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Infections Associated with Medical Devices

Pathogenesis, Management and Prophylaxis

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Abstract

The insertion or implantation of foreign bodies has become an indispensable part in almost all fields of medicine. However, medical devices are associated with a definitive risk of bacterial and fungal infections. Foreign body-related infections (FBRIs), particularly catheter-related infections, significantly contribute to the increasing problem of nosocomial infections. While a variety of micro-organisms may be involved as pathogens, staphylococci account for the majority of FBRIs. Their ability to adhere to materials and to promote formation of a biofilm is the most important feature of their pathogenicity. This biofilm on the surface of colonised foreign bodies is regarded as the biological correlative for the clinical experience with FBRI, that is, that the host defence mechanisms often seem to be unable to handle the infection and, in particular, to eliminate the micro-organisms from the infected device. Since antibacterial chemotherapy is also frequently not able to cure these infections despite the use of antibacterials with proven *in vitro* activity, removal of implanted devices is often inevitable and has been standard clinical practice. However, in specific circumstances, such as infections of implanted medical devices with coagulase-negative staphylococci, a trial of salvage of the device may be justified. All FBRIs should be treated with antibacterials to which the pathogens have been shown to be susceptible. In addition to systemic antibacterial therapy, an intraluminal application of antibacterial agents, referred to as the 'antibiotic-lock' technique, should be considered to circumvent the need for removal, especially in patients with implanted long-term catheters.

To reduce the incidence of intravascular catheter-related bloodstream infections, specific guidelines comprising both technological and nontechnological strategies for prevention have been established. Quality assurance, continuing education, choice of the catheter insertion site, hand hygiene and aseptic techniques are aspects of particular interest. Furthermore, all steps in the pathogenesis of biofilm formation may represent targets against which prevention strategies may be directed. Alteration of the foreign body material surface may lead to a change in specific and nonspecific interactions with micro-organisms and, thus, to a reduced microbial adherence. Medical devices made out of a material that would be antiadhesive or at least colonisation resistant would be the most suitable candidates to avoid colonisation and subsequent infection. Another concept for the prevention of FBRIs involves the impregnation of devices with various substances such as antibacterials, antiseptics and/or metals. Finally, further studies are needed to translate the knowledge on the mechanisms of biofilm formation into applicable therapeutic and preventive strategies.

1. Impact of Medical Device-Associated Infections

The insertion of indwelling or implanted foreign polymer bodies, such as prosthetic heart valves, cardiac pacemakers, total artificial hearts and total joint replacements or other orthopaedic devices, as well as intravascular catheters, renal dialysis shunts, cerebrospinal fluid (CSF) shunts or continuous ambulatory peritoneal dialysis catheters, has become an indispensable part of modern medical care. While medical devices are increasingly used in almost all

fields of medicine for diagnostic and/or therapeutic procedures (see table I for an overview), they are particularly necessary for managing the care of critically ill patients.

In general, the placement of a vascular access with increasingly sophisticated catheters is widely used and a considerable number of patients have one or more vascular catheters in place during their hospital stay.[1] In the US, 15 million central venous catheter (CVC) days (i.e. the total number of days of exposure to CVCs by all patients in the selected population during the selected time period) occur in intensive care units (ICUs) each year.[2] However, the use of foreign material has led to special complications associated with the presence of such material because insertion or implantation of medical devices is associated with a definitive risk of bacterial and fungal infections, that is, foreign body-related infections (FBRIs).

Table I. Implanted medical devices

Intravascular
Peripheral catheters (venous, arterial)
Midline catheters
Central venous catheters
non-tunnelled catheters (Cook, Arrow)
tunnelled catheters (Hickman, Broviac, Groshong)
Pulmonary artery catheters
Totally implanted ports (Port-a-Cath, MediPort, Infusaport)
Cardiovascular
Mechanical heart valves
Implantable defibrillators and related devices
Vascular grafts
Ventricular assist devices
Coronary stents
Implantable patient monitors
Neurosurgical
Ventricular shunts
Ommaya reservoirs
Intracranial pressure devices
Implantable neurological stimulators
Orthopaedic
Joint prostheses and other reconstructive orthopaedic implants
Spinal implants
Fracture-fixation devices
Urological
Inflatable penile implants
Gynaecological
Breast implants
Otolaryngological
Cochlear implants
Middle ear implants
Ophthalmological
Intra-ocular lenses
Glaucoma tubes
Dental
Dental implants

FBRIs comprise all entities with respect to local and bloodstream infections (BSI) associated with inserted or implanted medical devices. On the subject of catheter-related infections (CRIs), the confusing terminology and varying definitions in the literature have historically been a barrier to effective communication.[3,4] The definitions of CRIs and their microbiological criteria are given in table II. CRIs include colonisation of the device, localised catheter infections (exit site, pocket, tunnel infection) and catheter-related bloodstream infection (CRBI).[5-8] In the absence of a standard reference technique ('gold' standard), microbiological diagnostics of FBRIs are still a matter of debate (for detailed information, see table II and respective reviews[9-13]).

The contamination of the medical device most likely occurs by inoculation with only a few microorganisms from the patient's skin or mucous membranes during implantation. Sometimes, the pathogens may also be acquired from the hands of the surgical or clinical staff. According to the underlying patient characteristics, the micro-organisms that are implicated, and the type of the device, morbidity and mortality of device-associated infections may vary, but FBRIs, particularly CRIs, significantly contribute to the increasing problem of nosocomial infections.[1,18] It has been reported that rates for CRBIs range between 5.0 per 1000 central-line days in medical/surgical ICUs (major teaching hospitals) and 8.5 per 1000 central-line days in burn units.[1] The attributable cost per infection is an estimated $US34 508–$US56 000,[19,20] and the annual cost of caring for patients with CVC-associated BSIs

Table II. Definition of intravascular catheter-related infections and their diagnosis[5-8]

Type of infection	Definition	Microbiologically documented	Clinically documented
Catheter colonisation	Cultured catheter segment yields a significant number of bacteria according to the culture methods used (in the absence of any clinical signs of infection at the insertion site)	Quantitative technique (sonication, vortexing technique): ≥1000 cfu (sensitivity 94%; specificity 92%)[14] Semiquantitative technique (roll-plate method): ≥15 cfu (sensitivity 85%; specificity 85%)[15]	
Localised catheter infection (exit site infection)	Infection at the insertion site: periorificial cellulitis, purulence, tunnelitis and pocket infections (for totally implantable devices)	Positive (semi)quantitative catheter culture in the presence of clinical signs of infection at the insertion site	Clinical infection (erythema, tenderness, induration, purulence) at the insertion site
Catheter-related bloodstream infection[a]	Isolation of the same micro-organism[b] from a (semi)quantitative culture of the distal catheter segment and from the blood of a patient with clinical symptoms of sepsis and no other apparent source of infection	Standard blood cultures: two sets with at least one drawn percutaneously (sensitivity 91%; specificity 86%)[16] Quantitative blood culture: differential quantitative cultures of two sets with at least one drawn percutaneously (sensitivity 79%; specificity 94%)[16] Differential time blood culture: differential time of two sets drawn simultaneously one drawn percutaneously and the other from the suspected vascular access (sensitivity 91%; specificity 94%)[17]	Defervescence after removal of an implicated catheter from a patient with primary blood stream infection (indirect evidence in the absence of catheter culture)

a This term is preferred to the term 'catheter-related sepsis' because 'sepsis' does not imply the presence of bacteraemia and because this term is used to define the systemic inflammatory response syndrome associated with a septic focus. 'Catheter-related bacteraemia' is less accurate as blood cultures may grow fungal species (fungaemia).[5]

b That is, clonally identical isolates of the same species (ideally proven by genotyping techniques, practically at least by antibiogram).

cfu = colony-forming units.

ranges from $US296 million to $US2.3 billion.[21] A total of 250 000 cases of CVC-associated BSIs have been estimated to occur annually if entire hospitals are assessed rather than ICUs exclusively. In this case, attributable mortality is an estimated 12–25% for each infection, and the marginal cost to the healthcare system is $US25 000 per episode.[18,22]

While a variety of Gram-positive and -negative bacteria as well as fungi have been involved as causative organisms in FBRIs, staphylococci, particularly *Staphylococcus epidermidis* and other coagulase-negative staphylococci (CoNS) account for the majority of infections, both of temporarily inserted and of permanently implanted material.[23,24] Normally, these bacteria are found as normal inhabitants of human skin and mucous membranes. However, in the appropriate clinical setting, specifically when there is a possible infection of a medical device, CoNS may be associated with considerable hospital expenditures, morbidity and also an increased mortality rate.[25]

This article focuses on therapy and prevention of infections associated with medical devices with emphasis on the development of new devices designed to prevent infection. In the first part, this overview deals with the current knowledge on the pathogenesis of FBRIs, particularly due to CoNS, because the basic understanding of the pathogenesis is crucial for both the management and the prevention of those infections. Nevertheless, further studies are warranted to translate the knowledge on the mechanisms of biofilm formation into applicable therapeutic and preventive strategies.

2. Pathogenesis of Medical Device-Associated Infections

The ability to adhere to materials and promote formation of a biofilm is an important feature of the pathogenicity of bacteria involved in foreign body

infections. The fact that staphylococci represent the major organisms associated with infections of medical devices has greatly spurred research on pathogenic mechanisms, resulting in important advances in our understanding of biofilm formation. Thus, a battery of staphylococcal virulence factors have been identified and characterised in the past two decades leading to important insights, particularly with respect to the interaction of the bacteria with the surface of the implanted or inserted device. Normally, CoNS live in balanced harmony on our skin, forming the major component of the cutaneous microflora. Outside the setting of a medical device, these organisms rarely cause infections. However, in relation to an inserted or implanted foreign body, these bacteria are able to colonise the surface of a foreign body by the formation of a thick, multilayered biofilm.[25,26]

Biofilm formation proceeds in two stages: a rapid attachment of the bacteria to the surface of the implanted device is followed by a more prolonged accumulation phase that involves cell proliferation and intercellular adhesion (figure 1). For years, efforts have been made to identify bacterial factors responsible for each of both phases.

