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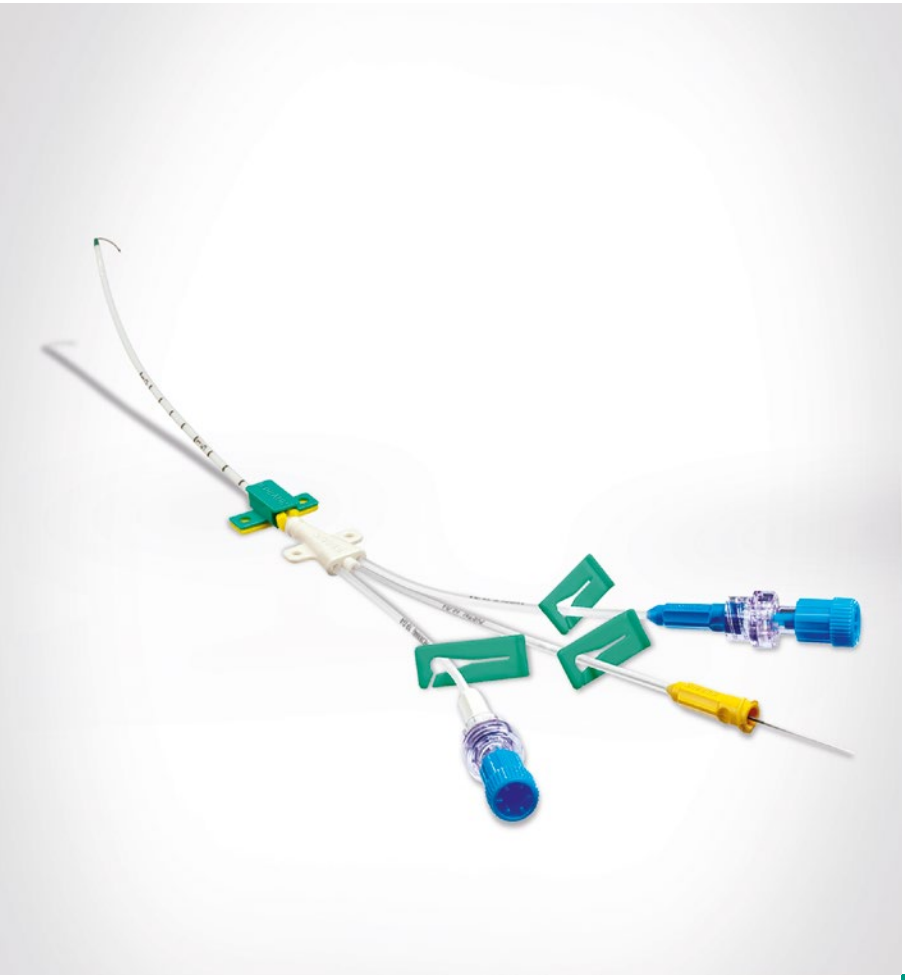

Certofix® protect

Catheter-related infections and their prevention

Resuscitation and intensive care of critically ill and injured patients are not possible without the use of intravascular catheters. Although life-saving, implanted artificial materials inevitably bear the risk of bacterial contamination, infection, and harm.[1] Microbial contamination leads to formation of bacterial and fungal biofilms on the surface of implanted medical devices.[2,3]

In the hospital setting, the majority of catheter-related infections are derived from the patient's own skin microflora.[4]

Catheter-related bloodstream infections (CRBSI) are associated with increases in mortality, morbidity and hospitalization costs.[15-18]

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Catheter-related bloodstream infections

1. Microorganisms and catheter-related infections

1.1 Introduction

Resuscitation and intensive care of critically ill and injured patients are not possible without the use of intravascular catheters, endotracheal tubes, and numerous other invasive or minimally invasive medical devices. Although lifesaving, implanted artificial materials inevitably bear the risk of bacterial contamination, infection, and harm.[1] Microbial contamination leads to formation of bacterial and fungal biofilms on the surface of implanted medical devices. In addition to mechanical hindrance, device-associated biofilms are a primary cause of hospital-acquired (nosocomial) infections that are difficult to eradicate due to the high tolerance of biofilms towards antimicrobial and host defences.[2, 3]

1.2 Pathogens in long-term catheter use and catheter-related bloodstream infections

In the hospital setting, the majority of catheter-related infections are derived from the patient´s own skin microflora.[4] A detailed description of the range of microorganisms causing catheter-related infections is given in Figure 1.

