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Review

Central venous catheter-related biofilm infections: An up-to-date focus on meticillin-resistant *Staphylococcus aureus*☆

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ABSTRACT

Central venous catheters are indispensable for the long-term treatment of seriously and chronically ill patients, but their use is often associated with a variety of complications; indeed, 90% of primary bloodstream infections are related to patients having a catheter. In studies performed in France, Germany and Italy, meticillin-resistant *Staphylococcus aureus* (MRSA) accounted for >50% of all *S. aureus* isolates obtained in catheter-related bloodstream infections (CRBSIs). These infections have a serious impact on long-term disability of the patient, a substantial additional financial burden for health systems, and high costs for patients. Decreasing the rate of CRBSIs requires a multidisciplinary approach, including behavioural and educational interventions and the insertion of the correct type of catheter. Although vancomycin remains the cornerstone of empirical therapy for CRBSIs caused by MRSA, combination of different antimicrobials and new approaches are indispensable to enhance the eradication of *S. aureus* biofilms and to manage the patient appropriately.
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Contents

1. Introduction

Biofilm production is a successful strategy for microbial survival and for the establishment of infection. Since host defence mechanisms and response to antimicrobials are severely prejudiced against bacteria living in the biofilm 'microniche', chronic infections and sepsis related to biofilms represent a major concern in nosocomial settings.

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Central venous catheters (CVCs), which include a variety of vascular access devices with a wide range of clinical applications, are disposed to biofilm infection because they offer a favourable surface for bacterial attachment [1].

Staphylococci are recognised as the most frequent bacteria responsible for biofilm-associated infections, and the involvement in catheter-related infections of meticillin-resistant *Staphylococcus aureus* (MRSA) has increased the challenge for the healthcare community [2,3].

Upon insertion into the patient, the surface of the catheter is quickly coated with host-derived matrix proteins such as fibrin, fibrinogen, fibronectin, collagen, elastin and laminin [4,5], which serve as scaffolding for bacteria that may have passed the skin barrier. *S. aureus* can bind to the catheter surface owing to a wide range of cell-wall surface proteins that possess binding domains for the host matrix, and such surface proteins are referred to as microbial surface components recognising adhesive matrix molecules (MSCRAMMs) [6]. Indeed, micro-organisms can start to colonise the medical device, forming biofilm, as early as 24 h after catheter placement [7], and bacteria may then flow into the systemic circulation resulting in a bloodstream infection (BSI).

Thus, although CVCs are indispensable for long-term treatment of seriously and chronically ill patients, their use is often associated with a variety of complications; indeed, 90% of primary BSIs are related to patients having a central line catheter [8,9].

Although there is debate about whether catheter-related BSIs (CRBSIs) are an independent risk factor for mortality, it is clear that these infections have a serious impact on long-term disability of the patient, a substantial additional financial burden for health systems, and high costs for patients and their families [10–12].

2. Inside catheter-related bloodstream infections: definition, pathogenesis and epidemiology

A CRBSI is clinically defined as 'systemic blood infection (bacteraemia) where the same microorganism is retrieved from both the blood and the catheter, without evidence of infection with the identical organism at any other site in the body' [13]. The most common routes for CVC contamination are migration of skin micro-organisms at the catheter insertion site along its surface tract, with subsequent colonisation of the catheter tip, and direct contamination of the catheter hub by contact with hands, contaminated fluid or devices. Less commonly, catheters might be contaminated haematogenously from another focus of infection [14].

From a nationwide surveillance study among 49 US hospitals over a 7-year period, it has been highlighted that the most frequent pathogens for CRBSIs were coagulase-negative staphylococci (31%), *S. aureus* (20%), enterococci (9%) and *Candida* spp. [15]. MRSA has become a concern in recent years in the USA, Europe and Japan owing to its increasing rate and, although it appears to have stabilised or even decreased in some European countries (Austria, Cyprus, Estonia, France, Greece, Ireland and the UK), it remains a public health priority since its proportion is still >25% in more than one-third of the reporting countries [16,17] and because among the staphylococci, meticillin-resistant isolates have been the most commonly reported as responsible for nosocomial BSIs [18,19].