2.1 Attachment of the Micro-organisms to the Surface of the Implanted Device

Microbial adherence to foreign bodies depends on the cell surface characteristics of the micro-organisms and on the nature of the foreign body material. Factors involved include physicochemical

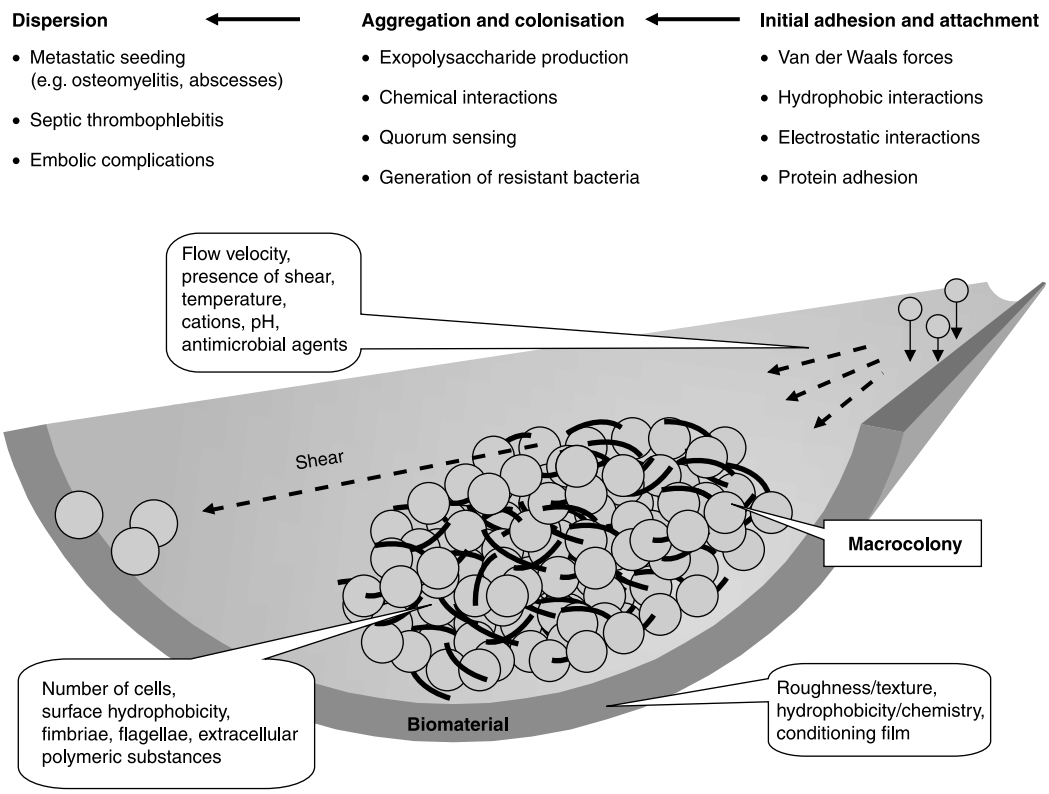

Fig. 1. Pathogenesis of foreign body-related infection: steps of biofilm formation on the surface of an intravascular catheter with rapid initial adhesion and attachment of micro-organisms to the polymer surface followed by a more prolonged accumulation phase that involves cell proliferation and intercellular adhesion. Finally, micro-organisms may disaggregate from the macrocolony and drift into the bloodstream resulting in metastatic and embolic complications.

forces such as polarity, London-van der Waal's forces and hydrophobic interactions.[27] Cell surface hydrophobicity and initial adherence of *S. epidermidis* to polystyrene have been attributed to two different bacterial surface-associated proteins, designated SSP-1 and SSP-2.[28] Initial attachment of *S. epidermidis* to a polymer surface may be also mediated at least in part by AtlE, a surface-associated autolysin.[29] The biofilm-associated protein Bap was reported to contribute to both phases of *S. aureus* biofilm formation, adhesion and accumulation,[30] while Bhp, a Bap-homologous protein, may contribute to *S. epidermidis* biofilm formation.[31] Aside from proteins, a polysaccharide structure called capsular polysaccharide/adhesin (PS/A) has been associated with initial adherence and slime production.[32] In a rabbit model of endocarditis, PS/A-deficient mutants were less virulent and immunisation with PS/A resulted in protection against infection.[33]

While the direct interaction between bacteria on one side and the unmodified and naked surface of the foreign body on the other side plays a crucial role in the early stages of the adherence process *in vitro* and probably also *in vivo*, additional factors may be important in later stages of adherence *in vivo*. Implanted devices rapidly become coated with plasma and connective tissue proteins, such as fibronectin, fibrinogen, vitronectin, thrombospondin, laminin, collagen and von Willebrand factor (vWf), which subsequently may serve as specific receptors for colonising micro-organisms.[34-36] In the vascular system at sites of increased flow, vWf may also play an important role in adhesion of staphylococcal cells to polymer surfaces because under high shear rates platelets do not appreciably bind to extracellular matrix proteins other than vWF.[35] Several host factor-binding proteins from *S. aureus* (e.g. the fibrinogen receptor ClfA and the fibronectin-binding proteins FbpA and FbpB) and from CoNS (e.g. the fibrinogen-binding protein Fbe and the fibronectin-binding autolysin Aas) have been identified and characterised. The *S. epidermidis* autolysin AtlE which mediates primary attachment to a polymer surface (see section 2) was also found to exhibit vitronectin-binding activity, suggesting not only a function in the early stages of adherence but also a contribution to later stages of adherence involving specific interactions with plasma proteins deposited on the polymer surface.[29] Aside from proteins, teichoic acid was suggested to function as a bridging molecule between the bacteria and fibronectin-coated polymer.[37]

2.2 Cell Proliferation and Intercellular Adhesion

Once adhered to the surface of the foreign body, micro-organisms multiply and accumulate in multilayered cell clusters, which requires intercellular adhesion. A specific polysaccharide antigen termed polysaccharide intercellular adhesin (PIA), which is involved in intercellular adhesion and biofilm accumulation and is chemically related to PS/A, has been detected and analysed in staphylococci.[38] Tn*917* mutants lacking PIA were not able to accumulate in multilayered cell clusters. The *icaADBC* operon that mediates cell clustering and the intercellular adhesin synthesis in *S. epidermidis* has been cloned and sequenced.[39,40] Later, three other gene loci were identified, which have a direct or indirect regulatory influence on expression of the synthetic genes for PIA and biofilm formation.[41] In a mouse model of subcutaneous foreign body infection as well as in a rat model of CVC-associated infection, a PIA-negative mutant was shown to be significantly less virulent than the isogenic wild-type strain.[42,43] A PIA/haemagglutinin-positive *S. epidermidis* strain was significantly more likely to cause a subcutaneous abscess than its isogenic PIA/haemagglutinin-negative mutant and was significantly less likely to be eradicated from the inoculation site by host defence. Furthermore, the wild-type strain was found to adhere to the implanted catheters more abundantly than the PIA/haemagglutinin-negative mutant.[43] In an investigation designed to study the pathogenic properties of *S. epidermidis* strains ob-

tained from blood of patients with FBRI, a strong association was detected between pathogenesis and both biofilm formation and presence of the *ica* gene cluster.[44] Most recently, it was shown that induction of biofilm formation could be completely inhibited by chloramphenicol, which – given at a later stage of biofilm accumulation – also inhibited further development of preformed biofilm. This indicates that continuous translation of an additional, *ica*ADBC-independent factor is required for the expression of a biofilm-positive phenotype.[45]

Other factors such as the 140 kDa extracellular protein AAP (accumulation-associated protein) also seem to be necessary for accumulation and biofilm formation.[46] AAP, which is lacking in an accumulation-negative mutant and detectable only in extracellular products from bacteria grown under sessile conditions, was shown to be essential for accumulative growth in certain *S. epidermidis* strains on polymer surfaces. Of 58 CoNS studied, 55% were 140 kDa antigen-positive and produced significantly larger amounts of biofilm than the other strains that were 140 kDa antigen-negative. An antiserum specific for AAP inhibited accumulation by up to 98% of the wild-type strain.[46]

Taken together, the factors described here lead to the consequence that bacteria, particularly staphylococci, are able to adhere rapidly to the surface of a foreign body. During the following accumulation phase, the bacteria proliferate to form multilayered cell clusters on the surface of a medical device. The presence of such large adherent biofilms on the surfaces of foreign bodies, particularly on explanted intravascular catheters, has been demonstrated by scanning electron microscopy.[26,47]

Intercellular signalling, often referred to as quorum sensing, has been shown to be involved in biofilm development by several Gram-positive and -negative bacteria such as *Streptococcus mutans*, *Burkholderia cepacia* and *Pseudomonas aeruginosa*. For example, under certain conditions, a quorum-sensing–defective mutant of *P. aeruginosa* is – in contrast to its parent strain – unable to form a highly differentiated biofilm structure.[48] The *S. aureus* quorum-sensing system is encoded by the accessory gene regulator (*agr*) locus that contributes to virulence in model biofilm-associated infections. Most recently, it was shown that, under some conditions, disruption of *agr* expression had no discernible influence on biofilm formation, while under others it either inhibited or enhanced biofilm formation. Under those conditions where *agr* expression enhanced biofilm formation (tested in a rotating-disk reactor), biofilms of an *agr* signalling mutant were particularly sensitive to rifampicin but not to oxacillin.[49]

The clinical experience with polymer-associated infections reveals that the host defence mechanisms often seem to be unable to handle the infection and, in particular, to eliminate the micro-organisms from the infected polymer device. In addition, antibacterial chemotherapy is frequently not able to cure these infections despite the use of antibacterials with proven *in vitro* activity (see section 3.3). Thus, the biofilm may protect the embedded bacteria against host response mechanisms as well as against antibacterial agents.[50,51]

3. Management of Medical Device-Associated Infections

3.1 General Considerations

Whenever an infection of an indwelling or implanted foreign body is suspected, a general decision has to be addressed: whether to remove the foreign body and/or whether to initiate calculated antimicrobial treatment (figure 2). Answering the following key questions may help the physician to manage these infections adequately based on a rationale approach.

1. Is an FBRI a plausible explanation for the patient's signs (e.g. fever, skin inflammation at the exit site, soft tissue inflammation along the tunnel of an implanted catheter, septic thrombophlebitis)?

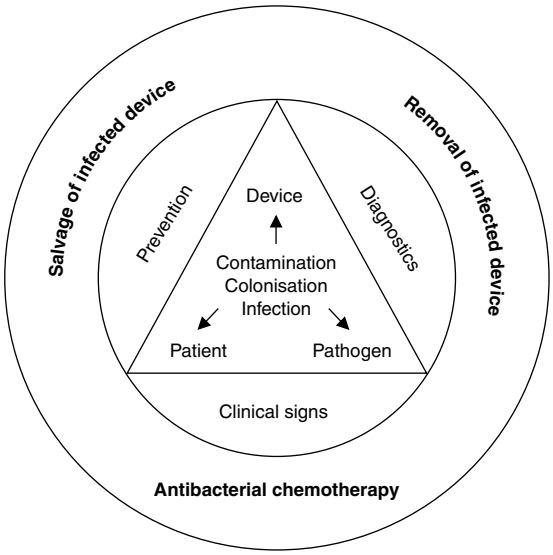

Fig. 2. Complex interactions of host (patient), pathogen and device to consider for decision on removal or salvage of infected device.

2. Are there any risk factors predisposing for FBRI (e.g. neutropenia, malignant haematological disorders, AIDS, type of catheter)?

3. In which clinical situation is the patient (e.g. sepsis, pregnancy, premature infant)?

4. In the light of a possible necessity to remove the foreign body, how important is the medical device for the patient regarding: (i) the survival of the patient (e.g. cardiac devices or 'highly needed' catheters, such as tunnelled Broviac-Hickman-type catheters or totally implantable venous access devices [i.e. ports] for intravenous administration of vital medications and parenteral nutrition); (ii) prosthetic therapy (e.g. prosthetic joints, lens); (iii) optimal intravenous application of fluids, medications and blood products (e.g. all kinds of vascular prostheses; haemodialysis shunts); and (iv) cosmetic and reconstructive surgery?