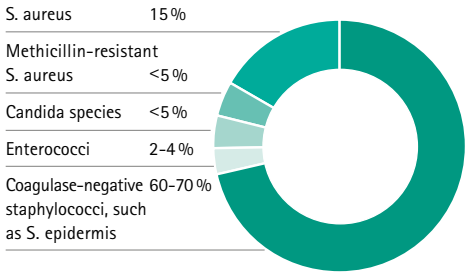

FIGURE 1 | Microorganisms and risk of catheter-related infections[4]

The most frequent pathogens responsible for catheter-related bloodstream infections in patients undergoing long-term central venous access are coagulase-negative staphylococci, such as S. epidermidis and Staphylococcus aureus.[5-7]

Coagulase-negative staphylococci, such as S. epidermidis and Staphylococcus aureus, are the most frequent cause of catheter-related bloodstream infections in patients.

Surveillance of catheter-related bloodstream infections during the National Nosocomial Infections Surveillance in Germany (KISS) showed that in 1994 the incidence of device-associated infections was 2.2 per 1,000 catheter days. After implementation of the Sterile Barrier Concept (hand hygiene and protective devices like gloves, drapes caps and masks), the catheter-related bloodstream infection rate (per 1,000 catheter days) could be reduced from 1.7 in 2003 to 1.1 in 2010.[9]

However, even with optimal skin preparation, total sterilization of the skin is not possible.[10]

Staphylococcus epidermidis is not only the predominantbacterial species in the normal flora of the human skin, but has also emerged as the most important pathogen in infections related to foreign-body materials, such as prosthetic joints and heart valves.[11-13]

Moreover, bacterial recolonization of the skin under an adhesive polyurethane drape has been demonstrated after optimal skin preparation during surgical interventions.[14]

The development of antimicrobial-coated central venous catheters is a further step towards reducing the rate of catheter-related bloodstream infections (see Chapter 4).

2. Physiopathology of CVC colonization

2.1 Introduction

The risk of infection is enhanced if a central venous catheter is inexpertly inserted or maintained. Catheter-related bloodstream infections (CRBSI) are associated with increases in mortality, morbidity and hospitalization costs. [15-18]

2.2 Biofilm-associated infections

Once the microorganism has access to the CVC, infection occurs as a result of the capacity of bacteria to adhere to the catheter surface and to colonize and develop biofilms. These biofilms are formed when the microorganisms are irreversibly attached to the external or internal surface of the catheter.

In this position they produce extracellular polymers that facilitate their adherence and form a structural matrix. The extension and location of CVC biofilms depend on how long the catheter has been in place. If it has been in place for less than 10 days, a biofilm typically forms on the external catheter surface. In the case of long-term central venous catheters, a biofilm forms on the internal surface. [8, 16, 20-21]

Many biofilm-associated infections occur in the hospital setting through contamination of indwelling medical devices from the epithelial flora of the patient or from healthcare personnel.[22]

The most common route for contamination of short-term central venous catheters is migration of skin organisms at the insertion site into the cutaneous catheter tract and along the surface of the catheter. Subsequent colonization of the catheter tip and direct contamination of the catheter hub occur through contact with hands or contaminated fluids or devices.[6]

2.3 Ways of colonization

There are several routes by which a central venous catheter may become colonized with bacteria. These include:

- Hematogenous seeding of the catheter
- Intraluminal and extraluminal infection

HEMATOGENOUS SEEDING OF THE CATHETER

The spread of pathogens via the blood stream – commonly referred to as hematogenous seeding – can result in pathogens gaining access to a catheter surface.[4, 23] Hematogenous seeding of the CVC from another focus of infection is rare.[6]

The main mechanisms of migration of microorganisms to the bloodstream in combination with a central venous catheter are intraluminal and extraluminal colonization.

