

Catheter-Related Infections: It's All About Biofilm

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Abstract

Almost all micro-organisms subsist in elaborate colonies that are embedded in biofilms of self-produced exopolymer matrices. The biofilm allows the micro-organisms to adhere to any surface, living or nonliving. The adaptive and genetic changes of the micro-organisms within the biofilm make them resistant to all known antimicrobial agents. Thus, the diagnostic and therapeutic strategies used to fight acute infections are not effective in eradicating medical device biofilm-related infections or chronic biofilm diseases. Today, vascular catheter-related bloodstream infections are the most serious and costly healthcare-associated infections. The purpose of this article is to describe the biofilm form of life, the mechanisms of resistance to current forms of treatment, and the clinical implications for effective strategies to diagnose and treat catheter-related bloodstream infections.

Introduction

Bacteria first appeared on earth about 3.6 billion years ago, long before the appearance of *Homo sapiens* around 100,000 years ago.^[1] Micro-organisms have developed extraordinary survival mechanisms that allow them to live in almost any environment on the planet. Man was unaware of the existence of bacteria until the 17th century, when Anton van Leeuwenhoek (1632-1723) invented a rudimentary compound microscope. Van Leeuwenhoek was the first person to visualize, graphically illustrate, and label "animalcules" (bacteria) that he found in plaque scraped from his own teeth.

It wasn't until almost 2 centuries later, in 1884, that Robert Koch described a method to identify a specific micro-organism as a cause of disease.^[2] This led to the establishment of pure culture techniques that today remain the cornerstone of diagnostic and prescriptive antibiotic therapy.

Microbiologists usually study micro-organisms in a liquid homogeneous suspension and plate culture format, which provides a very biased view of microbial life in nature and disease. More recent direct microscopic observations and direct quantitative recovery techniques demonstrate unequivocally that more than 99.9% of bacteria grow as aggregated "sessile" communities attached to surfaces, rather than as "planktonic" or free-floating cells in liquid.^[3] Micro-organisms commonly attach to living and nonliving surfaces, including medical devices, and form biofilms that lead to colonization and sometimes infection.

A biofilm develops when the attached cells excrete polymers that facilitate adhesion, matrix formation, and alteration of the organism's phenotype with respect to growth rate and gene transcription.^[4] The physical and genetic profiles of micro-organisms within the protected biofilm community are profoundly different from their existence as unprotected independent cells.

The hallmark of biofilm-related infections is the dramatic resistance to antimicrobials and to host defenses. Patients with chronic infectious diseases, such as otitis media and osteomyelitis, experience cycles of acute exacerbation and remission. Many chronic infections result in treatment failure, suppression of infection followed by reoccurrence, or the inability to culture micro-organisms despite obvious clinical symptoms.^[5] Medical device-related infections also fit this profile and typically require removal of the device, despite appropriate therapy as indicated by standard methods in hospital microbiology labs.

Microbial biofilms, which often are formed by antimicrobial-resistant organisms, are responsible for 65% of infections treated in the developed world.^[3] [Table 1](#) lists medical devices known to be associated with biofilm development, and [Table 2](#) lists chronic diseases known to be associated with biofilm infections.

Medical devices are critical in modern-day medical practice. At the same time, they are major contributors to morbidity and mortality. The use of a medical device is the greatest exogenous predictor of healthcare-associated infection.^[6] Most nosocomial infections occur at 4 major body sites -- the urinary tract, respiratory tract, bloodstream, and surgical wound sites -- and 3 of those are common sites for medical devices. In fact, 95% of urinary tract infections are associated with a urinary catheter, 86% of pneumonias are associated with mechanical ventilation, and 87% of bloodstream infections are associated with an intravascular device.^[7] The last type, catheter-related bloodstream infection (CRBSI), is the most life threatening and is associated with significant medical costs.

The increased incidence and associated risks of catheter-related infections have drawn considerable attention from national organizations such as the Institute of Medicine, the Centers for Disease Control and Prevention (CDC), the Agency for Healthcare Research and Quality, and the Joint Commission for Accreditation of Healthcare Organizations. Catheter-related infections will continue to pose a serious threat unless prevention strategies, diagnostic techniques, and treatment modalities are implemented to address the pathogenic mechanisms of CRBSI and the microbiology of biofilms associated with vascular access devices.