5. Which diagnostic methods should be applied to confirm the diagnosis?

6. Is calculated antimicrobial therapy necessary and, if so, which antibacterials should be given?

Several comprehensive reviews on the clinical management of infections due to an increasing palette of medical devices have been published focusing on different aspects concerning the removal of the infected device, antimicrobial therapy and on additional procedures to detect and prevent complications associated with FBRIs.[5,9,10,52-63]

3.2 Removal of the Device

The optimal treatment of a FBRI is the removal of the infected device when possible and its replacement if still needed. This is the therapy of choice, especially for easy-to-change devices such as short-term peripheral catheters.[5,9]

Regardless of the type of device, removal of implanted devices is recommended when the patient shows signs of severe sepsis, septic phlebitis and septic shock (table III). Furthermore, catheters should be removed in patients with bacteraemia persisting more than 48–72 hours. In addition, presence of local skin or soft tissue infections (e.g. tunnel infection, gross purulence at the exit site), metastatic complications (e.g. endocarditis, osteomyelitis, septic thrombosis) and/or relapse of infection after antibacterial therapy has been discontinued should lead to removal of the device. In addition, local debridement at the exit site of a medical device should be considered if a subcutaneous abscess or extensive tunnelitis is present. The removal of the device is regularly necessary if micro-organisms are isolated known to be difficult to eradicate or to be of high virulence such as *S. aureus*, *P. aeruginosa* or other non-fermenter, mycobacteria and yeasts.[64-67]

Studies have shown that long-term tunnelled catheters (mainly haemodialysis catheters) may be exchanged successfully with guidewire in patients with uncomplicated CRBI and no signs of exit, tunnel tract or pocket infection.[68-71]

3.3 Salvage of the Device and Treatment with Antimicrobial Agents

Removing the infected medical device is not always possible, easy to perform and/or without risk and, therefore, salvage of the device is sometimes

Table III. Aetiologically guided management of patients with tunnelled and non-tunnelled central venous catheter (CVC)- and surgically implanted device (ID)-associated bloodstream infections

CVC/ID[a]	Medical device-related bloodstream infection					
	complicated		uncomplicated			
	septic thrombosis, endocarditis, osteomyelitis	tunnel infection, port abscess	coagulase-negative staphylococci	*Staphylococcus aureus*	Gram-negative rods	*Candida* spp.
Non-tunnelled (removable) CVC	Removal of CVC, systemic antibacterial treatment for 4–6wk (6–8wk for osteomyelitis)	NA	For salvage of CVC: systemic antibacterial treatment ± 'antibiotic-lock' therapy for 10–14d	Removal of CVC, systemic antibacterial treatment for 14d[b]	Removal of CVC, systemic antibacterial treatment for 10–14d	Removal of CVC, systemic antifungal treatment for 14d after last positive blood culture
Tunnelled CVC, surgically ID	Removal of CVC/ID, systemic antibacterial treatment for 4–6wk (6–8wk for osteomyelitis)	Removal of CVC/ID, systemic antibacterial treatment for 10–14d	CVC/ID may retain with systemic antibacterial treatment for 7d + 'antibiotic-lock' therapy for 10–14d If CVC is removed, systemic antibacterial treatment for 5–7d	Removal of CVC/ID, systemic antibacterial treatment for 14d[c] For salvage of CVC/ID[c]: systemic antibacterial treatment + 'antibiotic-lock' therapy for 14d[d]	Removal of CVC/ID, systemic antibacterial treatment for 10–14d For salvage of CVC/ID: systemic antibacterial treatment + 'antibiotic-lock' therapy for 14d[e]	Removal of CVC/ID, systemic antifungal treatment for 14d after last positive blood culture

a The kind of the CVC/ID used and its basic necessity for the patient generally define the strategic decision for removal or salvage of the device. Duration of antimicrobial therapy and choice of antimicrobial depends on whether the infection is complicated or not and the causative pathogen. The therapeutic scheme is based on the guidelines for the management of intravascular catheter-related infections.[58]

b If transesophageal echocardiography is positive, extend systemic antibacterial therapy to 4–6wk.

c Provided that transesophageal echocardiography is negative.

d CVC/ID should be removed if there are clinical deterioration, persisting or relapsing bacteraemia.

e CVC/ID should be removed if there is no response; systemic antibacterial therapy should be continued for 10–14d.

NA = not applicable.

the preferred option. In particular, FBRIs associated with long-term or permanent catheters (such as Hickman-type catheter or Port-a-Cath) are frequently treated successfully 'through the line' (table III).[4,72,73]

Once a biofilm has formed on an implanted medical device it is difficult to treat such infections because of significantly decreased levels of susceptibility to antimicrobial agents (some 10 to 1000 times less) and lower levels of phagocytosis relative to the levels of resistance and phagocytosis for their planktonic counterparts (see pathogenesis, section 2).[74] Thus, supraphysiological concentrations of antibacterial agents may be required to eliminate the micro-organisms embedded in biofilms.[75] As shown in a number of experimental FBRIs, the pharmacokinetic parameters are modified and do not correspond to the efficacy of antibacterial treatment *in vivo* when a foreign body is implanted. These changes are obvious if mouse model-based results of *S. aureus*-caused intra-abdominal abscess surrounding intraperitoneally placed silicone catheter treated by meticillin and gentamicin are analysed.[76] Whereas both agents showed strong effects *in vitro* in time-kill studies on bacteria colonising catheters taken out of infected mice and on catheters contaminated *in vitro*, only poor results were observed *in vivo*, despite high local concentrations (greater than minimum inhibitory concentration [MIC] for at least 72 hours) of meticillin and high peak concentrations of gentamicin (>13 μg/mL). The failure was not caused by development of antibacterial resistance or influenced by protein concentration, pH or local presence of inhibitors of antibacterials in the pus.

Of importance, antibacterials administered in subinhibitory concentrations may influence the mechanisms of adherence and slime production, especially in staphylococci, for example, leading to higher polysaccharide intracellular adhesin production or to increased expression of fibronectin-binding proteins.[77-79]

The special conditions surrounding a foreign body have guided the search for alternative applications of antibacterials such as lipid-based sustained-release formulations. Roehrborn et al.[80] describe the use of such biodegradable, locally injectable formulation of amikacin in a mouse model in which Teflon® [1] tubes were subcutaneously implanted and challenged by inoculation of *S. aureus*. Whereas treatment with local or systemic free amikacin had no effect, the number of infected foreign bodies was reduced from 86% to 25% ($p = 0.02$) following treatment with encapsulated amikacin formulation, and log cfu (colony forming units) per gram of tissue was significantly decreased from 4.8 ± 0.9 to 1.3 ± 0.6.

Typically, initial treatment of catheter-related bacteraemia is administration of systemic antibacterials. Additionally, when a catheter-related infection is documented and a specific pathogen is identified, 'antibiotic-lock' therapy should be considered if salvage of the catheter is necessary. It is noteworthy that recommendations for the treatment of medical device-associated infections are based almost exclusively on observational studies, animal models, case reports and expert opinion rather than on the results of appropriate clinical trials.

3.3.1 Use of Lock Solutions for Intraluminal Therapy ('Antibiotic-Lock' Technique)

A technique of filling and closing a catheter lumen with a lock solution may prevent or cure catheter-related infections, as active ingredients can be maintained in direct contact with the internal surface of the device for prolonged periods of time (hours to days). Thus, to circumvent the need for catheter withdrawal, Messing et al.[81] were the first to describe the intraluminal application of antibacterial agents, referred to as antibiotic-lock technique. Avoiding systemic adverse effects, this method allows the delivery of a high concentration

1 The use of trade names is for product identification purposes only and does not imply endorsement.

of antibacterials (or, rarely, disinfectants) in the catheter in order to decontaminate the intraluminal surface of the catheter *in situ*. In an analysis of 14 open-label trials of standard parenteral therapy for the treatment of CRBI and the salvage of tunnelled catheters, a salvage in 342 (66.5%) of 514 episodes was documented.[58]

Currently, the antibiotic-lock technique is recommended for the treatment of uncomplicated catheter-related bacteraemia by several medical societies, such as the Infectious Diseases Society of America, the Society of Critical Care Medicine and the Society for Healthcare Epidemiology of America.[58] However, several parameters of intraluminal antibacterial therapy are not clearly defined, for example the duration of the antibiotic-lock therapy is not established. In most studies, this technique was administered for 7–14 days. Furthermore, the usefulness of different types of antibacterial agents, their optimum concentration and the necessity of simultaneous systemic treatment remain to be defined.[82] Glycopeptides, aminoglycosides and ciprofloxacin have been shown to be suitable agents.[67,81,83,84]

Some studies have used the antibiotic-lock technique in conjunction with the administration of systemic antibacterials and/or thrombolytic/anticoagulant agents.[83,85-87] However, bacteria such as staphylococci may survive and grow in heparin-locked catheters.[88] The drawback of using lock solutions containing antibacterials used for systemic therapy is that it may lead to the emergence of antibacterial resistance. In particular, the prophylactic and therapeutic long-term application of vancomycin could be of high risk for the development of staphylococcal subpopulations with reduced susceptibility against glycopeptides as a result of the existence of more or less 'occult' device-related infection sites.[89]

To meet concerns regarding a selection of highly resistant bacteria and an insufficient clearance of the device, the antimicrobial activity of alternative agents such as catheter lock solutions were investigated. Taurolidine, known as a nontoxic substance with antiadherence properties, was shown to be active against a broad range of bacteria as well as fungi.[90,91] The findings of Shah et al.[92] evaluating taurolidine-citrate (Neutrolin™, Biolink Corp., Norwell, MA, USA) for its antimicrobial and biofilm eradication activity in a catheter model suggested that this lock solution is a promising combination agent for the prevention and treatment of intravascular catheter-related infections.[92] Alternatively, ethanol (alcohol)-lock technique was introduced for the treatment of BSIs in patients with tunnelled CVCs and proven to be a safely used, well tolerated and effective way to treat central venous line infections.[93] However, further studies are needed to ascertain whether ethanol or taurolidine locks might be equal or superior to the antibiotic-lock technique. Since its effect does not depend on sensitivity to antibacterial agents, this approach may be of particular value for infections with multiresistant micro-organisms. Furthermore, highly antibacterial-resistant micro-organisms will not be selected by the use of disinfectants or other alternative agents and, in principle, its use could reduce the consumption of broad-spectrum antibacterials, especially vancomycin.

3.3.2 Recommendations for Calculated Antimicrobial Therapy

Because of the high risk of complications, CVC-related and surgically implanted venous access infections should be treated with parenteral drugs, using high doses and short courses (approximately 7–10 days), irrespective of the removal of the device.[94,95] Antimicrobial therapy for the time period prior to a microbiological diagnosis should be initiated on a calculated basis considering the spectrum of expected pathogens and their local/regional resistance situation. However, treatment should be de-escalated to narrow-spectrum drugs on the basis of susceptibility tests as soon as test results are available.

Taking into account that staphylococci (especially CoNS, such as *S. epidermidis* and *S. haemolyticus*) are by far the most frequent pathogens isolated

in FBRIs, calculated antimicrobial therapy should include the administration of a glycopeptide (especially vancomycin) with an aminoglycoside (e.g. gentamicin) or rifampicin because a significant percentage of staphylococci recovered from hospitalised patients are meticillin resistant.[58,63,96] In critically ill patients, coverage against Gram-negative bacteria, including *P. aeruginosa*, and even fungi may be considered until definitive data from microbiological diagnostics are available.

3.3.3 Recommendations for Aetiologically Guided Antimicrobial Therapy

Aetiologically guided antimicrobial therapy should be initiated as soon as possible on the basis of appropriate microbiological diagnostics. Choice and duration of this therapy depends mainly on the isolated causative micro-organism, the resistance pattern and the presence of complications, especially deep-seated soft tissue infections (table III).