INTRALUMINAL COLONIZATION

Microorganism colonization may occur from contamination of the catheter hub, its lumen, its guide wire during insertion, the catheter, the connectors to the infusion lines during handling, or the infusion administered through the catheter. [4, 8, 23]

Several approaches have been taken to reduce intraluminal catheter-related infections. These measures include redesigned catheter components (e. g. new hub designs with filled antiseptics, needleless connectors, in-line filters), the development of antimicrobial catheters, as well as patient-related measures (hand hygiene, disinfection of the insertion site, the use of catheter dressings and guidance for catheter replacement).[4]

EXTRALUMINAL COLONIZATION

Contaminating microorganisms on the skin, probably assisted by the action of capillarity, penetrate through the skin during the insertion of the catheter or on the days following the insertion. [4, 8, 22]

The implementation of the Sterile Barrier Concept is an important step towards reducing catheter-related bloodstream infections. Nevertheless, bacterial recolonization or microbial regeneration (for example under a polyurethane drape [14]) cannot be prevented.

3. Staphylococcus epidermidis and biofilm formation

3.1 Introduction

Staphylococcus epidermidis is a normal inhabitant of human skin. The pathogen is the most important cause of nosocomial infections and is the most often identified pathogen associated with medical devices.[1,6,21,23] According to the Centers for Disease Control and Prevention's National Nosocomial Infection Surveillance System, S. epidermidis is responsible for 33.5 % of nosocomial bloodstream infections.[24]

In comparison with many other clinically important bacterial pathogens, S. epidermidis is not particularly virulent in the traditional sense. Rather, its capacity to cause disease in critically ill patients is largely attributable to its tendency to produce tenacious biofilms on artificial surfaces.[1, 23]

In vivo animal studies demonstrate that rodents that lack a functional immune system are much more susceptible towards Staphylococcus epidermidis device-related infection than are immune-competent (healthy) rodents.[2, 23]

Colonization of venous access devices implanted in immunosuppressed rodents by Staphylococcus aureus or Staphylococcus epidermidis bacteria consistently led to rapid acute systemic infection and death, therefore illustrating the importance of host immune response in controlling

bacterial metastasis originating from persistent biofilms in colonized venous access devices.[2]

Clearance of this complex biomaterial is difficult, if not impossible, for host immune effectors, and the antibiotic resistance that biofilms confer on the bacteria they envelop often requires surgical removal and replacement of devices that become contaminated by this organism.[1]

3.2 Risk of biofilm formation

Biological background

The formation of a biofilm begins with the attachment of bacteria to a surface and is followed by proliferation and maturation, which ultimately lead to the characteristic 3D biofilm structure, with mushroom-shaped bacterial agglomerations surrounded by fluid-filled channels. Later, cells may detach from the biofilm in a process believed to be of crucial importance for the dissemination of a biofilm-associated infection. [15, 21]

Polysaccharide intercellular adhesin (PIA), a homoglycan composed of β-1,6-linked 2-deoxy-2-amino-D-glucopyranosyl residues, is considered to be the major functional component mediating intercellular adhesion in S. epidermidis biofilms. Biofilm formation mediated by PIA is a major virulence factor in experimental biomaterial-associated infection and also provides protection against opsonophagocytosis and activity of antimicrobial peptides. [25, 26]

