit site at the groin.

Question 2. What are the most frequent microorganisms causing C-RBSI and what is their pathogenesis?

In general, the most frequent microorganisms causing C-RBSI are Gram-positive cocci, in particular coagulase-negative staphylococci (CoNS) (50%-80%), followed by Gram-negative bacilli (15%-30%) and yeasts (5-20%) [4, 5]. However, in specific populations or catheter types, this distribution may change.

According to data from studies of the evolution of the etiology of CR-BSI, the distribution of microorganisms has fluctuated over the years, with variations according to country or type of catheter [5, 6]. Specifically, in a recent study carried out in 100 ICUs in 9 Latin American countries, it has been reported that the rates of Gram-positive and Gram-negative bacteria have been equalized with a rate of 48.5% [7]. However, these trends can be affected by different events, as was the case in the COVID-19 pandemic, where the rates of C-RBSI/1,000 admissions increased significantly compared to previous years, with CoNS being the major causative agent [8]. Likewise, there are peculiarities in the etiology of C-RBSI depending on the population, as is the case of patients with renal disease, in whom an increase in Gram-negative bacilli has been detected [9-12], as well as in the neonatal ICU, in solid organ transplant recipients or neutropenic patients [11, 13]. *Staphylococcus aureus* is frequently associated to bacteremias related to peripheral venous catheters (PVCs) conferring increased risk of morbidity [14].

In terms of specific microorganisms, it is also important to highlight the role of *Enterococcus* spp., which is the fourth leading cause of C-RBSI and whose incidence, mainly due to *E. faecalis*, has increased in recent years [15]. *Candida* spp. represents a smaller percentage of C-RBSI, but its incidence can be very variable depending on the centre, both in adults and children [16]. Finally, although C-RBSI caused by fast-growing non-tuberculous mycobacteria are rare and often occur in immunocompromised patients [17-19], a series of 19 cases in PICCs of immunocompetent injecting drug users has recently been described [20].

Regarding the pathogenesis of C-RBSI, it is important to remember that it is mainly by microorganisms that migrate through the catheter into the bloodstream from two main sources: the *extraluminal route,* from patient's skin microbiota, which is one of the most frequent, and typically appears 5-7 days after insertion; and *the intraluminal route,* from the manipulation of hub connectors during catheter maintenance, which appears normally >7 days after catheter insertion. There are, however, other less frequent routes of C-RBSI acquisition such as: infusion of a contaminated fluid or hematogenous dissemination from another source [21-23].

Question 3. What do we know about biofilm and bacterial quorum sensing in this situation?

Bacteria and fungi are able to adhere to both natural tissues and artificial devices forming a biofilm, which is a complex structure in which microorganisms are in a latent state surrounded by an extracellular matrix composed of proteins and extracellular DNA [24, 25]. One of the most important nosocomial infections mediated by biofilm formation is C-RBSI, in which microorganisms migrate to the catheter and begin to adhere to its surface developing biofilm [24, 25]. Biofilm

formation occurs through a 5-step cycle: reversible adhesion, irreversible adhesion, aggregation, maturation, and dispersion [25]. This phenomenon is primarily responsible for the lack of therapeutic success with systemic antibiotics, since biofilm confers antimicrobial tolerance, reduces antibiotic diffusion and penetration, and evades the host immune response. Recently, it has been described that the extracellular matrix is one of the main factors responsible for resistance, in addition to other intrinsic factors specific to each strain that directly affect biofilm formation and cell dispersion [26-31].

Quorum sensing (QS) is the ability of bacteria to communicate with each other through coordinated behavior by releasing molecules, called autoinducers, to regulate their physiological activities, such as: virulence, conjugation, motility, sporulation or biofilm production. This mechanism occurs when a threshold concentration of autoinducers is reached, indicating that the cell population has reached quorum and gene expression begins [32-35]. However, host factors can also interfere with QS, as can autoinducers in other bacterial species [36]. Therefore, the complexity of this phenomenon calls for the search for new QS inhibitors to combat biofilm-related infections [37].

Question 4. What are the diagnostic methods for catheter infection?

Catheter related infection (CRI) should be suspected if the patient presents with fever, chills or hypotension, with or without signs of infection of the catheter insertion site or in the skin overlying the subcutaneous tract of a tunneled catheter. The different strategies to achieve a diagnosis have deserved excellent reviews [38-43].

1. Diagnosis of C-RBSI without device removal (conservative diagnosis)

Differential time to positivity of blood cultures. In patients with suspected central-line associated bloodstream infection (CLABSI), at least, two pairs of blood cultures should be taken, one from a peripheral vein and the others from all catheter lumens. Blood cultures should be obtained prior to the initiation of antimicrobial therapy and using a strict aseptic technique. This is especially important since pathogens involved in C-RBSI are also the most frequent contaminants of blood culture bottles.

Several studies have confirmed that measuring the time difference to positivity (TDP) of conventional blood cultures obtained from a central venous catheter and a peripheral vein is very sensitive in diagnosing C-RBSI, although it does not exclude it. A TDP ≥ 120 min is associated with a sensitivity of 81% and specificity of 92% for short-duration catheters (<30 days) and a sensitivity of 93% and specificity of 75% for long-duration catheters (>30 days). An optimal cut-off point for the diagnosis of catheter-related candidemia has not been established [41].

Quantitative blood cultures have also been used, and a differential colony count (3-5 times) higher in the blood culture obtained through the catheter than in that obtained through the peripheral vein is suggestive of C-RBSI. Quantitative blood cultures are laborious and expensive, making them less viable for routine use [40].

Semiquantitative **cultures of the skin around the catheter insertion site and catheter connections** with counts ≥15 colony forming units (CFU) may be indicative of C-RBSI [9, 41, 42]. These procedures should be combined with the drawing of peripheral blood cultures if bacteremia is suspected. Gram stain of the connections and the peri-catheter skin may also be useful [44].

2. Diagnosis of C-RBSI with catheter removal

As a general recommendation, a catheter tip should only be sent for culture when an associated infection is suspected, thus avoiding unnecessary cultures and overtreatment. Several factors should be considered in determining whether a catheter should be removed: the type of catheter, the ease of insertion of a new catheter, the immune status, the severity of the patient's underlying disease, and the presence and severity of associated sepsis [45].

The most used laboratory technique for processing the catheter tip is the semi-quantitative method described by Maki, in which the catheter segment is rotated on a blood agar plate using sterile forceps. After 24 hours of incubation, the number of CFU on the plate is counted. The catheter is considered to be the focus of infection if the growth of a catheter tip culture is ≥15 CFU, while <15 CFU without associated clinical signs is considered catheter colonization. A limitation of this method is that it detects mainly colonization on the external surface of the catheter. Moreover, there is no established cut-off point for mycobacteria and fungi [46]. In the case of long-duration catheters, where the endoluminal route is the main pathogenic route, endoluminal surface culture techniques (Cleri, Brun-Bruisson or Liñares) can be performed [47]. For quantitative cultures (internal surface wash and vortex), the cut-off point has been set at 103 CFU/segment, again based on their association with bacteremia [48, 49]. In the case of CVCs with subcutaneous reservoir, cultures should be taken from the catheter tip, from the inside of the reservoir, and from the sonication broth of the silicone septum [50]. The latter procedure has shown the highest sensitivity and specificity (78% and 93%, respectively) for diagnosing device colonization with a cut-off point of 110 CFU/ml [39].

Question 5. What are the consequences of CRI in terms of morbidity, mortality, and cost for the National Health Systems?

Intravascular devices have become an essential component of modern medicine for the administration of intravenous fluids, medication, blood products and parenteral nutrition, as well as for monitoring hemodynamic status and performing hemodialysis. According to national data provided by the study on the prevalence of nosocomial infections in Spain (EPINE), it is estimated that around 70% of patients admitted to Spanish hospitals will carry one of these devices

at some time during their stay [51, 52]. Local or systemic infections represent one of the main associated complications. The incidence of CRI varies considerably depending on the type and intended use, the insertion site, the experience, and training of the person placing the catheter, the frequency with which the catheter is accessed, the duration of catheter placement, patient characteristics, and the use of proven prevention strategies.

C-RBSI is one of the most frequent in-hospital infections. According to current estimates, between 15% and 30% of all nosocomial bacteremias are catheter related. These infections lead to significant associated morbidity, increased hospital costs, estimated at approximately 11,000-56,000 euros per episode, and increased average length of stay. Attributable mortality ranges from 12% to 25% [53-55]. The costs of intravenous antibiotic treatment include acquisition costs, costs associated with disposable materials and overhead. Other expenses include nursing and medical intervention costs, as well as indirect costs associated with the specialized personnel who supervise or administer the medication.