Coagulase-Negative Staphylococci

Implant infections due to CoNS remain a therapeutic challenge since they frequently result in failure of conservative therapy and often require withdrawal of the foreign body. Although cure rates are not affected by removal, investigations on the impact of CVC removal on the recurrence of catheter-related CoNS bacteraemia have shown that there is a 20% chance of recurrence of bacteraemia when the CVC is not removed.[97,98] In contrast, the risk is significantly reduced to 3% if the catheter is removed.[97] This risk is especially high if the catheter stays in place for >3 weeks after bacteraemia.

Most CoNS isolates causing FBRI are meticillin resistant as a result of the possession of the *mecA* gene. As a result, these isolates are resistant to all β-lactam antibacterials. Thus, most CoNS infections require treatment with glycopeptides, in particular vancomycin. In addition, teicoplanin has potential for use as an alternative in the treatment of infections due to CoNS.[55] Notably, glycopeptides are poorly bactericidal against staphylococci. If an isolate is susceptible, replacement of vancomycin by a semisynthetic penicillin is advisable. Superior rapid action of rifampicin compared with vancomycin was noted in a mouse model of intraperitoneally implanted preformed bacterial biofilm catheter segments.[99] While simultaneous use of antibacterials of the cell wall-active class (including vancomycin) and rifampicin was shown to act synergistically, other antibacterials (including aminoglycosides) antagonised rifampicin activity.[100] However, combination of antibacterials is not generally recommended for CRBI due to CoNS.[58] Recently, two oxazolidinones, linezolid and eperezolid, were shown to achieve eradication of *S. epidermidis* biofilms more rapidly than vancomycin and gentamicin in an *in vitro* model using polyurethane coupons in a modified Robbins device.[101]

The duration of parenteral therapy may be quite short (5–7 days) when treating uncomplicated FBRI due to CoNS if the catheter is removed. If an intraluminal infection is suspected and an intravenous catheter or a surgically implanted device is retained, systemic antibacterial therapy and antibiotic-lock therapy for 10–14 days are recommended (table III).[58,83,102,103] It should be noted that persistent or relapsing fever and other signs of treatment failure are clear indications for removal of the device.[58]

The widespread use of vancomycin for the treatment of FBRIs is of concern because of the emergence of vancomycin-resistant enterococci and of staphylococci with reduced sensitivity to glycopeptides (vancomycin-/glycopeptide-intermediate *S. aureus*). Moreover, the most recent recovery of true vancomycin-resistant *S. aureus* strains underscores the need of control regarding the use of vancomycin in healthcare settings.[104,105]

Staphylococcus aureus

FBRIs caused by *S. aureus* infections are dreaded because of possible accompaniment by serious infectious complications such as severe sepsis, septic thrombosis and/or several deep-seated infections (endocarditis, osteomyelitis and other metastatic infections). Thus, it is generally accepted that the colonised foreign body, especially in the case of non-tunnelled CVC, must be removed.[58,106,107]

Tunnelled CVCs should be removed if there is evidence of exit-site infection as well as tunnel or pocket infections.[108,109] Only in selected cases of uncomplicated infections (table III) may tunnelled CVCs or medical devices be retained and treated with appropriate systemic antibacterial therapy accompanied by antibiotic-lock therapy (see section 3.3.1).[58,110,111]

Since metastatic infections may occur in the course of *S. aureus* infections, it is clinically important to rule out at least their most devastating consequence, that is, acute endocarditis. Transesophageal echocardiography, which has been shown to be a highly sensitive method to diagnose endocarditis, should be performed in each patient with *S. aureus* BSI unless contraindications are present.[112,113] Clinical symptoms of bone infections should lead to scintigraphic and radiographic examinations.[54] A recently published scoring system based on the presence or absence of four risk factors (community acquisition, skin examination findings suggesting acute systemic infection, persistent fever at 72 hours and positive follow-up blood culture results at 48–96 hours) accurately identified complicated *S. aureus* bacteraemia.[114]

In contrast to CoNS, most experts favour parenteral treatment for CRBI caused by *S. aureus* with a minimum duration of 10–14 days of parenteral antibacterials.[115,116] Some authors recommend a subsequent additional treatment with oral anti-staphylococcal antibacterials over a period of 1–2 weeks.[117] If persisting bacteraemia or complications such as prolonged fever, metastatic or deep-seated infection are occurring, much longer periods (4–6 weeks for endocarditis, 6–8 weeks for osteomyelitis) of parenteral anti-staphylococcal therapy are recommended.[4,58] The first choice for treatment of CRBIs caused by *S. aureus* should be the parenteral application of β-lactam antibacterials (penicillinase-resistant penicillins, e.g. flucloxacillin, oxacillin) when the isolate is susceptible.[58] First-generation cephalosporins, such as cefazolin, may be used for patients with penicillin allergy without anaphylaxis or angio-oedema.[58] For patients with serious allergy to β-lactams and for those infected with meticillin-resistant *S. aureus* (MRSA), vancomycin is the drug of choice.[58,118] However, vancomycin has higher failure rates than have penicillinase-resistant penicillins and some complications are difficult to treat with glycopeptide monotherapy for pharmacological reasons.[119,120] In the case of MRSA, lincosamide antibacterials (clindamycin) and newer fluoroquinolones as well as combinations with rifampicin, fusidic acid, cotrimoxazole and fosfomycin may be included into the therapeutic regimen if isolates are sensitive.[119] New antimicrobials such as the oxazolidinones, streptogramins and newer glycopeptides exhibit high activity against MRSA (and other multiresistant Gram-positive pathogens), but resistance to some of these agents has already occurred. In a recent study encompassing children with hospital-acquired pneumonia or bactaeremia due to multiresistant Gram-positive bacteria, linezolid was well tolerated. No significant difference was detected in clinical cure rates in the clinically evaluable population between the linezolid and vancomycin groups for patients with catheter-related bacteraemia.[121] However, the potential of these alternative agents for the treatment of CRBIs should be analysed in further trials.

Several animal models of FBRIs were developed in order to investigate the effects of antibacterial treatment (table IV).[122-126] In one study, Chuard et al.[123] showed that two- or three-drug combinations such as fleroxacin and rifampicin (and vancomycin), respectively, were highly effective and superior to single drugs in treating chronic staphylococcal FBRIs.[123] Applying different fluoroquinolones, partly in comparison with vancomycin, in two different experimental models (rat and guinea pig), it was shown that the newer fluoroquinolones, temafloxacin and sparfloxacin, were significantly more active than ciprofloxacin for the prophylaxis or treatment of FBRIs caused by a fluoroquinolone-susceptible MRSA strain. As with temafloxacin and sparfloxacin, vancomycin was also significantly

Table IV. Experimental animal models of foreign body infection to study effects of treatment with antibacterials

Study (year)	Animal	Foreign body model	Pathogen	Antibacterial treatment
Chuard et al.[123] (1991)	Rat	Subcutaneous tissue cages	*Staphylococcus aureus* (MRSA)	Vancomycin, fleroxacin, rifampicin
Gagnon et al.[99] (1992)	Mouse	Intraperitoneal catheter segments	*S. epidermidis*	Rifampicin, vancomycin
Espersen et al.[76] (1994)	Mouse	Intraperitoneal silicone catheter	*S. aureus*	Meticillin, gentamicin
Schaad et al.[125] (1994)	Guinea pig	Subcutaneous tissue cages	*S. aureus* (MRSA)	Teicoplanin, rifampicin
Schaad et al.[126] (1994)	Rat	Subcutaneous tissue cages	*S. aureus* (MSSA, MRSA)	Imipenem, oxacillin, vancomycin
Cagni et al.[124] (1995)	Guinea pig	Subcutaneous tissue cages	*S. aureus* (MRSA)	Sparfloxacin, temafloxacin, ciprofloxacin, vancomycin
Roehrborn et al.[80] (1995)	Mouse	Subcutaneous Teflon® tubes	*S. aureus*	Amikacin (lipid-based, slow-release)
Van Wijngaerden et al.[129] (1999)	Rat	Subcutaneous catheter	*S. epidermidis*	Teicoplanin, rifampicin
Rupp et al.[130] (2001)	Rat	Central venous catheter	*Enterococcus faecium* (VRE)	Oritavancin
Vaudaux et al.[122] (2002)	Guinea pig	Subcutaneous tissue cages	*S. aureus* (MRSA)	Levofloxacin, alatrofloxacin, vancomycin
Kuklin et al.[131] (2003)	Mouse	Subcutaneous Teflon® catheter	*S. aureus* (bioluminescent mutant)	Linezolid
Vaudaux et al.[128] (2003)	Rat	Subcutaneous tissue cages	*S. aureus*	Daptomycin, vancomycin

MRSA = meticillin-resistant *Staphylococcus aureus*; **MSSA** = meticillin-susceptible *S. aureus*; **VRE** = vancomycin-resistant enterococci.

more active than ciprofloxacin in decreasing the viable counts of MRSA in tissue cage fluids in the rat model.[124] A further comparison of fluoroquinolones with vancomycin for treatment of experimental FBRI by MRSA showed levofloxacin was significantly more active than vancomycin in decreasing the viable counts of MRSA.[122] A second-generation glycopeptide, oritavancin (LY 333328), was shown to be effective against *S. aureus* in a rat CVC infection model.[127] The therapeutic activity of daptomycin was compared with that of vancomycin in a rat model of subcutaneously implanted tissue cages chronically infected with *S. aureus*.[128] The authors concluded that a low-dose regimen of daptomycin was at least equivalent to vancomycin; however, three of four cages implanted in daptomycin-treated rats yielded subpopulations with reduced susceptibility to daptomycin.