Although the incidence of CRBSIs has recently decreased as a result of strict prevention efforts, *S. aureus* has been reported as one of the most frequently reported pathogens in intensive care unit (ICU)-acquired infections (21.8%) in studies performed in France, Germany and Italy [20,12], and MRSA accounted for >50% of all *S. aureus* isolates obtained in ICU CRBSIs [21].

3. Biofilm

Biofilm formation is a winning move for micro-organisms with respect to the planktonic lifestyle because its enables bacteria to adapt to altered environmental conditions and provides shelter from the host immune system (i.e. phagocytic elimination, opsonisation) and from antimicrobial/antifouling compounds [22].

Generally, biofilm development occurs via a mechanism termed 'quorum sensing' in which the expression of specific signal molecules, called 'autoinducers', is regulated in response to cell density and stressed environmental conditions [23]. *S. aureus* is able to produce a heterogeneous multilayered biofilm using different strategies, including: (i) expression of numerous surface proteins, including Bap, SasG, FnBPs or Spa; (ii) release of extracellular DNA (eDNA); and (iii) expression of the polysaccharide intercellular adhesin (PIA) by the *ica*ADBC operon [24].

Biofilm development is a complex mechanism and includes different stages that can differ from organism to organism. The steps of *S. aureus* biofilm production on intravenous (i.v.) catheters can be summarised as follows: (i) attachment to the catheter surface through electrostatic and hydrophobic forces, platelet binding and shear stress from the fluid environment cause attachment to the host matrix through MSCRAMMs; (ii) intercellular adhesion and growth of the bacteria into sessile multicellular communities through excretion of specific polymers; and (iii) detachment and dissemination of new divided cells to colonise other surfaces and to prevent density-derived starvation within the mature biofilm. Thus, biofilm embedded micro-organisms live in a self-producing exopolymeric matrix or 'slime' that alters the global micro-organism phenotype with respect to growth rate, gene expression and response to external attacks [25].

Nutrients and oxygen permeate the matrix through specific channels and the resulting gradient may generate a population of cells that differ substantially in their metabolism [26]. These cells, named 'persisters', have a low metabolic rate and live in a dormant state attributable to starvation and a low oxygen concentration in the environment, conditions that cause high tolerance to antibiotics [27]. However, persisters are not mutants; indeed, re-culturing of persisters produces a wild-type population with a new population of persisters [28,29]. In other words, persisters are stationary phase cells with increased resistance to killing owing to slow growth produced not only in biofilms but also in stationary phase planktonic populations [30].

Moreover, antibiotic penetration through the biofilm is limited by the exopolysaccharide matrix that acts like a diffusion barrier, limiting the antibiotic uptake rate and also reacting with these molecules [25]. For a long time it appeared that molecular weight was a limiting factor for antibiotic penetration into biofilms, however recent studies have demonstrated that the molecular dimensions of antibiotics have no significant relevance [31,32]. Indeed, in an in vitro study by Stewart et al., daptomycin, one of the antibiotics with a higher molecular weight, was confirmed to have freely diffusive penetration into a large, dense cluster of staphylococcal biofilms [33].

Thus, from a clinical point of view, the hallmark of biofilm-embedded micro-organisms is their resistance to large doses of traditional antimicrobial agents; they can actually be 100–1000-fold less susceptible than their planktonic counterparts [34]. For this reason, treatment of CRBSIs, which is regulated by standardised antimicrobial susceptibility tests performed with planktonic cells, can have an unsuccessful outcome and often relies on removal of the catheter [22].

4. Treatment

Although there is no unanimously accepted clinical pathway for the management of CRBSIs, several guidelines and recommendations have recently been published [34–37] and, in general, treatment of these infections should include oral or i.v. antibiotics or an antibiotic lock technique (ALT) and removal and re-insertion of the CVC in the case of *S. aureus* infection.