The molecular basis of biofilm maturation and detachment is poorly understood, but presumably it involves mechanisms to disrupt cell-cell adhesion. In vitro evidence indicates that cell-cell disruption may be accomplished by surfactants, while enzymatic digestion of biofilm matrix molecules appears to promote biofilm. These mechanisms are commonly under control of cell density ("quorum sensing") and are likely to ensure that biofilm expansion is tightly regulated. In staphylococci, the molecular effectors of cell-cell disruption during biofilm development are not known. Furthermore, there have been no studies in any bacterium of how biofilm detachment contributes to the in vivo dissemination of biofilm-associated infection.[21]

Nevertheless, the staphylococcal biofilm has potent immunomodulatory properties. Chemotactic responsiveness is diminished and degranulation of specific granule content is increased. Additionally, the biofilm inhibits the genesis of mononuclear cells, T and B lymphocytes, thus adversely affecting both cytotoxic and humoral defence responses.[26]

Biofilms provide significant resistance to antibiotics and innate host defences. Common mechanisms, such as drug-modifying enzymes, mutations, and efflux pumps, are not involved. Antibiotics penetrate poorly into the thick, acidic matrix. Bacteria in deep layers are metabolically inactive and are inherently insusceptible to antibiotics, whereas planktonic cultures of the same organism are not. This resistance is lost once the biofilm-attached bacteria revert to planktonic growth. To date, no standardized antimicrobial susceptibility tests are available to evaluate drug activity on adherent bacteria. Minimal inhibitory concentration and minimal bactericidal concentration evaluate only drug efficacy in planktonic bacteria in the logarithmic phases of growth.

For antibiotics acting on the cell wall to be effective in biofilms, 100 to 1,000 times the standard concentration is often required.[26]

Biofilm formation – step by step

According to knowledge of microbial biofilm formation on catheter surfaces and its role in causing persistent infections and/or sepsis, the pathogenesis of catheter-related sepsis presumably follows the following steps:
Catheter insertion > Microbial colonization > Biofilm formation > Infection / Sepsis

After CVC insertion, the intravascular portion of the device is rapidly covered by a thrombin layer, rich in host-derived proteins (e. g., fibrin, laminin, fibrinogen, fibronectin) that form a conditioning film. These proteins, acting as adhesins, promote surface adherence of microbes, whose binding is mediated by specific receptors targeting one or more of the above-mentioned proteins. After their irreversible attachment to the catheter, the microorganisms enter their sessile mode of growth, producing an exopolysaccharidic matrix known as slime, to form a biofilm.

Within the growing biofilm, bacterial density is regulated by the production of quorum-sensing molecules, which are responsible for bacterial crosstalk. As the biofilm thickens, there is progressive dispersal of single cells or clusters of different sizes.[27]

The continual increase in the use of central venous catheters has been associated with an increased risk of infectious complications. Bacterial aggregates detached from biofilm formation can become septic emboli that disperse via the bloodstream and cause disseminated infection and sepsis. Especially biofilms of Staphylococcus epidermis – the most relevant micro-organism of nosocomial bloodstream infections – have potent immunomodulatory properties and display significant resistance to antibiotics and innate host defences. Accordingly, the eradication of Staphylococcus epidermis on central venous catheters is an important step towards reducing catheter-related infections.

4. Bloodstream infections and dwell time

4.1 Introduction

Central venous catheters are vital for the medical management and monitoring of hospitalized patients. However, central line-associated bloodstream infections are serious healthcare-associated infections, with an attributable mortality of 12–25 %.[28-29]

Many strategies have been used to prevent central venous catheter-associated bloodstream infections. The range of preventive strategies range from technological approaches (e. g., locks and line coatings) to other interventions such as aseptic insertion technique and education of clinicians, catheter maintenance and reduced dwell time through early removal of catheters.[28, 30]

4.2 Dwell time and the risk of infection

Approximately 75 % of patients have a catheter dwell time of less than 7 days.[31] These patients have the lowest risk of catheter-associated bloodstream infections. Clinical trials have demonstrated that higher dwell time is associated with significantly higher central line-associated bloodstream infections.[28-29]