TREATMENT ADVANCES

Question 6. Which infected catheters should be removed immediately?

The clinical guidelines for the diagnosis and treatment of catheter-related bacteremias of the Spanish Society of Critical Intensive Care Medicine and Coronary Units (SEMICYUC) and the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) published in 2018 establish a series of recommendations in this regard [4]. Cases with suspicion of CRI and those in which there is microbiological confirmation should be differentiated.

Immediate and systematic removal of vascular catheters in patients with suspected related infection is not routinely recommended and would only be indicated in specific situations [56, 57].

CVCs should be withdrawn immediately upon suspicion of CRI in patients with suppuration at the site of infection, septic shock, organ dysfunction, intravascular devices or septic emboli. In patients in whom there is suspicion in other conditions, but it is not possible to perform quantitative or differential cultures, the device should also be withdrawn. In the case of documented CRI, it is mandatory to remove these devices in patients with difficult to treat infectious such as those caused by *S. aureus* and *Candida* spp. Catheter removal should be considered when there is isolation of Gram negative bacilli in the presence of septic shock, in patients with other implanted intravascular devices, or when there is an isolation of CoNS in the same circumstances [58,59].

In relation to infection of the insertion site: in PVCs, removal is mandatory if there is pain, induration, or erythema (A-I); non-tunneled CVCs should be removed in case of erythema or purulence (B-II) and in any case if clinical signs of infection persist 72 hours after the start of conservative treatment (B-II).

Question 7. What situations allow conservative treatment to be attempted?

In patients with suspicion of catheter related infection, immediate systematic removal of **non-tunneled** CVCs is **not** routinely recommended (conservative treatment) in hemodynamically stable patients, in patients without autoimmune disease or immunosuppressive therapy, in patient with no other intravascular devices or organ transplantation, suppuration at the insertion site or associated bacteremia/fungemia [21, 40, 56].

In the case of long-term **tunneled** CVCs in which the route of progression of microorganisms is the intraluminal, the use of antibiotic lock therapy, in addition to treatment with systemic antimicrobial agents, is recommended in stable patients with isolation of low virulence microorganisms, such as CoNS (except *Staphylococcus lugdunensis*). In stable patients without local or systemic complications, conservative treatment can also be attempted in bacteremia caused by enterococci, corynebacteria (except *Corynebacterium jeikeium*) and gram-negative bacilli (in these cases it is suggested to consult an infectious disease expert) [60-63].

The antibiotic lock solution should be prepared under sterile conditions. The recommended duration of the lock is around 10-14 days. The lock solution should remain in the catheter lumen for a minimum of 12 h per day and should be replaced every 24-72 h. Ethanol 70% and taurolidine solutions could also be used as lock solutions. However, there is no evidence to advocate their routine use [40].

Question 8. What is the empirical treatment of suspected CRI?

If CRI is suspected, antimicrobial therapy with an agent active against *S. aureus* and CoNS should be initiated as soon as possible, especially if associated with sepsis or septic shock [21, 40]. The initial choice of antimicrobial should be based on an assessment of the risk factors for infection, the severity of the clinical scenario, and the pathogens likely associated with the specific intravascular device. An effective empirical therapy is especially important in patients with *S. aureus* C-RBSI who are at high risk of hematogenous metastases, especially when the catheter cannot be removed and/or the antibiotic treatment is inadequate [64].

Since most CoNS are methicillin-resistant, the choice of empirical treatment should include antibiotics active against methicillin-resistant strains. In recent decades, vancomycin has been the most prescribed antimicrobial for methicillin-resistant *S. aureus* (MRSA) bacteremia. Studies comparing the efficacy and safety of glycopeptides (vancomycin vs. teicoplanin) for staphylococcal bacteremia (including MRSA) have not observed significant differences, although strains of *Staphylococcus epidermidis* and *Staphylococcus haemolyticus* with reduced susceptibility to teicoplanin have been described [65].

Daptomycin is probably more advantageous in cases of septic shock, acute renal failure, to patients with recent van-

comycin exposure (>1 week in the last 3 months) or if the local prevalence of *S. aureus* isolates with vancomycin MIC ≥1.5 mg/L is high [66].

Although there is lack of clinical trial-based evidence, ceftaroline or its combination with daptomycin is probably an alternative empirical anti-staphylococcal therapy.

Patients with suspected C-RBSI should also receive empirical coverage against gram-negative bacilli in the following circumstances: hemodynamic instability, neutropenia or hematologic neoplasia, solid organ or bone marrow transplantation, femoral catheter in place, high rate of gram-negative bacilli colonization, or prolonged ICU admission [67]. Antimicrobial therapy should be adapted to the local epidemiology.

Empiric therapy for suspected catheter-related candidemia should be considered in hemodynamically unstable patients with one or more of the following conditions: total parenteral nutrition, prolonged use of broad-spectrum antibiotics, malignancy, femoral catheterization, colonization due to *Candida* spp. at multiple sites, or prior intense anaerobicidal therapy [41,68].

Question 9. What should be the duration of treatment?

The duration of antimicrobial treatment of catheter infection depends on whether there is associated bacteremia, on the causative microorganism and the presence of complications, such as endocarditis, suppurative thrombophlebitis, or metastatic infections, which will be treated independently in this review.

In Table 1 we summarize the treatment duration recommendations according to the characteristics previously discussed.

Positive culture of the catheter tip, but without associated bacteremia

Starting with the least serious situation, which would be the isolation of a microorganism in the catheter, but without proven bacteremia, we will also take into account the microorganism cultured and the clinical situation of the patient. When a CoNS, enterococcus or enterobacteria is recovered, treatment may not be administered in a stable patient. However, isolation of *S. aureus, Pseudomonas aeruginosa* or *Candida* spp. although not constitute per se an indication of treatment, should lead to a clinical evaluation of the patient and if fever or clinical deterioration, consideration of whether the patient requires blood cultures if these have not been drawn recently. If the patient is septic some authors considered prudent to initiate treatment until blood cultures are proven to be negative [69-73].

However, it is necessary to clarify that these recommendations are not based on clinical trials, so decisions should be individualized.

It is necessary to emphasize that the recommended durations refer to days of effective systemic treatment and that days of empirical treatment should not be included if this was not optimal for the microorganism involved.

Table 1 **Duration of antimicrobial treatment in intravascular catheter-associated infections.**

Microorganism	Characteristics	Length of treatment
S. aureus, Candida spp.	No blood cultures (BC) obtained or negative BC	No indication of treatment per se in patients without symptoms. 3-5 days may be prudent until BC come negative in high-risk patients.
	BC + without complications	14 days since first negative BC
	BC + with complications[a]	4-6 weeks
CoNS, *Enterococcus* spp., enterobacteria	Negative BC	No therapy in stable patients[b]
	BC + without complications	5-7 days if the catheter has been removed, including observation without antibiotics if the patient is stable, has no risk factors (prosthetic material) and has transient bacteremia that disappears only with catheter removal (B-III)
		10-14 days with lock therapy if the catheter has been retained (C-III)
	BC + with complications	4-6 weeks
P. aeruginosa	Negative BC	3-5 days
	BC + without complications	7 days
	BC + with complications	4-6 weeks

CoNS: coagulase negative *Staphylococcus*; [a]Complicated bacteremia: persistent fever, presence of prosthetic material or septic metastasis, positive control blood cultures, failure to remove the catheter; [b]These proposals are based on low quality epidemiological data and are presented only as a guide. They should be modulated according to the clinical presentation of the patient, the existence of intravascular devices or immunosuppression.

Uncomplicated C-RBSI (catheter segment and peripheral blood with the same microorganism)

In this case the duration will essentially depend on the microorganism and whether or not the patient is considered to have a complicated bacteremia.

To be considered uncomplicated, C-RBSI must meet the following criteria:

- Catheter removal within five days of diagnosis.
- Rapid resolution of bacteremia with sterile blood cultures within 72 hours of initial positive culture.
- Clinical response and absence of symptoms or signs of metastatic infection.

- Patients without endovascular or orthopedic implants.
- For infections due to *S. aureus*, an additional criterion for bacteremia to be considered uncomplicated is an echocardiogram without evidence of endocarditis.