It is important to underline that the vast majority of *S. aureus* biofilm infections require long-term therapy and so it is crucial to take into account toxicities and drug interactions when selecting a specific regimen.

The ability of an antibiotic to eradicate MRSA embedded in biofilm depends on many factors such as its molecular mass, net charge, permeability coefficient and bactericidal activity. Antibiotics of low molecular weight are likely to diffuse more efficiently into the biofilm [38].

So, when considering staphylococcal biofilm treatment options, the ideal therapy would have several characteristics:

- bactericidal activity against slow-growing, stationary phase-like cells;
- low rate of resistance development;
- straightforward administration of the therapy to patients, with few side effects; and
- broad efficacy against all staphylococci and polymicrobial biofilm infections.

Even if the catheter has been removed and a new one has been inserted, an antibiotic regimen including antibiofilm activity must be considered. Indeed, colonisation of the new catheter by biofilm fragments dislodged from the one that has been removed is possible.

4.1. Current therapies

For the treatment of serious MRSA device-related infections, vancomycin remains the cornerstone of empirical therapy, but in the most recent 10 years *S. aureus* minimum inhibitory concentrations (MICs) to vancomycin have increased from 0.25 mg/L to 2 mg/L, associating its use with several therapeutic failures.

Guidelines indicate that patients with complicated MRSA infections should receive 4–6 weeks of vancomycin therapy, except those with a vancomycin MIC $>$ 2 mg/L, who should instead receive daptomycin or linezolid depending on susceptibility data [38].

Vancomycin acts by binding to the cell wall peptidoglycan chains and therefore preventing the cross-linking step during cell wall synthesis. This effect leads to a weakened cell wall, slowing growth and bacterial death [39].

Although vancomycin is considered bactericidal, its time-dependent mode of action, the i.v. administration required and the frequent side effects are serious limitations of this drug that can lead to longer hospital stays and higher costs for the institution [40].

Moreover, recently there have been conflicting results on the use of vancomycin monotherapy in the treatment of biofilm-embedded MRSA [41–43]. Rose and Poppens demonstrated that vancomycin exhibited bactericidal activity towards planktonic MRSA cells at low levels (1 μg/mL), but the MIC increased four- to eight-fold in a biofilm susceptibility assay, suggesting its use in combination with rifampicin or tigecycline [44]. In fact, also in other studies it has been shown that vancomycin efficacy increases in combination with other antibiotics (rifampicin, gentamicin, clindamycin), leading to better penetration of the drug into the depth of the biofilm [45,46].

In the face of emerging resistance to vancomycin and other glycopeptides, daptomycin is being used as an alternative first-line therapy against biofilm-embedded MRSA.

Daptomycin, a cyclic lipopeptide, is bactericidal towards log phase, stationary phase and metabolically inert Gram-positive bacteria owing to insertion of its lipophilic tail into the cell membrane, resulting in membrane depolarisation and cell death. In a study by Mascio et al., daptomycin demonstrated bactericidal activity against log phase *S. aureus* cells at low concentrations (2 mg/L) and against stationary phase cells at a higher concentration (100 mg/L) [47].

For the treatment of staphylococcal biofilm infections, daptomycin alone is more effective than other monotherapies. An in vitro study of 12 MRSA clinical isolates showed that daptomycin was the most effective of five antibiotics tested (compared with clindamycin, linezolid, tigecycline and vancomycin) at killing cells within biofilms; in fact, although total killing of biofilm cells was not achieved, daptomycin treatment eliminated 96% of biofilm-associated bacteria [43].

In combination therapy, daptomycin treatment with rifampicin or gentamicin has shown conflicting results, but its clinical use has proven successful against several forms of biofilm infections [48,49]. Finally, in a rat model study by Van Praagh et al., combined daptomycin ALT and systemic dosing resulted in clearance of *S. aureus* CVC-related infection after two daily ALT treatments [50].