Gram-Positive Rods (Including Rapidly Growing Mycobacteria)

The majority of intravenous line infections caused by *Corynebacterium* spp. and *Bacillus* spp. require catheter withdrawal. Vancomycin has been widely used to treat infections caused by these bacteria, although treatment should be de-escalated based on the results of susceptibility testing. Catheter removal is essential for successful treatment of CVC-related infections due to rapidly growing mycobacteria of the *Mycobacterium fortuitum* complex.[132] Since these mycobacteria exhibit variable, species-specific susceptibility to traditional antimycobacterial drugs and other antibacterials (including cefoxitin, imipenem/cilastatin, aminoglycosides, tetracyclines, macrolides and co-trimoxazole [trimethoprim/sulfamethoxazole]), therapy should be based on culture and susceptibility results.[133]

Gram-Negative Rods

Gram-negative rods are commonly associated with contaminated infusate and are usually found to be the cause of BSIs in immunocompromised patients with indwelling devices. Controlled studies regarding withdrawal of the infected device or the choice of optimal antibacterial agents and the duration of therapy are missing. However, patients with

catheter-related infections due to Gram-negative rods should have the catheter removed, if possible, and should receive appropriate antibacterial therapy. Patients with devices that cannot be removed should be treated for 2 weeks with systemic and antibiotic-lock therapy provided that the Gram-negative bacteraemia is not associated with organ dysfunction, hypoperfusion or hypotension.[58,134,135] In cases of catheter-related bacteraemia with non-fermenter species other than *P. aeruginosa*, *B. cepacia*, *Acinetobacter baumannii* and *Stenotrophomonas maltophilia*, some reports have demonstrated that catheter withdrawal reduces the rate of treatment failure and improves survival.[136] Approximately 10–14 days of parenteral therapy is recommended when treating CRBIs caused by Gram-negative rods. However, a longer duration (4–6 weeks) of antibacterial therapy should be performed if prolonged bacteraemia occurs despite catheter removal.[137]

Yeasts

Since several *Candida* species readily form biofilms, they are frequently isolated from patients with FBRIs.[138] *C. albicans* represents the predominant and most virulent species. However, the importance of infections caused by non-*albicans Candida* spp. and other unusual yeasts (e.g. *Malassezia* spp., *Rhodotorula* spp., *Hansenula anomala*) has emerged over the last decade.[139] Notably, current routine methods for yeast identification may be insufficient to identify isolates of lipophilic *Malassezia* spp., which have been found to be associated to a low but not negligible extent with infections of CVCs for parenteral nutrition-bearing lipid emulsions.[140] In particular, infections due to *C. parapsilosis* have been shown to correlate strongly with the presence of an intravascular device and the use of total parenteral nutrition due to the slime-forming ability of this species.[141]

In the case of CRBIs due to yeasts, removal of all existing intravascular catheters is desirable, if feasible.[142,143] Following isolation of *C. parapsilosis* and *C. glabrata* in blood, initial management must include withdrawal of the catheter.[144-146] The evidence for these recommendations is strongest in the non-neutropenic patient population.[147] In neutropenic patients it is difficult to determine whether the gut or a catheter may act as the primary source of fungaemia. Management of *Candida* infection by catheter removal alone is not sufficient because of an increased risk of disseminated and/or metastatic fungal infections.[148,149] Thus, it is recommended to treat catheter-related *Candida* infections with appropriate antifungal agents for a minimum duration of 2 or 3 weeks after the last positive blood culture.[61] Infections due to *Malassezia* spp. should include discontinuation of intravenous lipids.[150]

Since its introduction to the pharmaceutical market in the 1950s, amphotericin B has been the gold standard antifungal agent for life-threatening invasive fungal infections. However, its use is considerably hampered by the high rate of toxicity, which has led to the development of lipid-based formulations of amphotericin B with their superior safety profiles. These lipid formulations can be considered as suitable replacements for amphotericin B for primary therapy for many invasive fungal infections.[151] *C. albicans* is generally susceptible to all antifungal agents; however, its potential to develop azole resistance has been documented. In a randomised trial in patients without neutropenia and major immunodeficiency, high-dose fluconazole appeared to be effective as amphotericin B, with less toxicity.[152] In contrast, some *Candida* spp. other than *C. albicans* are characterised by decreased susceptibility against azoles. Thus, knowledge of the species is increasingly important for the choice of the specific antifungal treatment and, especially in the setting of infections due to non-*albicans Candida* spp., susceptibility testing by standardised methods is most helpful. Whereas *C. krusei* and *C. glabrata* are intrinsically/innately more resistant to fluconazole, *C. tropicalis*, *C. guillermondii* and *C. dubliniensis* are generally susceptible to azoles; however, fluconazole may be less active against these yeasts. In patients infected by these yeasts or in institutions

where isolates of these *Candida* spp. are more frequent, the prescription of amphotericin B or the administration of higher doses of fluconazole should be the preferred treatment until the susceptibility data are available.[144] Of note, the azole-sensitive species *C. lusitaniae* has innately higher MICs to amphotericin B.

The first of the second-generation triazole agents to receive regulatory approval is voriconazole, which has shown an expanded *in vitro* activity against a wide variety of yeasts and moulds. In addition, caspofungin, a new echinocandin antifungal agent with broad-spectrum activity against *Candida* and *Aspergillus* spp., was shown to be highly active against *Candida* isolates exhibiting high-level resistance to fluconazole and itraconazole.[153] In a recent study designed to compare the efficacy of caspofungin with that of amphotericin B, caspofungin was shown to be at least as effective as amphotericin B for the treatment of invasive candidiasis and, more specifically, candidaemia.[154] Regarding *C. glabrata*, *C. krusei* and *C. albicans*, voriconazole and caspofungin appear to have enhanced activity; however, the clinical relevance of these findings should be studied in treatment trials.[153,155,156]

Therapy of patients with FBRIs due to *Candida* spp. should be accompanied by ophthalmoscopic examination to rule out metastatic endophthalmitis. It should be kept in mind that candidal endocarditis has also been observed following FBRIs.

3.3.4 Use of Alternative Substances and Approaches

With the emergence of antibacterial-resistant staphylococci, the antibacterial enzyme lysostaphin has, in the past few years, gained renewed interest as an antistaphylococcal therapeutic agent.[157,158] This glycylglycine endopeptidase is specifically capable of cleaving the cross-linking pentaglycine bridges in the cell wall of staphylococci, making it highly active against both actively growing and quiescent bacteria. With a MIC_{90} of 0.001–0.064 μg/mL, lysostaphin kills planktonic *S. aureus* within minutes and is also effective against *S. epidermidis* at higher concentrations (MIC_{90}: 12.5–64 μg/mL).[159] Using biofilm plate assays, Wu et al.[159] demonstrated that lysostaphin is also effective against sessile staphylococci associated with biofilms. Once established, staphylococcal biofilms are very difficult to disrupt. Therefore, the fact that lysostaphin is specifically able to disrupt the extracellular matrix of *S. aureus* biofilms *in vitro* on plastic and glass surfaces (confirmed by scanning electron microscopy) has to be regarded as a major progress in the management of FBRIs. Various other enzymes have been studied for the removal and disinfection of bacterial biofilms; however, they are hampered by the fact that these procedures require two or more compounds – one enzyme for removal of the adherent bacteria in the biofilms and a further agent with antibacterial activity.[160]

Ultrasound, defined as acoustic energy or sound waves with frequencies >20 kHz, is commonly used to remove bacterial cells from the surface of foreign bodies, especially if applied as high-intensity ultrasound (>10 W/cm^2).[161] This intensity is known to lyse bacterial and eucaryotic cells on surfaces and in suspension. The application of low-frequency ultrasound to enhance the activity of vancomycin against implanted *S. epidermidis* biofilms was examined using polyethylene disks covered with a biofilm of *S. epidermidis* and implanted subcutaneously in rabbits on both sides of their spine.[162] Carmen et al.[162] reported that *S. epidermidis* biofilms responded favourably to combinations of ultrasound and vancomycin at 48 hours of insonation. In addition, pulsed ultrasound enhances the killing of *Escherichia coli* biofilms by aminoglycosides in a rabbit model with subcutaneously implanted polyethylene disks. Here, the ultrasound significantly reduced bacterial viability below that of nontreated biofilms without damage to the skin.[163] However, Pitt and Ross[164] found that low-frequency ultrasound (70 kHz) of low acoustic intensity (<2 W/cm^2) increased the growth rate of the cells compared with growth without ultrasound when *S. epidermidis*, *P. aeruginosa* and

E. coli cells adhered to and grew on a polyethylene surface.

4. Prevention Strategies

4.1 Nontechnological Recommendations to Reduce the Incidence of Intravascular Catheter-Related Bloodstream Infections

Guidelines providing evidence-based recommendations for preventing catheter-related infections have been prepared by a working group comprising members from professional organisations representing several clinical disciplines led by the Society of Critical Care Medicine.[22] Published in 2002, these guidelines provide healthcare practitioners who insert catheters and those responsible for surveillance and control of infections with background information and specific recommendations to reduce the incidence of intravascular CRBIs.

The recommendations given in table V and table VI should be considered in the context of the institution's experience and availability of personnel skilled in the placement of intravascular devices. In both tables, only those recommendations that are strongly recommended for implementation and strongly supported by well designed experimental, clinical or epidemiological studies (category IA) are included. For other categories, according to the system for categorising recommendations issued by the Centers for Disease Control and Prevention/Hospital Infection Control Practices Advisory Committee, that is, category IB (strongly recommended for implementation and supported by some experimental, clinical or epidemiological studies, and a strong theoretical rationale), category IC (required by state or federal regulations, rules or standards) and category II (suggested for implementation and supported by suggestive clinical or epidemiological studies or a theoretical rationale), see O'Grady et al.[22] In these guidelines, examples of clinical definitions for CRI (appendix A) and a summary of recommended frequency of replacements for catheters, dressings, administration sets and fluids (appendix B) are also given. Finally, recommendations regarding intravascular devices use in paediatric patients are provided in these guidelines.[22]

In the following subsections, some of the most important strategies for prevention of catheter-related infections are summarised, including those most recently published.

4.1.1 Standardisation of Aseptic Care

Quality assurance and continuing education are aspects of particular interest. Several studies have shown that the risk for intravascular device-associated BSIs declines following standardisation of aseptic care.[22,165-167] While insertion and maintenance of intravascular catheters by inexperienced staff (as well as nursing staff reductions) might increase the risk for catheter colonisation and CRBI, specialised 'IV (intravenous) teams' have shown effectiveness in reducing the incidence of infections and associated complications and costs.[167-169]

4.1.2 Choice of Catheter Insertion Site

The density of local skin flora and, thus, also the site of catheter insertion, influences the subsequent risk for CRI.[170-172] In adult patients, a subclavian site is preferred for infection control purposes, although other factors (e.g. the potential for mechanical complications or risk for subclavian vein stenosis) should be considered when deciding where to place the catheter.[173-175] Consideration of comfort, security and maintenance of asepsis as well as patient-specific factors (e.g. anatomic deformity and bleeding diathesis), relative risk (RR) of mechanical complications, the availability of bedside ultrasound and the risk for infection should guide site selection.[172]

In addition, phlebitis has long been recognised as a risk for infection. Lower extremity insertion sites are associated with a higher risk for phlebitis than are upper extremity sites (for adults), and hand veins have a lower risk for infection than do veins on the wrist or upper arm.[176]

Table V. General recommendations (category IA) to reduce the infectious complications associated with intravascular catheter use (according to guidelines for the prevention of intravascular catheter-related infections)[22]