When all criteria for uncomplicated bacteremia are met, a treatment duration of 5-7 days can be considered for CoNS, enterococci and enterobacteria, 7 days for *P. aeruginosa* and 14 days from the first negative blood culture for *S. aureus* [21,58].

In the presence of endovascular implant or orthopedic hardware (in the absence of evidence of IE or infection of the orthopedic hardware) and C-RBSI in patients in whom the catheter has been removed with rapid clearance of bacteremia, some authors recommend prolonging systemic antimicrobial therapy for 14 days taking into account the possibility of seeding of the prosthetic hardware.

In general, treatment is usually prolonged in patients with persistent bacteremia (>72 h after catheter removal), but the level of evidence is higher for *S. aureus* (A-II) than for other microorganisms (C-III) [21].

The duration of treatment of C-RBSI caused by Gram-negative bacilli has recently been shortened based on a recent meta-analysis of uncomplicated episodes and without the use of lock therapy and on a retrospective series comparing the evolution in patients with long or short treatment [74-76]. No significant differences were observed with respect to mortality or microbiological relapse between short- and long-duration systemic antibiotic treatment.

The duration of treatment of complicated bacteremia will be addressed in another question in this review.

Question 10. What is the role of new long half-life drugs?

In order to establish the role of these new antibiotics, it is important to consider three concepts: (1) not all catheter infections produce bacteremia, which has direct implications on the duration of antibiotic treatments; (2) the most frequent etiology of catheter infections are CoNS, which usually do not require more than 3 to 5 days of antibiotherapy even in the presence of bacteremia [77]; and (3) it is essential to determine which patients with CRI will require longer antibiotherapy based on microbiological and clinical determinants. With regard to microbiological determinants, it is necessary to distinguish *S. aureus* from the rest of the microorganisms due to their greater virulence, especially in complicated bacteremias. According to the clinical determinants, we should consider longer antimicrobial therapy in those patients who develop venous thrombophlebitis of medium or large caliber vessels, as well as those patients with endovascular devices, among others. Therefore, most cases of CRI (including those who develop bacteremia) will not require prolonged antimicrobial therapy, and oral sequential treatment can be used early [78]. In this regard, there are data from clinical trials that support the possibility of performing oral sequential treatment from day 5 in uncomplicated *S. aureus* bacteremia [79].

Therefore, long half-life drugs should be selected for those situations in which the patient presents some intestinal absorption problem, when there are no oral options with good availability (or the patient has already presented severe toxicity to those available), and for the first phase of treatment of complex infections. Glycopeptides are proving to be a very good alternative in these situations, with dalbavancin being the antibiotic for which there is most published clinical data [80,81]. Dalbavancin has shown comparable efficacy to other conventional intravenous options, with the advantage of having a 7-day half-life, thus reducing hospital stay and consequently the number of nosocomial infections.

Question 11. How should catheter-related suppurative thrombophlebitis be managed?

The most important issue in the clinical management of bacterial infections is the need for early focus control. Data on *S. aureus* bacteremia have demonstrated that the delay in focus control is directly related to a longer duration of bacteremia, and this in turn to the risk of septic metastasis as well as higher mortality on day 30 [82]. Once adequate antibiotic treatment has been started and the catheter has been removed, the use of anticoagulation may be considered in patients with significant thrombophlebitis. However the level of evidence is low, and most guidelines leave the decision to initiate anticoagulation and its duration to the attending clinician with uncertain data regarding indication and duration [40]. There is one single-center retrospective study of patients with *S. aureus* bacteremia and radiologically proven thrombophlebitis, in which anticoagulation was associated with lower mortality in the multivariate analysis [83]. Thrombolysis and surgical treatment are reserved for exceptional cases with persistent bacteremia despite optimized antibiotic treatment and after ruling out other potential foci [84].

Question 12. When and how can a catheter with suspected infection be replaced over guidewire?

Current indications for guidewire replacement of central catheters include mechanical complications such as (a) rupture of the external tract of the catheter, (b) secondary malposition (so-called tip migration), (c) substitution with a similar but more appropriate device (for instance, replacement of a single-lumen with a double-lumen catheter) [40, 85-87]. Guidewire replacement is known to be ineffective for prevention of C-RBSI; also, it is not considered useful for diagnosis or for treatment of catheter-related infection.

In fact, current contraindications for guidewire replacement are: (a) infected catheter (suspected infection or established diagnosis of infection), (b) colonized catheter, (c) presence of symptomatic or asymptomatic thrombosis, (d) presence of fibroblastic sleeve.

A catheter **with suspected infection** may be replaced over guidewire only in very exceptional cases, i.e., in patients requiring central venous access, carriers of a colonized or infected catheter, in whom extreme difficulty is foreseen for the placement of a new central venous access and in whom con-

servative treatment of infection or colonization is not indicated. In such cases, the catheter should be preferably replaced with an antimicrobial catheter (such as a catheter coated with chlorhexidine/silver-sulphadiazine or a catheter coated with antibiotics) [88]. This maneuver should be taken into consideration only if there is no evidence of septic shock or of endocarditis

NEW DEVELOPMENTS IN PREVENTION

Question 13. What steps should be followed in the implantation of a vascular line?

The first consideration would always be to question the need for the device, taking into account the risks and benefits for the patient. The use of daily objective checklists helps to evaluate the removal of catheters that are not indicated.

Regarding the implantation of a central venous catheter (CVC), the use of ultrasound during the insertion can be considered as it demonstrated to reduce mechanical complications during the procedure.

Checklists should also be used during the insertion process. They include verifying the competence of the professionals performing the procedure and supervision, as well as the fundamental aspects that should be contemplated during the procedure from informed consent, correct hand hygiene or barrier measures among others. This tool has been shown to significantly reduce the rate of C-RBSI [89]. Similarly, the availability of kits with all the necessary material for the implantation of a CVC has also demonstrated to be effective [90].

The Bacteremia Zero protocol, updated in 2021, establishes a series of recommendations (mandatory, optional, do not perform) in relation to the implantation of CVC [91], and there is ample scientific evidence applicable to other vascular devices [22]. The following recommendations stand out for their importance:

1. **Adequate hand hygiene** before and after palpating the insertion site, as well as before and after insertion. This can be done with soap and water or with hydroalcoholic solution according to recommendations. The use of sterile gloves does not exempt from hand hygiene (high evidence/strong recommendation).

2. **Skin disinfection with chlorhexidine**. Disinfect the skin with an alcoholic chlorhexidine solution containing a concentration between 0.5 and 2% and 70° alcohol before CVC insertion or with alcoholic iodine solution in case of contraindication [92]. (High evidence/strong grade of recommendation).

3. **Maximum protective barriers**. Adoption of maximum sterility barriers (cap, mask, sterile gown, sterile gloves, and large sterile drape covering the patient) during CVC insertion substantially reduces the incidence of C-RBSI [93]. (High evidence/degree of strong recommendation).

4. **Subclavian location preference**. The subclavian vein should be preferred, taking into account other factors such as the possibility of non-infectious complications, certain populations such as hemodialysis patients, and the skill of the practitioner when inserting the catheter [4, 94]. (High evidence/strong recommendation).

In the cannulation of PICCs, the basilic vein will be the first choice, since it has the largest caliber and the most direct route to the superior vena cava.

There are some recommendations applicable to high-risk patient subgroups, such as the use of catheters impregnated with antimicrobials, and don't do recommendations such as not administering prophylactic antibiotherapy prior to CVC insertion.

Question 14. What is the current role of ultrasound and other methods of vascular visualization?

Vascular visualization technology plays an increasing role in venous access, and should be part of the knowledge of any physician or nurse expert in vascular access, as recommended by the 2021 Standards of the Infusion Nursing Society (INS) and as demonstrated in different works [95-103].

Ultrasound is currently indispensable for the placement of peripheral venous access in DIVA patients (DIVA = Difficult Intra-Venous Access), both in adults and in children.