Biofilm Development on Catheter Surfaces

Biofilm development is a series of complex but discrete and well-regulated steps. The exact molecular mechanisms differ from organism to organism, but the stages of biofilm development are similar across a wide range of micro-organisms.^[8] The sequential stages of biofilm development on intravenous catheters are: (1) microbial attachment to the catheter surface; (2) adhesion, growth, and aggregation of cells into microcolonies; and (3) maturation and dissemination of progeny cells for new colony formation. An interactive illustration of the biofilm life cycle can be viewed at <http://www.erc.montana.edu/MultiCellStrat/default.html>.

Microbial Attachment

Direct contact of the micro-organism with the catheter surface is required for attachment and subsequent colonization. The mere "touch" of the cell wall with the biomaterial alters the micro-organism's phenotypic expression to begin production of a sticky adhesin that attaches the cell to the surface. The first opportunity for such contact is during insertion of the catheter, as it passes through the layers of normally colonized skin. Both transient and resident micro-organisms exist on the surface of the skin. About 80% of resident micro-organisms inhabit the first 5 cell layers of the stratum corneum. The remaining 20% survive in biofilms within the underlying epidermal layers, sebaceous glands, and hair follicles.^[5,9,10] The microbial density of the skin depends on the body location; normal counts at the jugular and subclavian catheter sites are about 1000-10,000 colony-forming units (cfu)/cm², compared with about 10 cfu/cm² at the antecubital space.^[11]

This step in the pathogenesis of CRBSI offers a significant opportunity for preventing infections, as most skin micro-organisms can be removed through meticulous preoperative skin cleansing and application of antiseptic agents. Even so, the catheter enters the bloodstream with some burden of bacteria attached to the tip and the length of the external catheter surface.

Upon arrival of the catheter into the venous system, circulating plasma proteins instantly collide and rapidly bind with the biomaterial. In the next few minutes, the coagulation cascade and the complement system are activated, attracting platelets and polymorphonuclear leukocytes to the foreign material. The matrix of absorbed protein, adherent leukocytes, aggregated platelets, and accumulated fibrin composes a "conditioning layer" that envelops the catheter as a fibrinous sheath. A partial or occlusive pericatheter thrombus may develop over the fibrin sheath within the next few days.^[12]

The matrix of host products serves as scaffolding for the simultaneously developing biofilm and provides receptor-binding sites for newly arriving bacteria. The effect of single blood proteins or of whole blood itself depends on the microbial strain.^[13] For example, whole blood promotes *Pseudomonas aeruginosa* biofilm formation, while plasma proteins such as fibrinogen and fibronectin enhance *Staphylococcus aureus* binding but inhibit *S. epidermidis* and Gram-negative bacteria adherence.

The circumstances under which micro-organisms contact the intraluminal surface of the catheter are quite different from the external lumen. Instead of having constant exposure to blood flow, the biomaterial of the internal lumen may be exposed to a wide range of flow rates of infused substances, including crystalloid solutions, drug admixtures, blood or blood products, and nutrition solutions; or it may be "locked" in a no-flow state. Particles from the infused substances may bind directly with the biomaterial or incorporate with the conditioning layer formed during blood sampling or transfusion.

Unless adequately disinfected, microorganisms gain entry into the flow system through any contaminated access portal or connection site. Once inside, contact with any internal surface component of the administration system such as extension tubing, needleless connector, hubs, or the conditioned or unconditioned catheter surface results in attachment.

Adhesion and Microcolony Formation

The attachment of a small number of bacterial cells is all that is needed to initiate biofilm formation anywhere along the system. Within a few seconds, the progression of phenotypic changes in the bacteria remarkably alters protein expression to further produce species-specific adhesions that irreversibly anchor the cell to the surface.^[14] Within as few as 12 minutes, the adherent cells upregulate genes that direct production of accumulation proteins and polysaccharides, which firmly attach the cells to the substratum and to each other as they undergo exponential binary division.