- Before the introduction of aseptic insertion, the risk of catheter-associated bloodstream infections was low but increased rapidly with dwell time from day 7.[31]
- After aseptic insertion was introduced (without early removal of CVC), the probability of infection increased rapidly after day 9.[31]
- The first 9 dwell days had the lowest risk of catheter-associated bloodstream infections, with a probability of less than 1 in 100 (rate of 0.09/1,000 CVC-days).[31]
- After a dwell time of nine days, the probability continued to increase to 13 in 100 (rate of 5.5/1,000 CVC-days).[31]
- In a cohort study in 2005 (1,375 patients and 7,467 CVC-days), the overall incidence of catheter-associated bloodstream infection was 3.7 cases per 1,000 catheter-days, whereas incidences during the intervals of 1–5, 6–15, and 16–30 days were 2.1, 4.5, and 10.2 cases per 1,000 catheter-days, respectively.[32]

These results suggest that early-onset catheter-associated bloodstream infection is a rare event, whereas prolonged dwell time is associated with more frequently occurring catheter-associated bloodstream infection.[29-30, 32-34]

5. Lack of efficacy of coated catheters in prolonged dwell times

5.1 Efficacy in short insertion times

Line coatings have been developed to reduce central venous catheter-related infections. However, research shows that antibiotic and chlorhexidine-silver sulfadiazine coatings are anti-infective for short insertion times (approximately one week).

- Two trials on antibiotic coating (343 CVCs) had an average insertion time of 6 days; the risk of bloodstream infection decreased from 5.1 % with control to 0 % with anti-infective catheters. There were no trials with longer average insertion times.[18]

- In three trials on silver collagen cuffs (422 CVCs), the average insertion time ranged from 5 to 8.2 days (median, 7 days); the risk of bloodstream infection was 5.6 % with control and 3.2 % with anti-infective catheters.[18]
- In five trials on chlorhexidine-silver sulfadiazine coating (1,269 CVCs), the average insertion time ranged from 5.2 to 7.5 days (median, 6 days); the risk of bloodstream infection decreased from 4.1 % with control to 1.9 % with anti-infective catheters.[18]
- In five additional trials on chlorhexidine-silver sulfadiazine coating (1,544 CVCs), the average insertion time ranged from 7.8 to 20 days (median, 12 days); the risk of BSI was 4.5 % with control and 4.2 % with anti-infective catheters.[18]

Antibiotic and chlorhexidine-silver sulfadiazine coatings are anti-infective for short (approximately one week) insertion times. For longer insertion times, there are no data on antibiotic coating, and there is evidence of lack of effect for chlorhexidine-silver sulfadiazine coating.[18]

For silver-impregnated collagen cuffs, there is evidence of lack of effect for both short- and long-term insertion.[18]

5.2 Adverse reactions

Antimicrobial impregnated central venous catheters can be divided into leaching and non-leaching catheter systems. Chlorhexidine or antibiotics may leach from impregnated catheter systems.

Leached chlorhexidine and sulfadiazide silver may sensitize patients, leading to life-threatening anaphylaxis on subsequent exposure.[33-35]

Antibiotic resistance after repeated exposure to minocycline and/or rifampicin-impregnated catheters can develop after bacteria have been exposed to subinhibitory concentrations of antibiotics that have failed to eradicate these organisms. Some authors have reported in vitro resistance to leachable rifampicin or a combination of minocycline and rifampicin after repeated use of catheters.[36-38]

Dwell times of central venous catheters have a great impact on catheter-related bloodstream infections – **higher dwell time is associated with significantly higher infections.**