Oxazolidinones inhibit ribosome function and prevent protein synthesis by targeting the assembly of ribosomal subunits. Linezolid is the only oxazolidinone approved for clinical use [51] and has encouraging properties, including broad-spectrum activity against Gram-positive bacteria, good tissue distribution and penetration, and bioavailability. Moreover, among the antibiotics used for the treatment of invasive MRSA infections, linezolid is one of the few that can be taken orally. Linezolid has demonstrated activity against biofilms both in in vitro and in vivo model systems. In a rabbit model of *S. aureus* endocarditis, linezolid cleared biofilm vegetations after 5 days of treatment when administered at high doses that maintained the blood level above the MIC [52], whilst in another recent study linezolid exhibited bactericidal activity in combination with rifampicin and prevented the development of infection at secondary sites [53].

Linezolid was also tested on staphylococcal biofilms utilising an in vitro pharmacokinetic model in which the biomass was developed on a cellulose filter and this was perfused with a solution containing the antibiotic. This study highlighted that linezolid was very effective at clearing biofilm if the infected device was exposed to the antibiotic for longer time periods, whilst success with short-term exposure varied and might be dependent on the type of infected device being treated [54]. In addition, a model of ALT gave conflicting results, showing that the amount of biofilm remaining after 5 days of linezolid exposure was similar to negative controls [55]. Instead, clinical use and combination therapy of linezolid to treat staphylococcal biofilm infections has been shown to be promising. In a study of prosthetic joint infections, treatment of patients (49 total) with combined therapy of linezolid and rifampicin cleared infection with a success rate of nearly 70% without implant removal [56].

Rifampicin has the capacity to kill metabolically dormant sessile bacteria, typical of biofilm, and has the ability to effectively penetrate the biofilm layer preventing its formation within only minutes of treatment. It has bactericidal activity and targets the bacterial RNA polymerase, inhibiting RNA synthesis. Numerous examples of in vitro studies, in vivo animal models of infection, and clinical studies demonstrated the efficacy of rifampicin in treating staphylococcal implant infections [57]. In one study evaluating antibiotics within ALT, co-administration of rifampicin with other

antibiotics resulted in enhanced eradication of MRSA biofilms more than any monotherapy.

The same study demonstrated that daptomycin, minocycline and tigecycline were more effective in decreasing viable biofilm-embedded MRSA after 24 h of exposure than linezolid or vancomycin. Addition of rifampicin to vancomycin or linezolid was synergistic against biofilm-embedded MRSA [55]. In addition to its bactericidal and fast-acting properties, rifampicin has good pharmacokinetic properties, achieving penetration into diverse tissue sites. It is lipid soluble, facilitating passage through biological membranes, perhaps improving its biofilm-penetrating capability.

Fosfomycin has been characterised in previous in vitro studies as an effective antibacterial against MRSA [58,59]; however, no in vivo studies on the effects of fosfomycin on biofilm-embedded MRSA have been published.

A recent study evaluated the activity of several anti-MRSA compounds, alone and in combination with fosfomycin, on bacterial colony counts in biofilm and demonstrated that fosfomycin enhances the activity of linezolid, minocycline, vancomycin and teicoplanin on MRSA in biofilm, even more than rifampicin combination regimens. The low molecular weight of fosfomycin may partially explain its enhanced antibacterial activity against biofilm-embedded micro-organisms [60].

4.2. New therapeutic approaches

Essential antimicrobial targets for inhibition of biofilm formation or for eradication of mature biofilm are not only the bacteria themselves but also destruction of biofilm matrix and interference with the biofilm signalling system [61].

Whilst antibiotics and novel derivatives have been the mainstay of empirical therapy, many efforts have been made to design more innovative therapeutic options such as nanosilver, the cytokine interleukin-12, nitric oxide or antistaphylococcal phages [62–65]. However, the clinical utility of these agents has yet to be demonstrated. One strategy for controlling biofilm growth is to weaken its structure by targeting the matrix components, which leads to dispersal of bacteria and consequently to a greater susceptibility to antibiotics [66].