I. Healthcare worker education and training
Educate healthcare workers regarding the indications for intravascular catheter use, proper procedures for the insertion and maintenance of intravascular catheters, and appropriate infection-control measures to prevent intravascular catheter-related infections
Assess knowledge of, and adherence to, guidelines periodically for all persons who insert and manage intravascular catheters
II. Surveillance
Do not routinely culture catheter tips
III. Hand hygiene
Observe proper hand hygiene procedures either by washing hands with conventional antiseptic-containing soap and water or with waterless alcohol-based gels or foams
Observe hand hygiene before and after palpating catheter insertion sites, as well as before and after inserting, replacing, accessing, repairing or dressing an intravascular catheter
Palpation of the insertion site should not be performed after the application of antiseptic, unless aseptic technique is maintained
Use of gloves does not obviate the need for hand hygiene
IV. Aseptic technique during catheter insertion and care
Maintain aseptic technique for the insertion and care of intravascular catheters
Wearing clean gloves rather than sterile gloves is acceptable for the insertion of peripheral intravascular catheters if the access site is not touched after the application of skin antiseptics. Sterile gloves should be worn for the insertion of arterial and central catheters
V. Catheter insertion
Do not routinely use arterial or venous cutdown procedures as a method to insert catheters
VI. Catheter site care/cutaneous antisepsis
Disinfect clean skin with an appropriate antiseptic before catheter insertion and during dressing changes. Although a 2% chlorhexidine-based preparation is preferred, tincture of iodine, an iodophor or 70% alcohol can be used
Do not apply organic solvents (e.g. acetone and ether) to the skin before insertion of catheters or during dressing changes
VII. Catheter-site dressing regimens
Use either sterile gauze or sterile, transparent, semipermeable dressing to cover the catheter site
Do not use topical antibacterial ointment or creams on insertion sites (except when using dialysis catheters) because of their potential to promote fungal infections and antimicrobial resistance
VIII. Selection and replacement of intravascular catheters
Select the catheter, insertion technique and insertion site with the lowest risk for complications (infectious and non-infectious) for the anticipated type and duration of intravenous therapy
Promptly remove any intravascular catheter that is no longer essential
IX. Replacement of administration sets, needleless systems and parenteral fluids
Replace administration sets, including secondary sets and add-on devices, no more frequently than at 72-hour intervals, unless catheter-related infection is suspected or documented
Replace tubing used to administer propofol infusions every 6 or 12 hours, depending on its use, as per the manufacturer's recommendation
X. Intravenous injection ports
Clean injection ports with 70% alcohol or an iodophor before accessing the system
XI. Preparation and quality control of intravenous admixtures
Do not combine the leftover content of single-use vials for later use
If multidose vials are used: cleanse the access diaphragm of multidose vials with 70% alcohol before inserting a device into the vial; use a sterile device to access a multidose vial and avoid touch contamination of the device before penetrating the access diaphragm; discard multidose vial if sterility is compromised
XII. In-line filters
Do not use filters routinely for infection-control purposes
XIII. Intravenous therapy personnel
Designate trained personnel for the insertion and maintenance of intravascular catheters
XIV. Prophylactic antimicrobials
Do not administer intranasal or systemic antimicrobial prophylaxis routinely before insertion or during use of an intravascular catheter to prevent catheter colonisation or bloodstream infection

Table VI. Recommendations (category IA) regarding specific devices according to guidelines for the prevention of intravascular catheter-related infections[22]

Peripheral venous catheters, including midline catheters, in adult and paediatric patients
I. Selection of peripheral catheter
avoid the use of steel needles for the administration of fluids and medication that might cause tissue necrosis if extravasation occurs
II. Selection of peripheral-catheter insertion site
in adults, use an upper- instead of a lower-extremity site for catheter insertion. Replace a catheter inserted in a lower-extremity site to an upper-extremity site as soon as possible
III. Catheter and catheter-site care
do not routinely apply prophylactic topical antimicrobial or antiseptic ointment or cream to the insertion site of peripheral venous catheters
CVCs, including PICCs, haemodialysis and pulmonary artery catheters, in adult and paediatric patients
I. Surveillance
conduct surveillance in intensive care units and other patient populations to determine catheter-related bloodstream infection rates, monitor trends in those rates and assist in identifying lapses in infection-control practices
II. General principles
designate personnel who have been trained and exhibit competency in the insertion of catheters to supervise trainees who perform catheter insertion
III. Selection of catheter insertion site
weigh the risk and benefits of placing a device at a recommended site to reduce infectious complications against the risk for mechanical complications (e.g. pneumothorax, subclavian artery puncture, subclavian vein laceration, subclavian vein stenosis, haemothorax, thrombosis, air embolism and catheter misplacement)
use a subclavian site (rather than a jugular or a femoral site) in adult patients to minimise infection risk for non-tunnelled CVC placement
place catheters used for haemodialysis and pheresis in a jugular or femoral vein rather than a subclavian vein to avoid venous stenosis if catheter access is needed
IV. Maximal sterile barrier precautions during catheter insertion
use aseptic technique including the use of a cap, mask, sterile gown, sterile gloves, and a large sterile sheet, for the insertion of CVCs (including PICCs) or guidewire exchange
V. Catheter and catheter-site care/catheter-site dressing regimens
replace the catheter-site dressing when it becomes damp, loosened or soiled, or when inspection of the site is necessary
Additional recommendations for peripheral arterial catheters and pressure monitoring devices for adult and paediatric patients
I. Care of pressure monitoring systems
keep all components of the pressure monitoring system (including calibration devices and flush solution) sterile
when the pressure monitoring system is accessed through a diaphragm rather than a stopcock, wipe the diaphragm with an appropriate antiseptic before accessing the system
do not administer dextrose-containing solutions or parenteral nutrition fluids through the pressure monitoring circuit
sterilisation or disinfection of pressure monitoring systems
sterilise reusable transducers according to the manufacturers' instructions if the use of disposable transducers is not feasible
Recommendations for umbilical catheters
I. Catheter-site care
do not use topical antibacterial ointment or creams on umbilical catheter insertion sites because of the potential to promote fungal infections and antimicrobial resistance

CVC = central venous catheter; **PICC** = peripherally inserted central catheter.

4.1.3 Hand Hygiene and Aseptic Technique

The most important and simple strategy to reduce the rate of FBRIs is the attention of an adequate hand hygiene and aseptic technique.[177-179] While for short peripheral catheters good hand hygiene before catheter insertion or maintenance combined with proper aseptic technique during catheter manipulation is of major importance, the level of barrier precautions needed to prevent infection during insertion of CVCs should be more stringent, that is, maximal sterile barrier precautions are necessary to

reduce the incidence of CRBI in patients with CVCs.

Good hand hygiene comprises the use of either a waterless, alcohol-based product or an antibacterial soap and water with adequate rinsing.[178] Maximal sterile barrier precautions should be achieved through the use of a cap, mask, sterile gown, sterile gloves and a large sterile drape.[179,180] For the insertion of peripheral venous catheters, a new pair of disposable nonsterile gloves can be used in conjunction with a 'no-touch' technique, thus, appropriate aseptic technique does not necessarily require sterile gloves.[22]

A review of data regarding handwashing and hand antisepsis in healthcare settings and recommendations to promote improved hand hygiene practices and reduce transmission of pathogenic micro-organisms to patients and personnel in healthcare settings is given in the "Guideline for Hand Hygiene in Health-Care Settings" by Boyce and Pittet.[181]

4.1.4 Skin Antisepsis and Catheter Site Dressing Regimens

Most recently, it was shown that most CRBIs with short-term percutaneously inserted, noncuffed CVCs were extraluminally acquired and derived from the cutaneous microflora. It was concluded that strategies achieving successful suppression of cutaneous colonisation can substantially reduce the risk of CRBI with short-term CVCs.[182] In the past, a number of different commercially available products for cleansing arterial catheter and CVC insertion sites have been studied.[183-186] Preparation of central venous and arterial sites with 2% aqueous chlorhexidine gluconate lowered BSI rates compared with site preparation with 10% povidone iodine or 70% alcohol.[185] In another prospective, randomised study of adults, a tincture of 0.5% chlorhexidine was shown to be as or less effective in preventing CRBI or CVC colonisation than 10% povidone iodine.[184] In contrast, in a study comprising neonates, 0.5% chlorhexidine reduced peripheral intravenous colonisation compared with povidone iodine.[186]

Different dressing regimens have also been compared. In the largest controlled trial of dressing regimens on 2000 peripheral catheters, the rate of colonisation among catheters dressed with transparent dressings (5.7%) was shown to be comparable with that of those dressed with gauze (4.6%).[187] No clinically substantial differences in either the incidences of catheter site colonisation or phlebitis were observed. In a meta-analysis assessing studies that compared the risk for CRBIs for groups using transparent dressings versus groups using gauze dressing, the risk was found not to differ between the groups.[188] A chlorhexidine-impregnated sponge placed over the site of short-term arterial and CVCs reduced the risk for catheter colonisation and CRBI.[189] Concerning catheter securement devices, a study – comparing a sutureless device with suture for the securement of peripherally inserted central catheters – revealed that CRBI was reduced in the group of patients who received the sutureless device.[190]

4.1.5 Catheter Material and In-Line Filters

The type of catheter material used is also of importance regarding the risk for subsequent infections. For example, several studies showed that Teflon® or polyurethane catheters are associated with fewer infectious complications than catheters made of polyvinyl chloride or polyethylene.[187,191] Steel needles have the same rate of infectious complications as do Teflon® catheters; however, their use is frequently complicated by infiltration of intravenous fluids into the subcutaneous tissues[192] (prevention by material modification [section 4.2] or by incorporation of antimicrobial agents [section 4.2.3]).

The routine use of intravenous in-line filters on infusion lines has been controversial for many years and is still under debate.[193,194] So far, no data have been published that support the efficacy of in-line filters in preventing infections associated with intravascular catheters and infusion systems; however,

they reduce the incidence of infusion-related phlebitis.[194] While these filters may reduce the risk for infection from contaminated infusate or proximal contamination (i.e. introduced proximal to the filter) or may reduce the risk for phlebitis in patients who require high doses of medication or in those in whom infusion-related phlebitis has already occurred, no strong recommendation can be made in favour of using in-line filters because infusate-related BSI are rare and in-line filters might become blocked, especially with certain solutions (e.g. dextran and lipids).

4.2 Prevention by Material Modification

4.2.1 Basic Considerations for the Prevention of Device-Related Infections Through Development of New Devices

As microbial adherence is an essential step in the pathogenesis of FBRI, inhibition of adherence appears to be a very attractive approach for prevention. All important steps in the pathogenesis, such as adhesion, accumulation and biofilm formation, represent possible targets against which prevention strategies may be directed (table VII). Although there is now a more detailed insight into the molecular pathogenesis of device-related infection, as outlined in section 2, this has not yet led to strategies directed against specific adherence mechanisms, especially because it is still unknown if a specific adhesin (e.g. protein, polysaccharide) is genus- or species-specific or merely strain-specific. Therefore, most of the recently developed strategies have focused on the modification of medical devices, especially of catheters.

Table VII. Possible strategies directed against specific factors in the pathogenesis of catheter-related infection

Step in pathogenesis	Possible preventive strategy
Adhesion	Antiadhesive surfaces by polymer surface modification
	Inhibition of specific adherence mechanisms
	Antimicrobial devices?
Accumulation	Inhibition of specific factors involved in accumulation (e.g. antibodies against polysaccharide/adhesin, accumulation-associated protein)
	Antimicrobial devices
Biofilm formation	Antimicrobial devices
	Interference with quorum sensing
	Electrical current, ultrasound + antimicrobials

Alteration of the material surface (e.g. of a polymeric catheter) leads to a change in specific and nonspecific interactions with micro-organisms. Such a surface modification of polymeric medical devices may lead to a reduced microbial adherence via altered interactions with proteins and platelets.

The development of so-called antimicrobial polymers is aimed predominantly at the prevention of microbial colonisation rather than microbial adherence. Devices containing antibacterials, disinfectants or metals have been evaluated experimentally or in clinical trials and are, in part, commercially available and already used in clinical applications, for example intravascular catheters. Destruction of the biofilm embedding surface-adherent micro-organisms by enzymes or ultrasound plus subsequent antibacterial therapy as well as the electrical enhancement of antibacterial penetration through biofilms[163,195-197] are all therapeutic strategies rather than preventive measures.