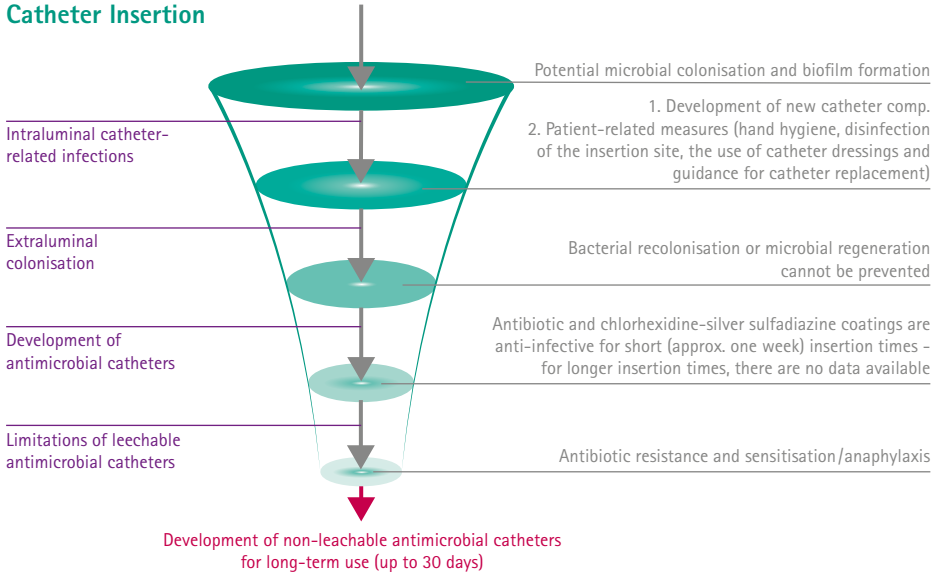

FIGURE 2 | Workflow for optimizing catheter care

One approach to reduce catheter-related infection is the impregnation of catheters with antiseptic or antimicrobial agents. According to a systematic review, antibiotic and chlorhexidine-silver sulfadiazine **coatings are anti-infective for short (approximately one week) insertion times.**

For longer insertion times, there are no data available. Accordingly, the reduction of microorganisms in the long-term use of central venous catheter (up to seven-nine days) is an important step to reduce catheter-related infections.

Moreover, leached chlorhexidine and sulfadiazide silver may sensitize patients (leading to life-threatening anaphylaxis) and leachable rifampicin or a combination of minocycline and rifampicin can develop antibiotic resistance.