As the cells continue to divide, the daughter cells spread outward and upward from the attachment point to form cell clusters. The production of exopolymer saccharides (EPS) or "slime" embeds the aggregating cells to form microcolonies. Typically, the microcolonies are composed of 10% to 25% cells and 75% to 90% EPS matrix, with a consistency similar to a viscous polymer hydrogel.^[5] Figure 1 shows the progression of bacterial attachment to layered and embedded microcolony formation.

The continued formation of the biofilm community evolves according to the biochemical and hydrodynamic conditions, as well as the availability of nutrients in the immediate environment.^[13] The structural organization is mainly influenced by hormone-like regulatory signals produced by the biofilm cells themselves in reaction to growth conditions. This interactive network of signals allows for communication among the cells, not only controlling colony formation but also regulating growth rate, species interactions, toxin production, and invasive properties.^[15] The cell clusters are structurally and metabolically heterogeneous, and both aerobic and anaerobic processes occur simultaneously in different parts of the multicellular community.^[15]

Cellular density typically increases to a steady state within 1-2 weeks, depending on the species and local environmental conditions. Expanded growth evolves into complex 3-D structures of tower- and mushroom-shaped cell clusters. Adjoining microcolonies are connected by water channels that serve as a primitive circulatory system for delivery of nutrients and removal of wastes.

The thickness of the biofilm is variable (13-60 mcm) and uneven, as determined by the balance between growth of the biofilm and detachment of cells.^[16] Depending on the initial number of attached organisms, the multilayered cell clusters develop as patchy networks or form a contiguous layer over the surface of the catheter (Figure 2).

The dimension of biofilms in vivo is only on the order of tens of micrometers, but they contain thousands of bacteria in a very compact space.^[17] Kite and colleagues measured average biofilm cell counts in infected catheters removed from hemodialysis patients at levels above 10⁵ cfu/cm

of intraluminal catheter surface.^[18] Considering that catheters are 20-60 cm or longer, there is potential for vast numbers of bacteria to be released into the bloodstream.

Dispersal and Dissemination of Biofilm Cells

The formation of biofilm is a universal strategy for microbial survival. In order to colonize new surfaces and to prevent density-mediated starvation within the mature biofilm, the cells must detach and disseminate. Dispersal is accomplished by shedding, detachment, or shearing.

Shedding occurs when daughter cells from actively growing bacteria in the upper regions of the microcolonies are released from the cell clusters. Increased cell density induces cell-cell signaling to direct chemical degradation of the EPS, sending clumps of biofilm into the circulation.^[19] Biofilms within vascular catheters are exposed to variable flow rates and shear forces. When the shear force of the infusion or catheter flush exceeds the tensile strength of the viscous biofilm, fragments break away. Clumps or fragments of detached biofilm may contain thousands of cells, but they leave behind an adherent layer of cells on the surface to regenerate the biofilm.^[5,20]

The dissemination of biofilm cells into the systemic circulation may result in bloodstream infection, depending on the host immune system and bioburden of cells released. Single cells released by shedding are susceptible to antibiotics and can be controlled by antimicrobial therapy and/or the host's immune system. However, those released in clumps retain antibiotic resistance and may embolize at a distant anatomic site to develop metastatic infections such as endocarditis or osteomyelitis.^[20] In one investigation, endocarditis developed in 25% of patients with central venous catheter (CVC) *S aureus* biofilms.^[21] In another study, CVCs colonized with *S aureus* biofilm were implicated as the source of metastatic infections in 31% of patients.^[22]

Biofilm Recalcitrance to Antimicrobials

The hallmark characteristic of biofilm microbes is their innate resistance to antimicrobial agents and host immune defenses. Phagocytic cells poorly penetrate the physical barrier of the biofilm matrix. Those phagocytes that do penetrate are unable to engulf the biofilm bacteria and are rendered useless by premature release of lysozymes.^[23]

Systemic dosing levels of antibiotics, which were developed according to the pharmacodynamics and pharmacokinetics of planktonic organisms, are relatively ineffective against biofilm micro-organisms. Biofilm micro-organisms have been shown to be 100-1000 times less susceptible to antibiotics than their planktonic counterparts.^[24] At least 4 mechanisms are attributed to this resistance: (1) restricted penetration of the antibiotic through the biofilm; (2) nutrient limitation, altered microenvironment, and slow growth of biofilm cells; (3) adaptive responses; and (4) genetic alteration to "persister" cells.