5. Prevention of catheter-related bloodstream infections

Decreasing the rate of CRBSIs requires a comprehensive and multidisciplinary approach, including behavioural and educational interventions of the hospital staff as well as the use of new technologies. There are several guidelines providing recommendations for the preventions of CRBSIs [67,68]. These guidelines examine the usefulness of various practices such as the choice of CVC, site of insertion, observance of an adequate aseptic technique, care and replacement of the catheter, and the choice of appropriate antibiotic therapy.

An initial and crucial step in preventing CRBSIs is to weight and consider the risks and benefits of using a CVC in order to avoid unnecessary placements; indeed, in a recent hospital survey it was calculated that among a total of 378 CVCs inserted in 292 patients, accounting for 2704 catheter-days, 130 catheter-days (4.8%) were unnecessary, with a higher proportion in non-ICU settings (6.6%) [69]. Various risk factors involving insertion or catheter handling have been described in the literature. Such risk factors have been named ‘modifiable’ [70] because they are the optimal candidates for CRBSI prevention strategies (Table 1).

These factors are as follows. (i) Aseptic measures: hygiene and aseptic techniques during placement, management and removal of catheters are essential in preventing infection. (ii) CVC duration: the overall proportion of CRBSIs is actually higher in long-term devices, and the length of stay in ICU settings increases the risk of CRBSI more than other risk factors [71]. (iii) CVC insertion site [72]: the site at which a catheter is placed influences the subsequent possibility for a catheter-related infection risk in terms of density of local skin flora and chance of developing thrombophlebitis. In some retrospective studies, catheters inserted into an internal jugular vein have usually been associated with a higher risk of CRBSI than those inserted into a subclavian site [73]. Femoral catheters have, on the other hand, been associated with a higher risk for venous thrombosis than internal jugular or subclavian catheters [74]. (iv) Introduction of the correct type of catheter. And (v) high workload: an optimum nurse-to-patient ratio has been correlated with a lower CRBSI rate [70].

Table 1
Modifiable risk factors for catheter-related bloodstream infections (CRBSIs).

Aseptic measures	Risk of infection declines following standardisation of aseptic care
CVC duration	Length of stay increases the risk of CRBSIs more than other risk factors
CVC insertion site	Insertion site increases the infection risk relative to the density of local skin flora and the chance of developing thrombophlebitis
Type of catheter	CVCs can be chosen with regard to material and whether or not to use an antimicrobial/anti-infective-coated catheter
Nurse-to-patient ratio	Education and training of nurses are critical for the prevention of CRBSIs

CVC, central venous catheter.

5.1. Behavioural interventions and educational programmes

Performing hand hygiene procedures before insertion or maintenance of a catheter is the first and most important basic rule of hygiene and, combined with proper aseptic techniques during catheter manipulation, provides protection against infection.

Reports in past years have clearly demonstrated that the risk of infection declines following standardisation of aseptic care [75–77]. Maximal sterile barriers, which include wearing a mask, cap, sterile gown and sterile gloves and covering the insertion site with a large surgical drape, were shown to be effective either alone or as a part of a multimodal CRBSI prevention strategy. These CRBSI bundles were, as reported in many published studies, very efficient and reduced the CRBSI incidence density, reported as the number of CRBSI episodes per 1000 catheter-days, by $\geq$70% [78].

Education, training and staffing are critical for the prevention of CRBSIs. Well organised programmes include education of healthcare personnel and periodically assessing knowledge of the guidelines for all personnel involved in the insertion and maintenance of catheters.

Recently, an educational programme demonstrated that a 1-day course on basic infection control practises and a demonstration of insertion both of arterial and CVCs illustrated to beginning post-graduate year 1 (PGY-1) physicians resulted in a significant reduction in CRBSI and primary BSIs from 3.3 to 2.4 per 1000 CVC-days [75]. Other recent studies demonstrated that specialised ‘IV teams’ have shown clear helpfulness in reducing the CRBSI incidence, associated complications and overall costs [79,80].

Although educational programmes have an impact on the healthcare institution and may not be sustainable over time, hospitals should try to provide clear guidelines for catheter insertion and maintenance and ensure their observance to maintain a high level of awareness of standard procedures [81].