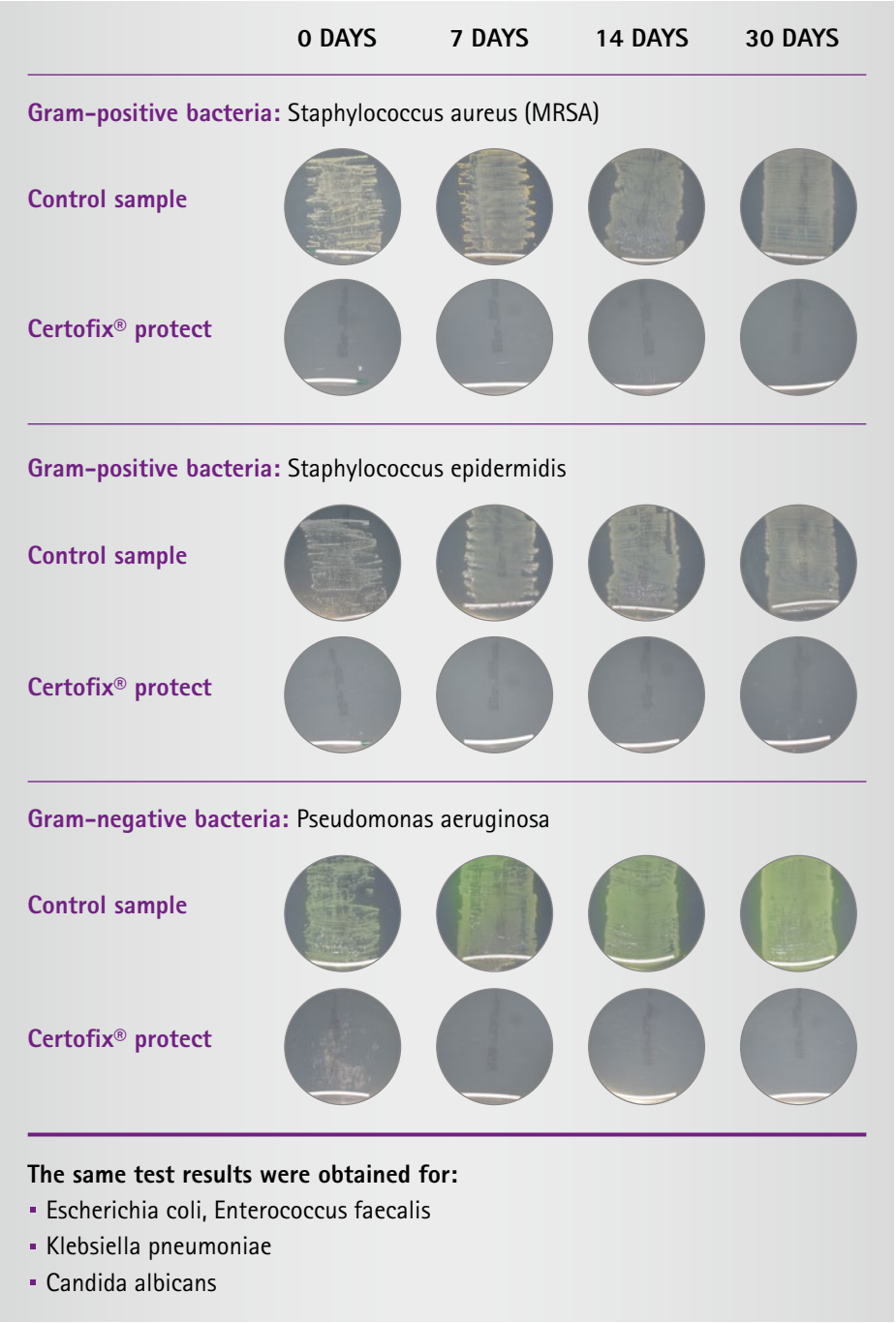

FIGURE 3 | Efficacy of Certofix® protect [25]

6. Certofix® protect for optimizing catheter care

For further optimisation of antimicrobially effective CVCs, new strategies and additives have to be considered.

With Certofix® protect, a third generation of CVCs has been developed. These are equipped with a protective internal and external non-leaching antimicrobial coating from the catheter tip to the connectors. The modified surface of Certofix® protect consists of a high molecular weight polymer which is non-covalently linked to the polyurethane catheter material. The protect coating has a broad anti-microbial spectrum and cell and tissue tolerability, as well as a low risk of contact sensitization and adjuvant effects to wound healing. No microbial resistance has been observed.

6.1 Efficacy of Certofix® protect in long-term use

The antimicrobial performance (30 days) of non-leaching antimicrobial CVCs on 7 typical CVC-associated infection bacteria was tested with the "Roll-Out" method, (Staphylococcus epidermidis, Staphylococcus aureus MRSA and E. coli, Enterococcus faecalis, Pseudomonas aerugionosa, Klebsiella pneumoniae and Candida albicans).

"Roll-Out" test show the following results (Figure 3)

- The in-vitro trials demonstrate that Certofix® protect exhibits antimicrobial efficacy and prevents biofilm formation from gram-positive, gram-negative bacteria and fungi for up to 30 days.
- The study was performed in direct comparison with a non-antimicrobial control catheter, on which all 7 test strains were able to grow to an established surface biofilm.[39]

SUMMARY
This is the first in-vitro study to demonstrate antibacterial surface activity and prevention of biofilm formation with antimicrobial, non-leaching CVCs by using the "Roll-Out" method over a period of 30 days. These results demonstrate that non-leaching antimicrobial CVCs can prevent microbial colonization and infection.

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Notes

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