Therefore, it seems obvious that, because of the particular pathogenesis of FBRI, approaches that are directed against bacterial colonisation of a device are very promising. Medical devices made out of a material that would be antiadhesive or at least colonisation-resistant *in vivo* would be the most suitable candidates to avoid colonisation and subsequent infection. In the last 15–20 years there have been a large number of studies dealing with this problem, in part using different strategies. A general overview is given in table VIII; most of the studies have been performed with intravascular catheters because of their widespread use. Thus, the main focus of this section is on the discussion of modified catheter materials.

Table VIII. Prevention strategies of device-related infections by material modification

Catheters and devices used in modification processes
Intravascular catheters
Urinary catheters
Ventricular catheters
Continuous ambulatory peritoneal dialysis catheters
Catheter hubs
Cuffs
Dressings
Tubing systems
Process of modification
Modification of basic polymers ('antiadhesive polymers')
Incorporation or superficial bonding of antimicrobial substances ('antimicrobial polymers')
antibacterials
antiseptics
Metals with antimicrobial activity

4.2.2 Development of Antiadhesive Polymer Materials by Physico-Chemical Modification

The most attractive approach to obviate FBRIs would be to develop a medical material that proves to be resistant against microbial adherence, even after insertion into the bloodstream and despite the ever-occurring interactions of the device surface with host factors such as proteins and cells. There is evidence that the intrinsic properties of a material might be of advantage regarding resistance to infection. Thus, improvement of the surface texture, tailoring the protein adsorption characteristics and improving the antithrombogenicity of a given material would be key factors in the development of innovative, infection-resistant materials. However, this goal has not yet been reached satisfactorily.

Several research groups have tried to develop polymers with new surface properties that would lead to a reduction of bacterial adhesion. Bridgett et al.[198] studied the adherence of three isolates of *S. epidermidis* to polystyrene surfaces that were modified with a copolymer of poly(ethylene oxide) and poly(propylene oxide). *In vitro*, a substantial reduction in bacterial adhesion was achieved with all surfactants tested. Similar results were found by Desai et al.,[199] who investigated the adhesion of *S. epidermidis*, *S. aureus* and *P. aeruginosa* to polymers that were surface-modified with poly(ethylene oxide). They observed reductions in adherent bacteria of between 70% and 95% compared with the untreated polymer. A photochemical coating of polymers was used by Dunkirk et al.,[200] demonstrating that the coating reduced adhesion of a variety of bacterial strains. Tebbs et al.[201] compared the adherence of five *S. epidermidis* strains to a polyurethane catheter and to a commercial hydrophilic, coated polyurethane catheter (Hydrocath®). Adhesion of three strains to the coated catheters was considerably reduced. Bacterial colonisation was further reduced by the addition of benzalkonium chloride to a hydrophilic polyurethane catheter (Hydrocath®).[202] Our own approaches to develop anti-infective materials comprised the modification of polymer surfaces by radiation or glow discharge techniques. By means of radiation grafting leading to a reduced *in vitro* adhesion of *S. epidermidis*, 2-hydroxymethylmethacrylate was covalently bonded to a polyurethane surface.[203,204]

More recent work on surface modification of polymer materials to prevent bacterial adhesion involved the use of sulfonated poly(ethylene oxide) as surfactant in a polyurethane[205] or the introduction of glycerophosphorylcholine as a chain extender in polyurethane.[206] Both approaches lead to increased water uptake and to lower bacterial adhesion. An overview mainly on experimental research on the surface modification of polymers and on binding macromolecules such as albumin to surfaces in order to prevent bacterial adherence can be found elsewhere.[207,208]

So far, the only such modified polymer used in clinical applications is a hydrophilic, polyvinylpyrrolidone-coated catheter (Hydrocath®) based on polyurethane. Its relatively low thrombogenicity and low *in vitro* bacterial adherence should also be of benefit regarding infection resistance; however, this has not yet been demonstrated in a clinical trial.

A major disadvantage of all of the previously described approaches, which aim primarily at the modification of the surface properties of basic

materials such as catheters or other devices, is the fact that – for thermodynamic reasons – the creation of surfaces that show a 'zero' adhesion is probably not feasible. In an experimental study that investigated the relationship between bacterial adhesion and the free surface enthalpy of adhesion of a large number of differently modified polymers, we demonstrated that it is impossible to develop a polymer surface that shows an absolute bacterial 'zero' adherence *in vitro*.[209] In particular, adherence of *S. epidermidis* to a variety of polymers with different surface properties, generated by means of the glow discharge technique, was investigated.[209] We found that adhesion of the bacteria to the modified materials decreased with increasing negative free enthalpy values. A certain minimum number of adherent *S. epidermidis* cells could be proved at positive free enthalpy values at which adhesion should be thermodynamically impeded. Hence, it seems impossible to design an absolute antiadhesive material that retains its properties even in the more complex *in vivo* situation, in which the native surface properties are masked by adsorption of bacterial and host components.

4.2.3 Incorporation of Antimicrobial Agents in Medical Devices

The loading of medical polymers with antimicrobial substances either for therapeutic or preventive purposes has a long tradition. The best known anti-infective, polymeric drug delivery systems are the polymethylmethacrylate-gentamicin bone cement and the polymethylmethacrylate-gentamicin beads (Septopal®) used for treatment of bone and soft tissue infections.[210,211] Vascular prostheses made from Dacron® have been treated with various antibacterial agents to create infection-resistant grafts but without routine clinical application to date.[212-214] In recent years, catheters or parts of the catheter system have been coated with antimicrobial drugs, and some of these antimicrobial devices are already commercially available. The main principle of such devices is that an antimicrobial substance (e.g. an antibacterial, disinfectant or metal ion) is bound superficially to a catheter – either directly or by means of a carrier – or incorporated into the interior of the polymer. If such a device comes into contact with an aqueous environment, release of the drug into the near vicinity occurs. The amount of the antimicrobial substance released is influenced by the processing parameters, loading dose, applied technique, molecular size of the drug and the physico-chemical properties of the polymeric device. A high antimicrobial concentration is reached (at least initially) in the very near vicinity of the device surface, mostly exceeding the MIC and minimum bactericidal concentration of susceptible organisms. Most such materials exhibit a release pattern according to first-order kinetics, with an initially high drug release and subsequent exponential decrease of the released drug; however, more sophisticated drug-release systems with defined release kinetics have also been developed.

As yet, it is unclear whether such a device is capable of inhibition of microbial adherence *per se*, or if its activity is more directed against colonisation; however, at least an elimination of already adherent micro-organisms should be achieved for the duration that the antimicrobial compound is released in the necessary concentrations. Thus, such materials are especially suitable to prevent, for example, infection in short-term catheters, which originates from contamination during the insertion or from hub contamination.

Antibacterials

There are a large number of studies on the bonding of antibacterials to biomaterials. Solovskij et al.[215] prepared polymers to which ampicillin and 6-aminopenicillanic acid were covalently bonded and which inhibited the *in vitro* growth of *S. aureus*. However, most studies have focused on the incorporation or superficial coating of antimicrobials rather than on covalent bonding by chemical reaction. Sherertz et al.[216] used a rabbit model to investigate intravascular catheters coated with several antimicrobial substances (dicloxacillin, clindamycin, fusidic acid and chlorhexidine). The frequency of

catheter infections was significantly reduced compared with the control group when the dicloxacillin-coated catheter was used. We have investigated the incorporation of flucloxacillin, clindamycin and ciprofloxacin into polyurethane polymers and demonstrated a considerable reduction of the *in vitro* adherence of *S. epidermidis*.[204,217] In another approach, a commercially available central venous, hydrophilic-coated polyurethane catheter (Hydrocath®) was loaded with the glycopeptide teicoplanin.[218] In *in vitro* studies as well as in a mouse model, the capability of this catheter to prevent colonisation with *S. epidermidis* and *S. aureus*, respectively, was proven for a period of at least 48 hours, rendering the catheter suitable to prevent early-onset infection.[218,219] To extend the antimicrobial spectrum of such a catheter to include Gram-negative bacteria and fungi, a combination of teicoplanin with silver was incorporated into Hydrocath® catheters, which exhibited considerable activity against *S. epidermidis*, *E. coli* and *C. albicans*.[209]

Kamal et al.[220] have evaluated the efficacy of a cefazolin-containing catheter (in which cefazolin was bound to benzalkonium chloride) in a prospective, randomised trial. There was a significant decrease in catheter colonisation (7-fold) as determined by the semiquantitative tip culture method;[15] no CRBI was observed in this study. In a more recent comparative study before and after the routine use of cefazolin catheters in the ICU, the authors described a marked reduction in the rate of CRBI from 11.5 to 5.1 infections per 1000 catheter days.[221]

Raad et al.[222,223] reported on the broad-spectrum activity against Gram-negative and -positive organisms and *C. albicans* of a minocycline-rifampicin catheter based on *in vitro* and animal data. This catheter has been marketed as the Cook Spectrum™ catheter (Cook Critical Care, Bloomington, IN, USA) and is coated on the inner and outer surface with minocycline and rifampicin, which have a synergistic or additive action in combination. In a prospective, randomised clinical trial,[224] the minocycline-rifampicin catheter was compared with an uncoated control catheter and demonstrated a statistically significant decrease in catheter colonisation (8% vs 26% for the control catheter, $p < 0.001$) and in CRBI (0% vs 5%, $p < 0.01$). In a large multicentre trial, the minocycline-rifampicin catheter was compared with another commercially available catheter containing chlorhexidine and silver sulfadiazine (the CHSS catheter), which is described further in the Antiseptics section.[225] It was found that the minocycline-rifampicin catheter was 3-fold less likely to be colonised (7.8% vs 22.6% for the CHSS catheter, $p < 0.0001$) and 12-fold less likely to lead to CRBI (0.3% vs 3.4%, $p < 0.002$). This difference has been explained by the fact that minocycline-rifampicin catheters are coated internally and externally (in contrast with the first-generation CHSS catheter), the combination of minocycline and rifampicin showing superior surface activity than chlorhexidine and, finally, that the minocycline-rifampicin catheters retain surface antimicrobial activity longer *in situ*.[226] Although resistance against minocycline and rifampicin could not be detected in clinical trials, this remains of concern as *in vitro* development of resistance has been demonstrated.[227]

More recent work on antibacterial-containing catheters included, for example, the adsorption of cefamandole nafate on functionalised urethane catheters that were then used to coat a commercial CVC[228] or the use of a combination of an antibacterial substance (rifampicin) in combination with an antifungal substance (miconazole) in a polyurethane catheter.[229]

A disadvantage of all of these approaches might result from the risk for development of resistance against the antimicrobial agents, especially if antibacterials considered as first-line drugs in the therapy of infections are used as an active part of the modified catheters.

Antiseptics

Antimicrobial substances that differ from antibacterials, such as antiseptics, have also been used

to develop new catheter materials. The disinfectant Irgasan® was incorporated into several polymer catheters, showing a reduction of infections in rabbits.[230] We used the hydrophilic Hydrocath® catheter to incorporate iodine, leading to a polyvinylpyrrolidone-iodine-complex on the inner and outer catheter surface.[218] *In vitro* adherence of various micro-organisms (*Staphylococcus* spp., *E. coli*, *Candida* spp., *Pseudomonas* spp.) was completely inhibited for the time of iodine release. After iodine exhaustion, re-loading of the catheter was possible. Tebbs and Elliott[202] incorporated benzalkonium chloride into triple-lumen Hydrocath® catheters and demonstrated a long-lasting antimicrobial activity of the catheters against staphylococci and a somewhat lesser activity against Gram-negative bacteria and *C. albicans*.