Restricted Penetration

Once the biofilm forms, delivery of nutrients to the cells is dependent on diffusion through the EPS. The substances in the EPS act as a diffusion barrier, either by limiting the rate of molecule transport to the biofilm interior or by chemically reacting with the molecules themselves.^[25] Restricted diffusion protects the cells from large molecules such as complement. Biofilms are mostly water, so solutes the size of antibiotics will readily diffuse through the biofilm matrix.^[26] However, the negatively charged EPS restricts permeation of positively charged molecules of antibiotics, such as aminoglycosides, by chemical interaction or molecular binding.^[27] If the antibiotic is inactivated or ionically bound in the surface layers, its delivery to the depths of the biofilm can be profoundly retarded.^[28] Microbial biofilms formed in conditioning films present an even greater problem, because antimicrobials poorly penetrate fibrin or host protein complexes.

Nutrient Limitation, Altered Microenvironment, and Slow Growth

Limited diffusion of nutrients and oxygen generates physiological gradients throughout the biofilm. Cells in the outer microns close to the flowing liquid have ready access to nutrients and

oxygen. These cells are metabolically active, normal in size, and similar to planktonic organisms.

The near complete consumption of oxygen and glucose in the surface layers creates anaerobic niches in the depths of the biofilm where the cells downregulate into an extremely slow-growing or nongrowing state in order to survive.^[23] Growth rate is one of the factors that changes bacterial cells' susceptibility to antimicrobial agents, along with temperature, pH, and prior exposure to subeffective concentrations of antibiotics.^[17] Subsequently, those antibiotics readily diffused through the biofilm are ineffective in killing the slow and nongrowing cells in the anaerobic regions of the biofilm.

The age of the biofilm also affects its susceptibility to antibiotics. Older (10-day-old) biofilms are significantly more resistant than 2-day-old biofilms.^[25] This emphasizes the need for prompt diagnosis and treatment.

Adaptive Responses

Biofilm cells adapt to environmental fluctuations in temperature, pH, osmolarity, and nutrient availability, through the expression of multiple stress-response genes. The genetic alteration not only ensures survival in community living but also affords protection from the host immune system, environmental toxins, and antimicrobials.^[28-30] Antibiotic resistance is further enhanced by the horizontal exchange of resistant plasmids. Plasmids are extrachromosomal circles of DNA that may encode resistance to antimicrobial agents, including beta-lactams, erythromycin, aminoglycosides, tetracycline, glycopeptides, trimethoprim, and sulfonamides.^[4,31] The high cell densities and greater probability of contact between the cells in the biofilm clusters favor the higher rates of horizontal transfer of plasmid DNA. This phenomenon has contributed to the dramatic increase of antimicrobial resistance among nosocomial pathogens.^[32]

Genetic Alteration

The majority of cells in the upper regions of the biofilm are susceptible to prolonged exposure to antibiotics. Most die rapidly when treated with a cidal antibiotic such as ciprofloxacin that effectively kills slow-growing cells. It is now thought that the presence of a subpopulation of "persister" cells within the biofilm may account for the profound resistance to complete eradication of biofilm bacteria. Persisters are phenotypic variants of wild-type cells that neither grow nor die in the presence of bactericidal agents and that exhibit multidrug tolerance.^[33]

The population of persister cells has been estimated to reach about 0.1% to 10% of all cells in a biofilm.^[34] Their purpose is to ensure the survival of the population in the presence of lethal factors and to reseed the community in the event of catastrophic killing. This subpopulation persists even during prolonged exposure or escalated concentrations of antimicrobial agents. When antimicrobial therapy is discontinued, the unaffected persister cells reverse the phenotype and become metabolically viable to regrow the biofilm. Infection may reoccur at a later time or may linger for months, years, or even a lifetime, or until the colonized device is removed.^[35]