More importantly, ultrasound is currently indispensable for the placement of any central venous access device. It plays a role not only for venipuncture but – as described in the 2020 guidelines of the European Society of Anesthesia (ESA) - in many different aspects of the procedure, both in adults and in children:

1. pre-procedural evaluation of the veins, preferably using a systematic and standardized approach such as the RaCeVA protocol for CICCs (RaCeVa = Rapid Central Venous Assessment), the RaPeVA protocol for PICCs (RaPeVA = Rapid Peripheral Venous Assessment), and the RaFeVA protocol for FICCs (RaFeVA = Rapid Femoral Venous Assessment);
2. ultrasound-guided puncture and cannulation of the vein, with different techniques, depending on the vein to be accessed (out-of-plane in short axis; in-plane in short axis; in-plane in long axis; in-plane in oblique axis);
3. diagnosis of immediate complications related to venipuncture (pneumothorax, hematomas); in particular, pleural scan with a linear probe has a very high accuracy in excluding the presence of pneumothorax, and should be performed soon after any venipuncture for PICC insertion;
4. control of the progression of the guidewire and/or the catheter; ultrasound scan by a linear probe is the easiest method for 'tip navigation' (safer and more accurate than fluoroscopy);
5. intraprocedural localization of the tip; all current guidelines recommend intraprocedural 'tip location': though the most recommended method is intracavitary ECG, whenever such method is not applicable or not feasible, the easiest method for intraprocedural tip location is trans-thoracic echocardiography, using the 'bubble test' (as standardized in the ECHOTIP protocol); ultrasound-based tip location is safer and more accurate than fluoroscopy, and is particularly useful in neonates;

6. diagnosis and follow-up of all late complications. With the exception of infectious complications, ultrasound plays a pivotal role in the diagnosis and management of all non-infective complications (venous thrombosis, fibroblastic sleeve, secondary malposition, etc.).

On the other hand, also near infrared (NIR) technology may have a role in the field of vascular access. NIR technology allows proper visualization of superficial veins (i.e., veins at less than 7 mm from the surface of the skin) and is currently recommended in two types of situations:

- in all placements of epicutaneo-cava catheters and short PVCs in the neonate;
- in the placement of short PVCs in the infant with DIVA.

Question 15. What should be the daily care of implanted catheters?

Intravascular catheters are indispensable devices for the correct management of patients, so their use is frequent and so they are their complications. Preventive measures are essential both at insertion, as we have just seen, and at daily maintenance.

The COVID-19 pandemic has revealed that the measures implemented are difficult to maintain under stress and this has been reflected in the increase in CRI rates [8, 104]. The American guidelines [105], as well as the new recommendations of the SEMICYUC-SEEIUC [91] have incorporated in addition to the previous mandatory measures, new recommendations such as pre-prepared insertion kits to reduce catheter cannulation time, daily hygiene of patients with chlorhexidine, coverage with chlorhexidine-impregnated dressings on CVCs in patients over 2 months of age, passive disinfection with antiseptic-impregnated caps on bio connectors to ensure compliance with disinfection of bio connectors before use, continuous infusion system replacement at 7 days coinciding with bio connector replacement, the need to remove unnecessary catheters and an appropriate nurse-patient ratio.

Regarding the care of PVCs [106], the recommended measures include: hand hygiene before and after each manipulation, skin disinfection with 2% alcoholic chlorhexidine [107], use of sterile gloves if it is not guaranteed not to touch the catheter after applying antiseptic, coverage of catheter entry site with semi-permeable transparent dressings, use of closed connectors, disinfection of the bio connectors with single-dose wipes impregnated with antiseptic or passive disinfection before use, catheter replacement only when clinically indicated, daily monitoring of the insertion point, maintenance preferably with pre-filled syringes of saline solution per shift and removal of the catheter when it is not necessary.

In conclusion, it is necessary to implement all measures in all catheters and throughout the hospital.

Question 16. What are the problems and limitations of the teaching procedures on CRI prevention?

Different studies have demonstrated the poor professionals' knowledge regarding the recommendations in the prevention of CRI [108-110]. A review including 19 studies, observed the low adherence of professionals to the recommendations on CRI prevention [111].

Training of all professionals (nurses, physicians, residents and students), has shown different impacts on improving knowledge and CRI rates. In a study conducted in Spanish internal medicine units, the implementation of an educational program with posters and leaflets did not have a great impact on improving healthcare professionals' knowledge, although quality of catheter care was better [112]. In a review including 10 studies, the training of all neonatal ICU professionals demonstrated a decrease in CRI rates in 8 of them [113]. Continuous training seems to be the most effective approach in order to achieve lower rates of CRI, as shown in a study conducted in medical wards with mandatory continuing education and audits for 4.5 years [114].

Real-time training and feedback was associated with increased compliance in PVC care in an emergency unit [115], but the study underlined some of the barriers such as lack of time, no space for training, lack of materials, roles not identified, etc [116].

Therefore, continuous training of all professionals is necessary, but the degree of compliance with all recommendations must be measured and it is necessary to have feed-back with professionals to achieve better results.

Question 17. How can new teaching and instrumentation technology help training in this area?

The COVID-19 pandemic has exposed the deficiency of the healthcare system to maintain the recommendations on CRI prevention. The inability to conduct face-to-face training has promoted the use of telemedicine and on-line training.

Simulation through standardized teaching sessions in a safe environment reinforces best practices in nosocomial infection prevention [117], although in a study conducted both in one medical and one surgical ICU, it only reduced CRI rates in the medical ICU [118].

Other technologies, such as augmented reality glasses have helped in improving CVC insertion techniques [119] and can be used to improve the knowledge of all practitioners.

In addition, technology can help to identify variables, such as age, comorbidity, or treatment, that are associated with an increased risk of developing CRI [120].

A pilot study with a sensor implanted in a reservoir helped to detect signs of infection [121].

In conclusion, technology can help to improve the training of all professionals and help in prevention of nosocomial infections identifying risk factors of non-adherence to the recommendations.

Question 18. What has been the impact and current status of "zero tolerance" programs on catheter infection?

Before the implementation of the "Zero Projects", the surveillance of nosocomial infection in the ICU was consolidated in Spain through the "ENVIN-ICU" registry (National Surveil-

lance Study of Nosocomial Infection in the ICU) since 1994. This registry is an activity of the Working Group on Infectious Diseases and Sepsis (GTEIS) of the SEMICYUC and currently collects information from more than 80% of the country's ICUs. It is a voluntary, multicenter, prospective registry that includes information on device-related infections, bacteremia secondary to other foci and other infections. Between 1994 and 2006, the incidence density (ID) of primary bacteremia (PB) ranged from 5.04 to 7.9 episodes x 1,000 CVC days, 14.6-23.6 for ventilator-associated pneumonia per 1,000 mechanical ventilation days (VAP) and 4.9-7.4 for urinary tract infections per 1,000 IBC days (UTI) (https://proyectoszero.semicyuc.org/). These figures are significantly higher than those reported by the "National Nosocomial Infections Surveillance" (NNIS) in North American ICUs [122].

During the implementation period of the "Zero Bacteremia Project" (January 2009 - June 2010), 192 ICUs joined the program, which represented 68% of the country's ICUs. At the end of participation, the ID of primary bacteremia decreased from a median of 3.07 to 1.12 episodes per 1,000 CVC days ($p < 0.001$). The adjusted incidence rate showed a 50% [95% CI, 0.39-0.63] reduction in the risk of bacteremia at the end of the follow-up period from baseline. The rates decreased independently of hospital size and type [123]. In addition, CVC utilization ratio was reduced by 4.9%. The Zero Pneumonia and Zero Resistance projects have also demonstrated a significant reduction in healthcare-associated infections (HCAI) and multi-resistances [124].

During the pandemic, the structural, functional, and organizational changes implemented in the ICUs to meet the care-needs made it difficult to apply the recommendations of the critical patient safety projects (Projects Zero) to prevent the development of HCAI. Data from the 2021 ENVIN-HELICS report (ENVIN-ICU '02 (vhebron.net) confirm the impact of the pandemic on ICU infection indicators. Rates of patients acquiring one or more infections during ICU stay remained elevated (14.36 per 100 admitted patients), figures far from the 4.76 per 100 admitted patients in 2019. The DI of all device-related infections remains high reaching in PB 4.42 episodes per 1,000 catheter days; in VAP 11.33 episodes per 1,000 MV days and in UTIs 4.67 episodes per 1,000 IBC days, all figures higher than the previous ones in 2019 (2.5 PB per 1. 000 days of CVC; 5.41 VAP per 1,000 days of MV and 2.85 UTIs per 1,000 days of ED, respectively) and very similar to those existing at the start of the "Bacteremia Zero"; "Pneumonia Zero" and "UTI-SU Zero" programs. This has led to the implementation of new specific measures to reduce HCAIs related to ICU devices, updating protocols and promoting the training of all Intensive Care Medicine professionals. At present, there is already evidence of a reduction in all device-associated HCAIs in the ICU.

Question 19. What do we know about the administrative situation of this problem in Spain?