The benefits of preventing CRBSIs are numerous, and if we think that a large proportion of them are preventable, it is clear that a

strong attempt has to be made from the healthcare community to face this problem.

5.2. Choice of the correct central venous catheter (material and antiseptic/antimicrobial-coated catheters)

In recent years, significant efforts have been made to design new catheters aimed at reducing the risk of CRBSIs.

Major choices for the clinician when inserting a CVC are regarding its material and whether or not to use an antimicrobial/anti-infective-coated catheter.

Regarding the material, important considerations have been made on this topic, i.e. polytetrafluoroethylene (Teflon®) or polyurethane catheters have been associated with fewer infectious complications than catheters made of polyvinyl chloride or polyethylene [82]. Catheter material is critical in the prevention of CRBSIs; it should be biocompatible/biostable, chemically neutral, and drug/sterilisation proof [83].

The underlying principle for the use of a coated CVC is the possibility of modifying the catheter surface to minimise bacterial adhesion and consequently biofilm formation. The decision to insert an antibiotic-coated CVC has to be taken in view of the single risk factors for an infection of a given patient and overall rates of CRBSI for a specific hospital. Following the US Centers for Disease Control and Prevention (CDC) Healthcare Infection Control Practices Advisory Committee guidelines, coated catheters should be inserted in adult patients if the CVC is to remain place for >5 days as well as in institutions with high CRBSI rates [67].

Coated CVCs are available with different impregnated materials: (i) chlorhexidine and silver sulfadiazine (CSS); (ii) minocycline–rifampicin (MR); and (iii) silver in a carbon/platinum (SPC) matrix. One meta-analysis and one randomised controlled trial have demonstrated that first-generation CSS catheters, which are coated only on the external luminal surface, are associated with a reduced risk of CRBSI compared with standard non-coated catheters. In fact, chlorhexidine and silver salts act synergistically, disrupting the cytoplasmic membrane and increasing silver uptake, which is extremely toxic for micro-organisms [84,85].

Second-generation CSS catheters are now available with chlorhexidine also coating the internal surface, but a limited number of control trials have been carried out [86,87]. CSS catheters are more expensive than standard catheters, however there is a debate on the real cost saving per catheter despite adherence to other preventive strategies; one study showed that CSS catheters could lead to a cutback per catheter in settings with a high CRBSI rate ranging between US$391 and US$68 [88].

MR CVCs have broad-spectrum activity and have been studied both in vitro and in vivo in randomised clinical trials, which have demonstrated that these catheters are effective against biofilm-producing bacteria and are associated with a lower rate of CRBSIs [89,90].

Compared with first-generation CSS catheters, MR CVCs have also been found to be related to lower CRBSI rates, but their evaluation against second-generation CSS CVCs has to be further investigated. Although no MR-resistant organisms were reported in several studies [91–93], there are still some concerns about the potential for development of rifampicin-resistant bacteria. Finally, several studies revealed that these catheters are associated with superior cost saving compared with standard catheters [94] and with first-generation CSS CVCs [95,96].

SPCs are only available in the USA and some studies have evaluated their effectiveness against uncoated or MR catheters, but their association with a lower rate of CRBSIs has not yet been clearly demonstrated [97].

5.3. Catheter antibiotic lock therapy

Given the cost, difficulty and complication associated with the removal of a long-term CVC, some guidelines have suggested the use of catheter ALT for the prevention of CRBSI and salvage of the CVC in high-risk patients [38,98].

ALT consists of the 'lockage' of a specified antibiotic in the CVC when the catheter is not in use (generally 18–24 h) with or without heparin at concentrations 100–1000 times higher than the target micro-organism's MIC measured for systemic therapy. The recommended duration of ALT is 2 weeks [99].

Ideally, the use of concentration-dependent killing antibiotics is optimal, rather than time-dependent killing antibiotics such as glycopeptides, so that minimum biofilm eradicating concentrations can be achieved without dependence on dwell time.