Diagnosis of Catheter-Related Bloodstream Infections

Accurate and early diagnosis to validate that the catheter is the primary source of bacteremia and to identify which luminal surface is involved is essential to guide the management of catheter-related local and systemic infections.^[36] Insertion site inflammation, tunnel tract infections, and port pocket infections are soft-tissue biofilm infections associated with the external surface of the catheter or port septum, and may or may not coexist with bloodstream infection.^[36] CRBSIs associated with percutaneously placed nontunneled catheters that occur within the first 10 days of insertion are most often correlated with extraluminal biofilm formation.^[37,38] However, more recent studies have documented the internal lumen as the primary source in short-term CVCs as early as 4 to 6 days after insertion.^[39,40] Bloodstream infections related to catheters in place for longer than 10 days are almost always associated with intraluminal biofilm.^[38,41,42]

Clinical Findings

The most common clinical signs and symptoms of CRBSI are inflammation or purulence at the catheter site, as well as the acute onset of fever, chills, and hypotension with no other apparent source of infection but the catheter.^[43] While common, these clinical findings alone are insufficient and unreliable for a diagnosis because of their poor specificity and sensitivity.^[43,44] Fever with or without chills is the most sensitive but nonspecific clinical finding associated with CRBSI. Inflammation or the presence of purulence at the catheter insertion site of nontunneled CVCs is a more specific finding, but it has poor sensitivity in the prediction of CRBSI.

In a prospective study of 1353 CVCs conducted in a university hospital, 73% of the 11 patients with CRBSI had no signs of local inflammation.^[45] The sensitivity and positive predictive value of local inflammation for identification of CRBSI was 27% and 1.5%, respectively; however, purulence at insertion site -- although rare -- was found to be highly predictive of CRBSI (relative risk, 27.1; $P < .005$). Because of the high specificity of this finding, removal of the device is strongly recommended.

Diagnostic Tests

When bacteremia is present and CRBSI is suspected, the following question must be pursued: is the catheter the primary source of the micro-organisms present in the blood? Failure to obtain the appropriate cultures to address this question may lead to a false-negative or false-positive diagnosis. A false-negative diagnosis certainly may increase patient morbidity, while a false positive may result in unnecessary catheter removal or inappropriate prescription of antibiotics. This outcome is particularly dangerous because it promotes the emergence of antibiotic-resistant pathogens and generates excess costs.^[42]

Disparity in the definition of CRBSI has led to highly variable practices in the clinical setting. The CDC provides 3 standard definitions in *Guidelines for the Prevention of Intravascular Catheter-related Infections*.^[46] It is very important to use these definitions for their intended purposes. The definitions for "laboratory-confirmed BSI" and "catheter-associated BSI" are surveillance definitions that are meant to be used for benchmarking institutional performance and directing performance improvement. The clinical definition of "catheter-related BSI" presented in [Table 3](#) is specific to the question of whether the catheter is the primary source of bacteremia. The criteria are applicable to both short- and long-term CVCs. An algorithm for selecting diagnostic tests is presented in Figure 3.

Catheter Cultures

The obvious disadvantage of using catheter cultures to diagnose CRBSI is the required removal of the device. If clinical indications warrant removal, catheter cultures in addition to catheter drawn blood cultures obtained prior to removal can facilitate treatment decisions by identifying the causative organism(s) and confirming the source of bacteremia. The CDC recommends the use of either quantitative or semiquantitative catheter segment culture techniques.

The semiquantitative roll-plate method is most commonly used because of its simplicity. A 5-cm catheter tip segment is rolled over a blood agar plate, and colony forming units are counted after incubation overnight.^[35] The clinical usefulness of semiquantitative catheter cultures is questioned because it does not detect intraluminal colonization, risking a false-negative result.

Quantitative culture, accomplished by vortex, sonication, or centrifugation of the catheter segment in broth followed by serial dilution and plating on blood agar, is the most reliable catheter culture technique because it harvests most of the adherent biofilm bacteria from both the internal and external catheter surfaces.^[35,44,47,48] A yield of $\geq 10^3$ cfu/catheter segment by quantitative method, or a count of ≥ 15 cfu/catheter segment by semiquantitative method with accompanying signs of local or systemic infection indicates CRBSI.^[48]

Blood Cultures

Peripheral blood cultures detect the presence of bacteria or yeast in the bloodstream but provide no information regarding the source of the micro-organisms. The CDC recommends one of 2 blood culture techniques for diagnosing CRBSI: paired quantitative blood cultures, or paired qualitative blood cultures observing a differential time to positivity (DTP). Both require the simultaneous draw of blood from a peripheral vein and from the CVC. These methods are particularly useful when retention of the catheter is desirable.