Patient safety, a key component of quality of care, has acquired great relevance in recent years both for patients and their families, who wish to feel safe and confident in the healthcare they receive, and for managers and professionals who wish to offer safe, effective and efficient healthcare (https://seguridaddelpaciente.sanidad.gob.es/presentacion/home.htm).

The Ministry of Health (MS), in its responsibility to improve the quality of the healthcare system as a whole, as established in Law 16/2003, on Cohesion and Quality of the National Health System, has placed patient safety at the center of healthcare policies as one of the key elements of quality improvement, as reflected in strategy number 8 of the Quality Plan for the National Health System, which has been developed since 2005 in coordination with the Autonomous Communities (AC).

Since 2006, the Spanish MS, in collaboration with the AC, has been establishing safe practices in various areas, one of them being the prevention of nosocomial infection and surgical infections. Strict surveillance of infection in the ICU is a basic, essential instrument that increases the safety of patients and saves lives.

The "Zero Projects" led by the Spanish Society of Intensive Care Medicine, Critical Care and Coronary Units (SEMICYUC) and the Spanish Society of Intensive Care Nursing and Coronary Units (SEEIUC), in collaboration with the MS and the AC, have been an opportunity to introduce a culture of safety in the ICU. These projects, with proven sustainability over time, have become working tools in the ICU with successful results. Moreover, they have led not only to an improvement in the incidence of HCRI in the ICU and a reduction in the number of patients with multi-resistant bacteria, but also to a change in the way of working and planning critical patient care as a whole, as well as, in short, a boost in the safety culture.

Zero Tolerance Projects have been incorporated into the Safety strategies of the AC that have promoted their development at the local level. In many of them, hospital program contracts include among their objectives participation in these projects and the achievement of the established quality standard. This undoubtedly boosted their implementation in ICUs. Moreover, in some communities the results of these indicators are published periodically to improve transparency.

Numerous activities have been carried out to disseminate these projects and updated training programs have been developed and made available to all professionals caring for ICU patients (https://proyectoszero.semicyuc.org/).

All this demonstrates the commitment of the Administration, health care institutions and professionals to improving safety and specifically to reduce HCAIs related with ICU devices.

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CONFLICTS OF INTEREST

The author declares no conflicts of interest

REFERENCES

1. Pittiruti M, Scoppettuolo G. Manuale GAVeCeLT dei PICC e dei Midline (2nd edition). Published by EDRA, 2022. 2022.
2. Pittiruti M, Capozzoli G. Manuale pratico dell'accesso venoso (2a edition). Published by Antonio Delfino Editore. 2022.
3. Biasucci DG, Disma NM, Pittiruti M. Vascular access in neonates and children. Published by Springer. 2022.
4. Chaves F, Garnacho-Montero J, Del Pozo JL, Bouza E, Capdevila JA, de Cueto M, et al. Executive summary: Diagnosis and Treatment of Catheter-Related Bloodstream Infection: Clinical Guidelines of the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC) and the Spanish Society of Intensive Care Medicine and Coronary Units (SEMICYUC). Enferm Infecc Microbiol Clin (Engl Ed). 2018;36(2):112-9.
5. Rodríguez-Créixems M, Muñoz P, Martín-Rabadán P, Cercenado E, Guembe M, Bouza E. Evolution and aetiological shift of catheter-related bloodstream infection in a whole institution: the microbiology department may act as a watchtower. Clin Microbiol Infect. 2013;19(9):845-51.
6. Pitiriga V, Bakalis J, Theodoridou K, Dimitroulia E, Saroglou G, Tsakris A. Comparison of microbial colonization rates between central venous catheters and peripherally inserted central catheters. Antimicrob Resist Infect Control. 2023;12(1):74.
7. Rosenthal VD, Chaparro GJ, Servolo-Medeiros EA, Souza-Fram D, Escudero D, Gualtero-Trujillo SM, et al. An eight-year multicenter study on short-term peripheral intravenous catheter-related bloodstream infection rates in 100 intensive care units of 9 countries in Latin America: Argentina, Brazil, Colombia, Costa Rica, Dominican Republic, Ecuador, Mexico, Panama, and Venezuela. Findings of the International Nosocomial Infection Control Consortium (INICC). Infect Control Hosp Epidemiol. 2021;42(9):1098-104.
8. Pérez-Granda MJ, Carrillo CS, Rabadán PM, Valerio M, Olmedo M, Muñoz P, et al. Increase in the frequency of catheter-related bloodstream infections during the COVID-19 pandemic: a plea for control. J Hosp Infect. 2022;119:149-54.
9. Bouza E, Rojas L, Guembe M, Marín M, Anaya F, Luño J, et al. Predictive value of superficial cultures to anticipate tunneled hemodialysis catheter-related bloodstream infection. Diagn Microbiol Infect Dis. 2014;78(3):316-9.
10. Calò F, Retamar P, Martínez Pérez-Crespo PM, Lanz-García J, Sousa A, Goikoetxea J, et al. Catheter-related bloodstream infections: predictive factors for Gram-negative bacteria aetiology and 30 day mortality in a multicentre prospective cohort. J Antimicrob Chemother. 2020;75(10):3056-61.
11. Laporte-Amargos J, Sastre E, Bergas A, Pomares H, Paviglianiti A, Rodriguez-Arias M, et al. Increasing Gram-Negative Catheter-Related Bloodstream Infection in Cancer Patients. Pathogens. 2023;12(2).
12. Mandolfo S, Anesi A, Rognoni V. The epidemiology of central venous catheter-related bloodstream infection in our renal units is changing. J Vasc Access. 2022;23(2):328-9.
13. Bayoumi MAA, van Rens M, Chandra P, Masry A, D'Souza S, Khalil AM, et al. Does the antimicrobial-impregnated peripherally inserted central catheter decrease the CLABSI rate in neonates? Results from a retrospective cohort study. Front Pediatr. 2022;10:1012800.
14. Guembe M, Pérez-Granda MJ, Capdevila JA, Barberán J, Pinilla B, Martín-Rabadán P, et al. Nationwide study on peripheral-venous-catheter-associated-bloodstream infections in internal medicine departments. J Hosp Infect. 2017;97(3):260-6.
15. Reigadas E, Rodríguez-Créixems M, Guembe M, Sánchez-Carrillo C, Martín-Rabadán P, Bouza E. Catheter-related bloodstream infection caused by Enterococcus spp. Clin Microbiol Infect. 2013;19(5):457-61.
16. Phua AI, Hon KY, Holt A, O'Callaghan M, Bihari S. Candida catheter-related bloodstream infection in patients on home parenteral nutrition - Rates, risk factors, outcomes, and management. Clin Nutr ESPEN. 2019;31:1-9.
17. Al Yazidi LS, Marais BJ, Hazelton B, Outhred A, Kesson A. Nontuberculous Mycobacteria in Children: A Focus on Bloodstream Infections. Pediatr Infect Dis J. 2017;36(4):374-8.
18. Nagata A, Sekiya N, Najima Y, Horiuchi M, Fukushima K, Toya T, et al. Nontuberculous mycobacterial bloodstream infections after allogeneic hematopoietic stem cell transplantation. Int J Infect Dis. 2020;97:131-4.
19. Comba IY, Tabaja H, Almeida NEC, Fida M, Saleh OA. Bloodstream infections with rapidly growing nontuberculous mycobacteria. J Clin Tuberc Other Mycobact Dis. 2021;25:100288.
20. Mizusawa M, Vindenes T, Buckley S, Armstrong C. A case series of rapidly growing mycobacterial catheter-related bloodstream infections among immunocompetent patients. J Clin Tuberc Other Mycobact Dis. 2020;21:100196.
21. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;49(1):1-45.
22. O'Grady NP. Prevention of Central Line-Associated Bloodstream Infections. N Engl J Med. 2023;389(12):1121-31.
23. O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, et al. Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis. 2011;52(9):e162-93.
24. Di Domenico EG, Oliva A, Guembe M. The Current Knowledge on the Pathogenesis of Tissue and Medical Device-Related Biofilm Infections. Microorganisms. 2022;10(7).
25. Toyofuku M, Inaba T, Kiyokawa T, Obana N, Yawata Y, Nomura N. Environmental factors that shape biofilm formation. Biosci Biotechnol Biochem. 2016;80(1):7-12.
26. Guzmán-Soto I, McTiernan C, Gonzalez-Gomez M, Ross A, Gupta K, Suuronen EJ, et al. Mimicking biofilm formation and development: Recent progress in in vitro and in vivo biofilm models. iScience. 2021;24(5):102443.
27. Sivori F, Cavallo I, Kovacs D, Guembe M, Sperduti I, Truglio M, et al. Role of Extracellular DNA in Dalbavancin Activity against Methicillin-Resistant Staphylococcus aureus (MRSA) Biofilms in

Patients with Skin and Soft Tissue Infections. Microbiol Spectr. 2022;10(2):e0035122.