The most promising development in this field in the last few years was a catheter using a combination of an antiseptic (chlorhexidine) and silver sulfadiazine (CHSS catheter). This catheter became available ~10 years ago, is polyurethane-based and impregnated with minute amounts of chlorhexidine and silver sulfadiazine (ArrowGard, Arrow International, Reading, PA, USA). A synergistic effect of chlorhexidine and sulfadiazine has been shown *in vitro*.[231] This 'first-generation' CHSS catheter is coated only on the exterior surface and exhibits antimicrobial properties for ~15 days. Since its introduction >8 million catheters have been sold worldwide and a considerable number of randomised clinical trials have been performed with this type of catheter.[173,232-241] In the study with the greatest patient numbers, which also used molecular methods for the confirmation of CRBI, the CHSS catheter was associated with a 2-fold reduction in the incidence of catheter colonisation and a 5-fold reduction of CRBI (RR 0.21, 95% CI 0.03, 0.95; p = 0.03).[238] As of 2004, seven meta-analyses or systematic reviews have been published.[2,226,242-246] Veenstra et al.[243] investigated randomised clinical trials with CHSS versus control catheters up to 1998 and found summary odds ratios for catheter colonisation of 0.44 (95% CI 0.36, 0.54; $p < 0.001$) and of 0.56 for CRBI (95% CI 0.37, 0.84; p = 0.005). From an analysis of six prospective studies, Mermel[2] also concluded that short-term use of CHSS catheters reduces the risk for catheter-related BSI. In one study with longer catheter dwelling times (mean duration 20 days), no such difference in the incidence of CRBI was observed, which probably reflects less antimicrobial efficacy over time due to a loss of activity to 25% of the baseline value after 10 days *in situ*.[237] As the 'first-generation' CHSS catheters are coated only externally, colonisation of the inner lumen as a result of hub contamination might also be of greater relevance with longer duration of placement. For these reasons, a new second-generation CHSS catheter has recently been developed that is coated both internally and externally, and that exhibits enhanced chlorhexidine activity (ArrowGard Plus, Arrow International, Reading, PA, USA). Clinical trials with this new type of catheter are currently being performed. In one already published study, a significant reduction in catheter colonisation and a trend to reduction of infection episodes was associated with the antimicrobial catheter.[247]

Development of resistance to chlorhexidine has been demonstrated *in vitro*.[248] However, *in vivo* resistance to either chlorhexidine or silver sulfadiazine associated with the use of the antimicrobial catheter has not yet been observed. Anaphylactoid reactions, probably due to chlorhexidine, have been reported from Japan and UK, but have not been observed in the US so far.[249]

Metals

Among metals with antimicrobial activity, silver has raised the interest of many investigators because of its good antimicrobial action and low toxicity.[250] Silver has also extensively been used for the development of infection-resistant urinary catheters.

Sioshansi[251] used ion implantation to deposit silver-based coatings on a silicone rubber, which thereafter demonstrated antimicrobial activity. Silver-copper surface films, sputter-coated onto cathe-

ter materials, also showed antibacterial activity against *P. aeruginosa* biofilm formation.[252] In a more recent piece of research, an ion beam technique applying low implantation energy has been used for the formation of silver nano-particles on the surface of polymers that exhibited an improved effect on bacterial adhesion.[253] We developed an antimicrobial polymer by binding silver ions to acid-modified, negatively charged polyurethane surface.[209] Another approach is loading of a hydrophilic polyurethane catheter with silver nitrate.[254] In addition, surface-coated polyurethane catheters with a silver surface thickness of 15–20Å have been investigated with regards to their biocompatibility and antimicrobial efficacy, showing markedly decreased adherence of Gram-positive and -negative micro-organisms *in vitro*.[255] Further interest has been raised regarding devices in which silver is distributed in form of nano-particles or in combination with other elements such as carbon and platinum. The 'Erlanger' silver catheter uses a microdispersed silver technology to increase the quantity of available ionised silver.[256] The 'Oligon' catheters are composed of polyurethane in which carbon, silver and platinum particles are incorporated, which leads to an electrochemically driven release of silver ions in the outer and inner vicinity of the catheter surface. However, a peripherally implanted central catheter based on this technology (Olimpicc™, Vygon, Cirencester, UK) has been withdrawn from the market at least in Germany because of mechanical problems associated with this type of catheter. A more recent development is the Oligon Vantex® catheter (Edwards Life Sciences, Irvine, CA, USA).[257] Other approaches are catheters with 'active iontophoresis' technology in which micro-organisms are repelled by electrical current generated from a carbon-impregnated catheter[258] or where low-amperage current is produced by two electrically charged parallel silver wires helically wrapped around the proximal segment of silicone catheters.[259]

Several clinical studies have been performed with silver-containing intravascular catheters. In a randomised, prospective study in haemato-oncological patients, a silver sulfate-polyurethane catheter (Fresenius AG, Bad Homburg, Germany UK) was associated with a significantly lower rate of CRBI compared with the control group (10.2% vs 22.5%, $p = 0.01$).[260] In three trials, the 'Erlanger' silver catheter in which the silver is microdispersed was evaluated.[256,261,262] In the adult population, a reduction in catheter colonisation and in 'catheter-associated sepsis' was observed; however, the authors used criteria for determining CRBI that differed from most other studies. A more recent clinical investigation failed to show a statistically significant difference in the colonisation rate of the silver catheter compared with a control catheter.[262] Ranucci et al.[257] compared the Oligon Vantex® catheter, composed of silver, carbon and platinum with a benzalkonium chloride-treated catheter (Multi-Med, Edwards Life Sciences, Irvine, CA, USA) in a prospective randomised trial. Use of the Oligon Vantex® catheter decreased the rate of catheter colonisation by 11%, while the rate for CRBI did not differ significantly between the Oligon Vantex® and control groups.

4.2.4 Neurological Prostheses

Infection of CNS (hydrocephalus) shunts is a major problem in patients with ventricular drainage. Therefore, efforts have also been made to develop infection-resistant hydrocephalus shunts or other neurological prostheses. Bridgett et al.[263] reported on the reduced staphylococcal adherence to Hydromer®-coated and, thus, hydrophilic CSF shunts; however, there were technical difficulties in achieving a uniform Hydromer® layer on the silicone rubber.[263] Bayston et al.[264-267] have published a considerable amount of experimental work on impregnation of silicone shunt catheters with various antimicrobials. In particular, a combination of rifampicin and clindamycin proved to be clearly superior to other agents tested. In a newer study, it was shown *in vitro* that the rifampicin-clindamycin-

impregnated catheters are able to kill adhered staphylococci completely within 48–52 hours.[268,269]

We have also developed an incorporation method for rifampicin and other hydrophobic antibacterials into silicone ventricular catheters.[270] In an animal model using New Zealand white rabbits, rifampicin-loaded catheters were implanted into the ventricular space and infection was induced by inoculation of certain dosages of *S. epidermidis* or *S. aureus*.[271] None of the animals that received the rifampicin-loaded catheter showed clinical signs of infection, nor could the infecting strain be recovered from the catheter, brain tissue or CSF. In contrast, all animals with the uncoated catheters showed signs of severe meningitis or ventriculitis, and the infecting strains were cultivated in each case from the catheter and from surrounding tissue. As an improvement of the catheter, especially to prevent development of resistance of staphylococci to rifampicin, a combination of rifampicin and trimethoprim was used for the impregnation process.[272] Recently, two cases were reported in which the rifampicin catheter was successfully used for the treatment of patients with a complicated course of shunt infection.[273]

Furthermore, a silicone catheter with a combination of three antimicrobials (rifampicin, fusidic acid and mupirocin) has been described with a long-lasting drug release of up to ~100 days; however, no animal or clinical data are available so far for this type of catheter.[274] Zabramski et al.[275] performed a prospective, randomised clinical trial with an external ventricular drain catheter coated with minocycline and rifampicin. The antibacterial-impregnated catheters were one-half as likely to become colonised as the control catheters (17.9% vs 36.7%, $p < 0.0012$), and CSF cultures were seven times less frequently positive in patients with the modified catheters than in the control group (1.3% vs 9.4%, $p = 0.002$).

4.2.5 Innovative Approaches for the Prevention of Device-Related Infections

A very interesting approach to prevent biofilm formation as a prerequisite for CRI has been suggested by Khoury et al.[196] They found that by application of an external stimulus, for example an electric field together with antibacterials, the killing of biofilm-embedded bacteria is dramatically enhanced (e.g. killing of *P. aeruginosa* by tobramycin). Although it is more of a therapeutic strategy than a preventive measure, the use of an electric current might be useful for the prevention of CRI, as was previously pointed out. Related approaches aimed at eradication of biofilms include the combined use of ultrasound together with antibacterials[163,197] and, possibly, the bactericidal effect of extracorporeal shock waves on *S. aureus*.[276]

Another approach to create anti-infective surfaces has been developed on the basis of so-called 'intelligent polymers'. Because a disadvantage of the currently available antimicrobial catheters is the continuous leaching out of active substances once the device is in contact with blood (or other body fluids), a system was developed in which an antimicrobial compound is released on demand. This could be achieved by binding iron to a chemically modified polymer surface; then in a second step, a fluoroquinolone was coupled. *In vitro* experiments with *P. aeruginosa* demonstrated liberation of the antibacterial only in the presence of the bacteria.[277]

5. Conclusion

The increasing use of indwelling foreign bodies has become essential in modern day clinical practice; however, their use is associated with a multitude of complications, the most common being infection. Nowadays, it is generally accepted that the consequences of FRBIs are substantial, both in terms of morbidity and mortality as well as in terms of financial resources expended. The causative pathogens attach to surfaces of the medical devices and develop biofilms, leading to an evasion of host defence mechanisms and to a phenotypic resistance

to antimicrobial agents. Thus, conservative management of FBRIs is frequently unsuccessful and can be dangerous for the patient. Antimicrobial agents have a role in preventing medical device-related complications, such as metastatic sepsis, yet in most situations it is impossible to eradicate the primary focus of infection on the implant. In the light of the emergence of multiresistant micro-organisms, such as meticillin-resistant staphylococci with reduced susceptibility or with resistance towards glycopeptides, prudent use of antimicrobials is advised. Innovative and multidisciplinary approaches for prophylaxis and management should result in novel, more effective control strategies.

In the future, the development of medical devices based on modified anti-infective materials will lead to a further reduction of the incidence of FRBIs. However, even the best technology will fail if standard hygienic procedures, with their often easy-to-perform preventive techniques based on recommendations of the respective national guidelines, are not implemented.

Some of the new developments, such as antimicrobial catheters, have already been adopted, but more, good quality clinical studies are needed to better define their impact on reducing FRBIs, patient morbidity and mortality, and their cost effectiveness. These studies are needed before recommending a broader use of these devices. Although antimicrobial materials obviously have the potential to decrease infections, there is a major point of criticism/concern: that of development of antimicrobial resistance against the agents used. This should still be carefully monitored when using such devices and should be an important issue in forthcoming clinical studies.

The most important challenge will be to implement all of the current knowledge in daily practice. In addition, translating the recent data on the mechanisms of biofilm formation and bacterial interference into applicable strategies and innovative materials may avoid the unnecessary and expensive removal of, in particular, highly needed and/or difficult to replace medical devices.

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