A positive result for paired quantitative blood cultures yields a $\geq 5:1$ ratio of bacteria cultured from the CVC blood sample vs the peripheral sample. A single quantitative culture of blood drawn from the CVC that yields at least 100 cfu/mL is also diagnostic without a companion culture of the peripheral blood.^[35,48,49] This may be of particular benefit to patients who have very limited peripheral access, or to the pediatric population where peripheral sticks are physically and emotionally problematic. Unfortunately, the use of the quantitative culture technique, although the most accurate, is limited because of its complexity, cost, and lack of methods in most hospitals to perform the test.^[48,50]

An effective alternative is the paired qualitative method by differential time to positivity.^[35,48,50] This technique offers accuracy comparable to quantitative blood cultures, and most hospitals do have capability to perform this comparatively inexpensive test. The DTP method monitors for bacterial growth and compares the time to positivity for both the peripheral and the CVC blood samples. A catheter-drawn blood culture that turns positive 2 hours or more before a simultaneously drawn peripheral blood culture confirms the catheter as the source of infection. The cultures should be drawn, if possible, before beginning systemic antibiotics, to avoid false-negative peripheral cultures.

When CRBSI is suspected in the presence of a multilumen catheter, each lumen should be considered a potential source of infection. Dobbins and colleagues conducted a prospective evaluation to determine the relative rates of microbial colonization in individual lumens of triple-lumen catheters and calculated the chance of detecting CRBSI if only 1 lumen was sampled.^[51] They found that CVCs causing CRBSI had significant biofilm colonization in 1, 2, and 3 lumens in 10 (40%), 10 (40%), or 5 (20%) cases, respectively. Overall, the random sampling of only 1 lumen had only a 60% chance of detecting significant colonization. Therefore, sampling from each lumen is recommended to avoid false-negative results.

The decision to discard or submit the first drawn sample from the catheter that includes the heparin or saline lock solution is of frequent debate. The first drawn sample contains planktonic bacteria shed from the biofilm within the static lock solution left to dwell in the catheter. The shear effect on biofilm created by aspiration will also harvest sessile bacteria from the surface of the biofilm clusters. Discarding this sample may discard the answer being sought.

Everts and Harding assessed the benefit of discarding or flushing away the heparin lock before collecting blood for culture in tunneled and hemodialysis catheters.^[52] They found no significant difference in false contamination rates between first-drawn and second-drawn samples, and no significant difference in bacterial yield or time-to-positivity results.

Guiot and colleagues assessed the value of using heparin lock fluid cultures for diagnosing

CRBSI before the onset of bacteremia or clinical symptoms.^[53] They found that the heparin lock fluid could detect relevant colonization of the catheter. Three or more positive heparin lock fluid cultures sampled on subsequent days correlated with the occurrence of CRBSI with a positive predictive value of 100%. To date, there is no evidence to support discarding the first-drawn sample; using it affords the benefit of reducing blood volume loss in the case of frequent blood sampling.

Treatment of Catheter-Related Bloodstream Infections

Treatment should begin promptly following diagnosis, as the delay of appropriate antimicrobial therapy and/or catheter removal is associated with increased morbidity and mortality.^[54-56] The treatment of CRBSI involves 2 strategies, the first consisting of antimicrobial therapy for systemic infection (bacteremia and accompanying metastatic disease, if present) and the second being the treatment of the catheter-associated biofilm as the source of infection.

Empiric broad-spectrum systemic antimicrobial therapy is initiated after the collection of appropriate samples, depending on the pathogen profile present in a given institution and the severity of the patient's illness. However, treatment should be de-escalated to narrow-spectrum antibiotics dependent on susceptibility testing of the isolated causative micro-organism(s) and the presence of associated complications. Therapeutic regimens for treatment of bacteremia and focal infection are well described in the evidence-based document, *Guidelines for the Management of Intravascular Catheter-related Infections*.^[48]

Although antibiotic therapy and activated host defenses effectively kill planktonic organisms in the bloodstream, there is currently no form of treatment that will completely eradicate all biofilm cells associated with a catheter.^[5] For this reason, removal of the device should be considered when an infection occurs. Prompt removal is strongly recommended in all cases complicated by metastatic infection or when the infection is caused by highly virulent or difficult to eradicate biofilm microorganisms such as *S aureus*, *P aeruginosa*, *Corynebacterium* spp., *Bacillus* spp., mycobacteria, and yeasts.^[57] An overview of the recommended therapeutic approach to CRBSI is presented in Figure 4.