28. Kavanaugh JS, Flack CE, Lister J, Ricker EB, Ibberson CB, Jenul C, et al. Identification of Extracellular DNA-Binding Proteins in the Biofilm Matrix. mBio. 2019;10(3).
29. Díaz-Navarro M, Piqueras JC, Díez R, Hafian R, Manzano I, Muñoz P, et al. Understanding the diagnosis of catheter-related bloodstream infection: Real-time monitoring of biofilm growth dynamics using time-lapse optical microscopy Front Cell Infect Microbiol. 2023;In Press.
30. Lamret F, Varin-Simon J, Velard F, Terryn C, Mongaret C, Colin M, et al. Staphylococcus aureus Strain-Dependent Biofilm Formation in Bone-Like Environment. Front Microbiol. 2021;12:714994.
31. Macias-Valcayo A, Aguilera-Correa JJ, Broncano A, Parron R, Auñon A, Garcia-Cañete J, et al. Comparative In Vitro Study of Biofilm Formation and Antimicrobial Susceptibility in Gram-Negative Bacilli Isolated from Prosthetic Joint Infections. Microbiol Spectr. 2022;10(4):e0085122.
32. Duddy OP, Bassler BL. Quorum sensing across bacterial and viral domains. PLoS Pathog. 2021;17(1):e1009074.
33. Eickhoff MJ, Bassler BL. SnapShot: Bacterial Quorum Sensing. Cell. 2018;174(5):1328-.e1.
34. Mukherjee S, Bassler BL. Bacterial quorum sensing in complex and dynamically changing environments. Nat Rev Microbiol. 2019;17(6):371-82.
35. Naga NG, El-Badan DE, Ghanem KM, Shaaban MI. It is the time for quorum sensing inhibition as alternative strategy of antimicrobial therapy. Cell Commun Signal. 2023;21(1):133.
36. Williams P, Hill P, Bonev B, Chan WC. Quorum-sensing, intra- and inter-species competition in the staphylococci. Microbiology (Reading). 2023;169(8).
37. Wang M, Lian Y, Wang Y, Zhu L. The role and mechanism of quorum sensing on environmental antimicrobial resistance. Environ Pollut. 2023;322:121238.
38. Ferrer C, Almirante B. [Venous catheter-related infections]. Enferm Infecc Microbiol Clin. 2014;32(2):115-24.
39. Del Pozo JL, Alonso M, de la Torre M, Aguinaga A. Infections related to totally implantable venous-access ports. Lancet Infect Dis. 2014;14(8):676.
40. Chaves F, Garnacho-Montero J, Del Pozo JL, Bouza E, Capdevila JA, de Cueto M, et al. Diagnosis and treatment of catheter-related bloodstream infection: Clinical guidelines of the Spanish Society of Infectious Diseases and Clinical Microbiology and (SEIMC) and the Spanish Society of Spanish Society of Intensive and Critical Care Medicine and Coronary Units (SEMICYUC). Med Intensiva (Engl Ed). 2018;42(1):5-36.
41. Bouza E, Alcalá L, Muñoz P, Martín-Rabadán P, Guembe M, Rodríguez-Créixems M. Can microbiologists help to assess catheter involvement in candidaemic patients before removal? Clin Microbiol Infect. 2013;19(2):E129-35.
42. Bouza E, Alvarado N, Alcalá L, Pérez MJ, Rincón C, Muñoz P. A randomized and prospective study of 3 procedures for the diagnosis of catheter-related bloodstream infection without catheter withdrawal. Clin Infect Dis. 2007;44(6):820-6.
43. Bouza E, Burillo A, Muñoz P. Catheter-related infections: diagnosis and intravascular treatment. Clin Microbiol Infect. 2002;8(5):265-74.
44. León M, García M, Herranz MA, González V, Martínez A, Castillo F, et al. [Diagnostic value of Gram staining of peri-catheter skin and the connection in the prediction of intravascular-catheter-related bacteremia]. Enferm Infecc Microbiol Clin. 1998;16(5):214-8.
45. Pascual A, Cercenado E, Salavert M, Elías García-Sánchez J, Eiros JM, Liñares J, et al. Update on pathogenesis and diagnosis of intravascular catheter-related infections. Enferm Infecc Microbiol Clin. 2011;29 Suppl 4:16-21.
46. Dooley DP, Garcia A, Kelly JW, Longfield RN, Harrison L. Validation of catheter semiquantitative culture technique for nonstaphylococcal organisms. J Clin Microbiol. 1996;34(2):409-12.
47. Bouza E, Alvarado N, Alcalá L, Sánchez-Conde M, Pérez MJ, Muñoz P, et al. A prospective, randomized, and comparative study of 3 different methods for the diagnosis of intravascular catheter colonization. Clin Infect Dis. 2005;40(8):1096-100.
48. Cleri DJ, Corrado ML, Seligman SJ. Quantitative culture of intravenous catheters and other intravascular inserts. J Infect Dis. 1980;141(6):781-6.
49. Brun-Buisson C, Abrouk F, Legrand P, Huet Y, Larabi S, Rapin M. Diagnosis of central venous catheter-related sepsis. Critical level of quantitative tip cultures. Arch Intern Med. 1987;147(5):873-7.
50. Bouza E, Martín-Rabadán P, Echenagusia A, Camúñez F, Rodríguez-Rosales G, Simó G, et al. Diagnosis of venous access port colonization requires cultures from multiple sites: should guidelines be amended? Diagn Microbiol Infect Dis. 2014;78(2):162-7.
51. EPINE-EPPS E. Prevalencia de infecciones y uso de antimicrobianos en hospitales de agudos Informe nacional: España nº 32. 2022.
52. Registro de Infección Nosocomial en UCI ENVIN-HELICS. 2022.
53. Hollenbeak CS. The cost of catheter-related bloodstream infections: implications for the value of prevention. J Infus Nurs. 2011;34(5):309-13.
54. Dimick JB, Pelz RK, Consunji R, Swoboda SM, Hendrix CW, Lipsett PA. Increased resource use associated with catheter-related bloodstream infection in the surgical intensive care unit. Arch Surg. 2001;136(2):229-34.
55. Stevens V, Geiger K, Concannon C, Nelson RE, Brown J, Dumyati G. Inpatient costs, mortality and 30-day re-admission in patients with central-line-associated bloodstream infections. Clin Microbiol Infect. 2014;20(5):O318-24.
56. Rijnders BJ, Peetermans WE, Verwaest C, Wilmer A, Van Wijngaerden E. Watchful waiting versus immediate catheter removal in ICU patients with suspected catheter-related infection: a randomized trial. Intensive Care Med. 2004;30(6):1073-80.
57. Lorente L, Martín MM, Vidal P, Rebollo S, Ostabal MI, Solé-Violán J. Should central venous catheter be systematically removed in patients with suspected catheter related infection? Crit Care. 2014;18(5):564.

58. Timsit JF, Baleine J, Bernard L, Calvino-Gunther S, Darmon M, Dellamonica J, et al. Expert consensus-based clinical practice guidelines management of intravascular catheters in the intensive care unit. Ann Intensive Care. 2020;10(1):118.

59. Timsit JF, Ruppé E, Barbier F, Tabah A, Bassetti M. Bloodstream infections in critically ill patients: an expert statement. Intensive Care Med. 2020;46(2):266-84.

60. Rijnders BJ, Van Wijngaerden E, Vandecasteele SJ, Stas M, Peetermans WE. Treatment of long-term intravascular catheter-related bacteraemia with antibiotic lock: randomized, placebo-controlled trial. J Antimicrob Chemother. 2005;55(1):90-4.

61. Del Pozo JL, García Cenoz M, Hernáez S, Martínez A, Serrera A, Aguinaga A, et al. Effectiveness of teicoplanin versus vancomycin lock therapy in the treatment of port-related coagulase-negative staphylococci bacteraemia: a prospective case-series analysis. Int J Antimicrob Agents. 2009;34(5):482-5.