Whilst ALT has been shown to decrease the rate of CRBSIs in haemodialysis patients with long-term catheters, the benefit in ICU patients with short-term CVCs is less clear [98].

More rigorous clinical studies are needed before antibiotic lock solution can be universally recommended, in part because of the concern for the generation of multidrug-resistant micro-organisms [99]. Choosing the correct ALT prevention treatment is crucial because the agent selected has to be able to penetrate the thick biofilm matrix and act against microbial cells growing in a stationary-like state.

6. Health economic aspects of the problem

Use of a medical device is the greatest exogenous predictor of healthcare-associated infection (HAI), and CRBSIs, together with surgical-site infections, ventilator-associated pneumonia and catheter-associated urinary tract infections, account for approximately three-quarters of HAIs [100].

Although global estimations of HAIs are not available, by integrating data from several published studies it is clear that hundreds of millions of patients are affected every year worldwide, with the burden of disease much higher in low- and middle-income countries [101].

Recent data regarding the costs and numbers of HAIs are available from the European Centre for Disease Prevention and Control (ECDC), which has calculated that HAIs involve 4.1 million patients annually in the European Union; furthermore, as reported by the World Health Organisation (WHO) in 2011, only direct costs associated with HAIs account for about €7 billion annually [16,18].

In particular, it is important to underline that MRSA accounts for 44% (n = 171 200) of these HAIs and causes 22% (n = 5400) extra deaths and 41% (n = 1 050 000) extra days of hospitalisation, with extra attributable in-hospital costs of ca. €380 million annually [16].

The CDC has recently estimated the annual hospital costs of HAIs in the USA to be between US$28 billion and US$45 billion per year [34], and MRSA-associated costs are ca. US$10 billion/year, occurring in 31.3/100 000 hospitalised people, 20% of which result in fatal infections [102].

As the use of CVCs has increased over the last years, so the number of CRBSIs has risen [103]. It has been estimated that in the USA over 5 million medical devices are used per annum and ca. 4% of patients develop CRBSI; the number of deaths has been estimated at 12.5%, equating to 0.5% of CVC insertions [104]. The problem is even more serious among ICUs where in the ca. 250 000 CRBSIs occurring every year in the USA, ca. 28 000 lead to deaths in ICU patients only, with an annual cost of up to US$2.3 billion [105].

Furthermore, as reported by Tacconelli et al. in a study performed among four European countries, additional length of hospital stay per CRBSI episode varies between 4 days and 14 days,

with additional associated costs from €4200 to €13 030 per episode, representing an annual cost to the national healthcare systems of between €53.9 million in the UK and €130 million in France [106]. Nevertheless, it should be underlined that cost-effectiveness studies might be of limited value because sometimes they lack precision and do not have large economic perspectives, resulting in poor quality reports. For instance, cost reports of a single episode of CRBSI in the literature vary between US$3000 and US$56 000, hence data from different types of analyses must be interpreted with caution [10,11,107].

Usually three key components should be included in a complete global socioeconomic cost analysis of HAIs: direct medical costs that directly impact hospital finances; indirect costs (related to productivity); and non-medical costs or intangible costs related, e.g. to the diminished quality of life of the patient. In a 2-year, prospective, case–control study, Tarricone et al. evaluated direct healthcare costs of central line-associated BSIs according to a microcosting approach and found not only that central line-associated BSIs pose a significant increase in utilisation of hospital resources but also that the use of innovative and relatively simple technologies, in this case closed infusion containers, can significantly reduce the incidence of HAIs without additional weight on the overall hospital budget [108].

From these numbers, not only the magnitude of the CRBSI burden worldwide but also the need to urgently establish a reliable system for healthcare-associated infection and CRBSI surveillance to gather data on the actual numbers and costs as frequently as possible is clear. Moreover, evaluation of the key determinants of CRBSIs is an essential step to identify strategies and measures for prevention. In fact, robust evidence supports that CRBSIs can be prevented and the burden reduced by as much as 50% [109].

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Competing interests

None declared.

Ethical approval

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