62. Del Pozo JL, Rodil R, Aguinaga A, Yuste JR, Bustos C, Montero A, et al. Daptomycin lock therapy for grampositive long-term catheter-related bloodstream infections. Int J Clin Pract. 2012;66(3):305-8.

63. Carmona-Torre F, Yuste JR, Castejon S, Ramos A, Del Pozo JL. Catheter-related bloodstream infections in patients with oncohaematological malignancies. Lancet Infect Dis. 2017;17(2):139-40.

64. Kimmig A, Hagel S, Weis S, Bahrs C, Löffler B, Pletz MW. Management of Staphylococcus aureus Bloodstream Infections. Front Med (Lausanne). 2020;7:616524.

65. Falcone M, Russo A, Pompeo ME, Vena A, Marruncheddu L, Ciccaglioni A, et al. Retrospective case-control analysis of patients with staphylococcal infections receiving daptomycin or glycopeptide therapy. Int J Antimicrob Agents. 2012;39(1):64-8.

66. Chaftari AM, Hachem R, Mulanovich V, Chemaly RF, Adachi J, Jacobson K, et al. Efficacy and safety of daptomycin in the treatment of Gram-positive catheter-related bloodstream infections in cancer patients. Int J Antimicrob Agents. 2010;36(2):182-6.

67. Sreeramoju PV, Tolentino J, Garcia-Houchins S, Weber SG. Predictive factors for the development of central line-associated bloodstream infection due to gram-negative bacteria in intensive care unit patients after surgery. Infect Control Hosp Epidemiol. 2008;29(1):51-6.

68. Nagao M, Hotta G, Yamamoto M, Matsumura Y, Ito Y, Takakura S, et al. Predictors of Candida spp. as causative agents of catheter-related bloodstream infections. Diagn Microbiol Infect Dis. 2014;80(3):200-3.

69. Pérez-Parra A, Muñoz P, Guinea J, Martín-Rabadán P, Guembe M, Bouza E. Is Candida colonization of central vascular catheters in non-candidemic, non-neutropenic patients an indication for antifungals? Intensive Care Med. 2009;35(4):707-12.

70. Guembe M, Rodríguez-Créixems M, Martín-Rabadán P, Alcalá L, Muñoz P, Bouza E. The risk of catheter-related bloodstream infection after withdrawal of colonized catheters is low. Eur J Clin Microbiol Infect Dis. 2014;33(5):729-34.

71. Muñoz P, Fernández Cruz A, Usubillaga R, Zorzano A, Rodríguez-Créixems M, Guembe M, et al. Central venous catheter colonization with Staphylococcus aureus is not always an indication for antimicrobial therapy. Clin Microbiol Infect. 2012;18(9):877-82.

72. Ekkelenkamp MB, van der Bruggen T, van de Vijver DA, Wolfs TF, Bonten MJ. Bacteremic complications of intravascular catheters colonized with Staphylococcus aureus. Clin Infect Dis. 2008;46(1):114-8.

73. Hetem DJ, de Ruiter SC, Buiting AGM, Kluytmans J, Thijsen SF, Vlaminckx BJM, et al. Preventing Staphylococcus aureus bacteremia and sepsis in patients with Staphylococcus aureus colonization of intravascular catheters: a retrospective multicenter study and meta-analysis. Medicine (Baltimore). 2011;90(4):284-8.

74. Ruiz-Ruigómez M, Aguado JM. Duration of antibiotic therapy in central venous catheter-related bloodstream infection due to Gram-negative bacilli. Curr Opin Infect Dis. 2021;34(6):681-5.

75. Ruiz-Ruigómez M, Fernández-Ruiz M, San-Juan R, López-Medrano F, Orellana M, Corbella L, et al. Impact of duration of antibiotic therapy in central venous catheter-related bloodstream infection due to Gram-negative bacilli. J Antimicrob Chemother. 2020;75(10):3049-55.

76. Muff S, Tabah A, Que YA, Timsit JF, Mermel L, Harbarth S, et al. Short-Course Versus Long-Course Systemic Antibiotic Treatment for Uncomplicated Intravascular Catheter-Related Bloodstream Infections due to Gram-Negative Bacteria, Enterococci or Coagulase-Negative Staphylococci: A Systematic Review. Infect Dis Ther. 2021;10(3):1591-605.

77. Badia-Cebada L, Carmezim J, Pérez-Rodríguez MT, Bereciartua E, López LE, Montenegro MR, et al. Randomized Clinical Trial of the Need for Antibiotic Treatment for Low-Risk Catheter-Related Bloodstream Infection Caused by Coagulase-Negative Staphylococci. Antibiotics (Basel). 2023;12(5).

78. Tamma PD, Conley AT, Cosgrove SE, Harris AD, Lautenbach E, Amoah J, et al. Association of 30-Day Mortality With Oral Step-Down vs Continued Intravenous Therapy in Patients Hospitalized With Enterobacteriaceae Bacteremia. JAMA Intern Med. 2019;179(3):316-23.

79. Kaasch AJ, López-Cortés LE, Rodríguez-Baño J, Cisneros JM, Dolores Navarro M, Fätkenheuer G, et al. Efficacy and safety of an early oral switch in low-risk Staphylococcus aureus bloodstream infection (SABATO): an international, open-label, parallel-group, randomised, controlled, non-inferiority trial. Lancet Infect Dis. 2024.

80. Hidalgo-Tenorio C, Vinuesa D, Plata A, Martin Dávila P, Iftimie S, Sequera S, et al. DALBACEN cohort: dalbavancin as consolidation therapy in patients with endocarditis and/or bloodstream infection produced by gram-positive cocci. Ann Clin Microbiol Antimicrob. 2019;18(1):30.

81. Gonzalez PL, Rappo U, Akinapelli K, McGregor JS, Puttagunta S, Dunne MW. Outcomes in Patients with Staphylococcus aureus Bacteremia Treated with Dalbavancin in Clinical Trials. Infect Dis Ther. 2022;11(1):423-34.

82. Minejima E, Mai N, Bui N, Mert M, Mack WJ, She RC, et al. Defining the Breakpoint Duration of Staphylococcus aureus Bacteremia Predictive of Poor Outcomes. Clin Infect Dis. 2020;70(4):566-73.

83. Wilson Dib R, Chaftari AM, Hachem RY, Yuan Y, Dandachi D, Raad, II. Catheter-Related Staphylococcus aureus Bacteremia and Septic Thrombosis: The Role of Anticoagulation Therapy and Duration of Intravenous Antibiotic Therapy. Open Forum Infect Dis. 2018;5(10):ofy249.

84. Kim M, Kwon H, Hong SK, Han Y, Park H, Choi JY, et al. Surgical treatment of central venous catheter related septic deep venous thrombosis. Eur J Vasc Endovasc Surg. 2015;49(6):670-5.

85. Cellini M, Bergadano A, Crocoli A, Badino C, Carraro F, Sidro L, et al. Guidelines of the Italian Association of Pediatric Hematology and Oncology for the management of the central venous access devices in pediatric patients with onco-hematological disease. J Vasc Access. 2022;23(1):3-17.

86. Gorski LA, Hadaway L, Hagle ME, Broadhurst D, Clare S, Kleidon T, et al. Infusion Therapy Standards of Practice, 8th Edition. J Infus Nurs. 2021;44(1S Suppl 1):S1-s224.

87. Lamperti M, Biasucci DG, Disma N, Pittiruti M, Breschan C, Vailati D, et al. European Society of Anaesthesiology guidelines on peri-operative use of ultrasound-guided for vascular access (PERSEUS vascular access). Eur J Anaesthesiol. 2020;37(5):344-76.

88. Chaftari AM, El Zakhem A, Jamal MA, Jiang Y, Hachem R, Raad I. The use of minocycline-rifampin coated central venous catheters for exchange of catheters in the setting of staphylococcus aureus central line associated bloodstream infections. BMC Infect Dis. 2014;14:518.

89. Wichmann D, Belmar Campos CE, Ehrhardt S, Kock T, Weber C, Rohde H, et al. Efficacy of introducing a checklist to reduce central venous line associated bloodstream infections in the ICU caring for adult patients. BMC Infect Dis. 2018;18(1):267.

90. Berenholtz SM, Pronovost PJ, Lipsett PA, Hobson D, Earsing K, Farley JE, et al. Eliminating catheter-related bloodstream infections in the intensive care unit. Crit Care Med. 2004;32(10):2014-20.

91. Gallart E, Delicado M, Nuvials X. [Update of the recommendations of the Bacteraemia Zero Project]. Enferm Intensiva. 2022;33:S31-s9.

92. Yasuda H, Sanui M, Abe T, Shime N, Komuro T, Hatakeyama J, et al. Comparison of the efficacy of three topical antiseptic solutions for the prevention of catheter colonization: a multicenter randomized controlled study. Crit Care. 2017;21(1):320.

93. Hu KK, Lipsky BA, Veenstra DL, Saint S. Using maximal sterile barriers to prevent central venous catheter-related infection: a systematic evidence-based review. Am J Infect Control. 2004;32(3):142-6.

94. Parienti JJ, Mongardon N, Mégarbane B, Mira JP, Kalfon P, Gros A, et al. Intravascular Complications of Central Venous Catheterization by Insertion Site. N Engl J Med. 2015;373(13):1220-9.

95. Annetta MG, Marche B, Dolcetti L, Taraschi C, La Greca A, Musarò A, et al. Ultrasound-guided cannulation of the superficial femoral vein for central venous access. J Vasc Access. 2022;23(4):598-605.

96. Bertoglio S, Annetta MG, Brescia F, Emoli A, Fabiani F, Fino M, et al. A multicenter retrospective study on 4480 implanted PICC-ports: A GAVeCeLT project. J Vasc Access. 2022:11297298211067683.

97. Brescia F, Pittiruti M, Ostroff M, Biasucci DG. Rapid Femoral Vein Assessment (RaFeVA): A systematic protocol for ultrasound evaluation of the veins of the lower limb, so to optimize the insertion of femorally inserted central catheters. J Vasc Access. 2021;22(6):863-72.

98. Iacobone E, Elisei D, Gattari D, Carbone L, Capozzoli G. Transthoracic echocardiography as bedside technique to verify tip location of central venous catheters in patients with atrial arrhythmia. J Vasc Access. 2020;21(6):861-7.

99. Greca A, Iacobone E, Elisei D, Biasucci DG, D'Andrea V, Barone G, et al. ECHOTIP: A structured protocol for ultrasound-based tip navigation and tip location during placement of central venous access devices in adult patients. J Vasc Access. 2023;24(4):535-44.

100. Passaro G, Pittiruti M, La Greca A. The fibroblastic sleeve, the neglected complication of venous access devices: A narrative review. J Vasc Access. 2021;22(5):801-13.

101. Pittiruti M, La Greca A. How to choose the most appropriate ultrasound-guided approach for central line insertion: introducing the rapid central venous assessment protocol. P Lumb, D Karakitsos, eds 1th Ed Philadelphia, USA: Elsevier Saunders. 2014:76-9.

102. Qin KR, Pittiruti M, Nataraja RM, Pacilli M. Long peripheral catheters and midline catheters: Insights from a survey of vascular access specialists. J Vasc Access. 2021;22(6):905-10.

103. Spencer TR, Pittiruti M. Rapid Central Vein Assessment (RaCeVA): A systematic, standardized approach for ultrasound assessment before central venous catheterization. J Vasc Access. 2019;20(3):239-49.

104. Baker MA, Sands KE, Huang SS, Kleinman K, Septimus EJ, Varma N, et al. The Impact of Coronavirus Disease 2019 (COVID-19) on Healthcare-Associated Infections. Clin Infect Dis. 2022;74(10):1748-54.

105. Buetti N, Marschall J, Drees M, Fakih MG, Hadaway L, Maragakis LL, et al. Strategies to prevent central line-associated bloodstream infections in acute-care hospitals: 2022 Update. Infect Control Hosp Epidemiol. 2022;43(5):553-69.

106. Pittiruti M, Van Boxtel T, Scoppettuolo G, Carr P, Konstantinou E, Ortiz Miluy G, et al. European recommendations on the proper indication and use of peripheral venous access devices (the ERPIUP consensus): A WoCoVA project. J Vasc Access. 2023;24(1):165-82.

107. Guenezan J, Marjanovic N, Drugeon B, Neill RO, Liuu E, Roblot F, et al. Chlorhexidine plus alcohol versus povidone iodine plus alcohol, combined or not with innovative devices, for prevention of short-term peripheral venous catheter infection and failure (CLEAN 3 study): an investigator-initiated, open-label, single centre, randomised-controlled, two-by-two factorial trial. Lancet Infect Dis. 2021;21(7):1038-48.

108. Labeau SO, Vandijck DM, Rello J, Adam S, Rosa A, Wenisch C, et al. Centers for Disease Control and Prevention guidelines for preventing central venous catheter-related infection: results of a knowledge test among 3405 European intensive care nurses. Crit Care Med. 2009;37(1):320-3.

109. Badparva B, Ghanbari A, Karkhah S, Osuji J, Kazemnejad Leyli E, Jafaraghaee F. Prevention of central line-associated bloodstream infections: ICU nurses' knowledge and barriers. Nurs Crit Care. 2023;28(3):419-26.

110. Esposito MR, Guillari A, Angelillo IF. Knowledge, attitudes, and practice on the prevention of central line-associated bloodstream

infections among nurses in oncological care: A cross-sectional study in an area of southern Italy. PLoS One. 2017;12(6):e0180473.

111. Burke C, Jakub K, Kellar I. Adherence to the central line bundle in intensive care: An integrative review. Am J Infect Control. 2021;49(7):937-56.
112. Guembe M, Pérez-Granda MJ, Capdevila JA, Barberán J, Pinilla B, Bouza E. Impact of a training program on adherence to recommendations for care of venous lines in internal medicine departments in Spain. Eur J Clin Microbiol Infect Dis. 2018;37(6):1163-8.
113. Semelsberger CF. Educational interventions to reduce the rate of central catheter-related bloodstream infections in the NICU: a review of the research literature. Neonatal Netw. 2009;28(6):391-5.
114. Dumyati G, Concannon C, van Wijngaarden E, Love TM, Graman P, Pettis AM, et al. Sustained reduction of central line-associated bloodstream infections outside the intensive care unit with a multimodal intervention focusing on central line maintenance. Am J Infect Control. 2014;42(7):723-30.
115. Fakih MG, Jones K, Rey JE, Takla R, Szpunar S, Brown K, et al. Peripheral venous catheter care in the emergency department: education and feedback lead to marked improvements. Am J Infect Control. 2013;41(6):531-6.
116. LeMaster CH, Hoffart N, Chafe T, Benzer T, Schuur JD. Implementing the central venous catheter infection prevention bundle in the emergency department: experiences among early adopters. Ann Emerg Med. 2014;63(3):340-50.e1.
117. Kang M, Nagaraj MB, Campbell KK, Nazareno IA, Scott DJ, Arocha D, et al. The role of simulation-based training in healthcare-associated infection (HAI) prevention. Antimicrob Steward Healthc Epidemiol. 2022;2(1):e20.
118. Allen GB, Miller V, Nicholas C, Hess S, Cordes MK, Fortune JB, et al. A multitiered strategy of simulation training, kit consolidation, and electronic documentation is associated with a reduction in central line-associated bloodstream infections. Am J Infect Control. 2014;42(6):643-8.
119. Khouli H, Jahnes K, Shapiro J, Rose K, Mathew J, Gohil A, et al. Performance of medical residents in sterile techniques during central vein catheterization: randomized trial of efficacy of simulation-based training. Chest. 2011;139(1):80-7.
120. Noaman AY, Ragab AHM, Al-Abdullah N, Jamjoom A, Nadeem F, Ali AG. WMSS: A Web-Based Multitiered Surveillance System for Predicting CLABSI. Biomed Res Int. 2018;2018:5419313.
121. Gil B, Lo B, Yang GZ, Anastasova S. Smart implanted access port catheter for therapy intervention with pH and lactate biosensors. Mater Today Bio. 2022;15:100298.
122. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. Am J Infect Control. 2004;32(8):470-85.
123. Palomar M, Álvarez-Lerma F, Riera A, Díaz MT, Torres F, Agra Y, et al. Impact of a national multimodal intervention to prevent catheter-related bloodstream infection in the ICU: the Spanish experience. Crit Care Med. 2013;41(10):2364-72.
124. Álvarez-Lerma F, Palomar-Martínez M, Sánchez-García M, Martínez-Alonso M, Álvarez-Rodríguez J, Lorente L, et al. Prevention of Ventilator-Associated Pneumonia: The Multimodal Approach of the Spanish ICU "Pneumonia Zero" Program. Crit Care Med. 2018;46(2):181-8.