For uncomplicated cases of CRBSI with long-term catheters where removal is difficult or increases patient risk, or where venous access is limited, the antibiotic-lock salvage technique (ALT) might be attempted cautiously in conjunction with systemic therapy. The ALT consists of the instillation of an antibiotic sensitive to the causative organism with or without heparin at concentrations 100-1000 times higher than the target minimum inhibitory concentrations measured for systemic therapy.^[48,58,59] The specified antibiotic in a concentration of 1-5 mg/mL mixed with 50-100 units of heparin (if compatible) or normal saline are "locked" in the catheter when the catheter is not in use (usually 12 hours over night).^[48] The use of concentration-dependent-killing antibiotics such as the fluoroquinolones or aminoglycosides is optimal, rather than time-dependent-killing antibiotics such as beta-lactams or glycopeptides, so that minimum biofilm eradicating concentrations can be achieved without dependence on dwell time.^[58] The recommended duration of therapy is 2 weeks.^[48,57,58]

Two recent literature reviews evaluating the antibiotic lock technique provide an excellent overview of its use to date.^[57,58] Most of the data in support of ALT relate to uncomplicated cases of coagulase-negative staphylococcal infections.^[58] Due to the risk of infection recurrence or antimicrobial resistance with suboptimal dosing, and due to the difficulty of eradicating *S aureus*, *Pseudomonas* spp., or fungi, catheter removal is recommended in all but exceptional circumstances.

Antimicrobial agents other than antibiotics have been investigated for the treatment of intraluminal biofilm infection. The use of taurolidine,^[60] ethanol,^[61] hydrochloric acid,^[62] and minocycline-EDTA^[63] (M-EDTA) has produced limited and variable results. None of these agents are currently available commercially. Of the 4, M-EDTA appears to be the most effective, but minocycline is no longer being produced.

Another agent, tetrasodium EDTA, has been tested in vitro and ex vivo with explanted infected hemodialysis catheters.^[64-66] Complete kill of biofilm bacteria and yeasts was observed within 24 hours of exposure. The ability to eradicate intraluminal biofilm within a few days would be quite advantageous over an extended and costly 2-week period. This agent is also a potent anticoagulant that could replace the use of heparin and eliminate the risk of heparin-induced thrombocytopenia. It appears to be a very promising agent for the prevention and treatment of CRBSI due to its capability to dissolve biofilm matrices, including those in conditioning films, and to eradicate all biofilm cells promptly. Further investigation is ongoing.

Summary

Revolutionary findings in microbiology have dramatically increased the understanding of the pathogenesis of vascular CRBSIs. As a survival mechanism, micro-organisms attach to the surface of a medical device and form biofilms, or microcolonies embedded in exopolymer substances. Chemical intercellular signaling and adaptive responses create a heterogeneous environment within the biofilm that affords protection against antimicrobial agents and host immune defenses. The radical changes in gene expression of biofilm cells provide the most significant explanation of antimicrobial resistance and heighten the understanding of the profound differences between adherent sessile organisms and their free-floating planktonic counterparts.

The understanding of biofilm ecology and recalcitrance to antimicrobials is paramount in directing prevention, diagnostic, and treatment interventions. Prevention is aimed at diverting access of micro-organisms to the external and internal surfaces of the catheter so that biofilm cannot form. Diagnosis must include accurate techniques that allow for quick recognition of the catheter as the source of infection, followed by prompt treatment strategies that are based on the organism(s) identified in the biofilm and the luminal source of infection.

Future developments in science and technology will provide answers to the control of biofilm formation and disease. In the meantime, healthcare providers must adopt established best practices to reduce the risk of catheter-related infections and associated morbidity and mortality. Prompt and accurate diagnosis and treatment of CRBSI will reduce the promotion of antimicrobial resistance and will help reduce healthcare costs.

Figures for:

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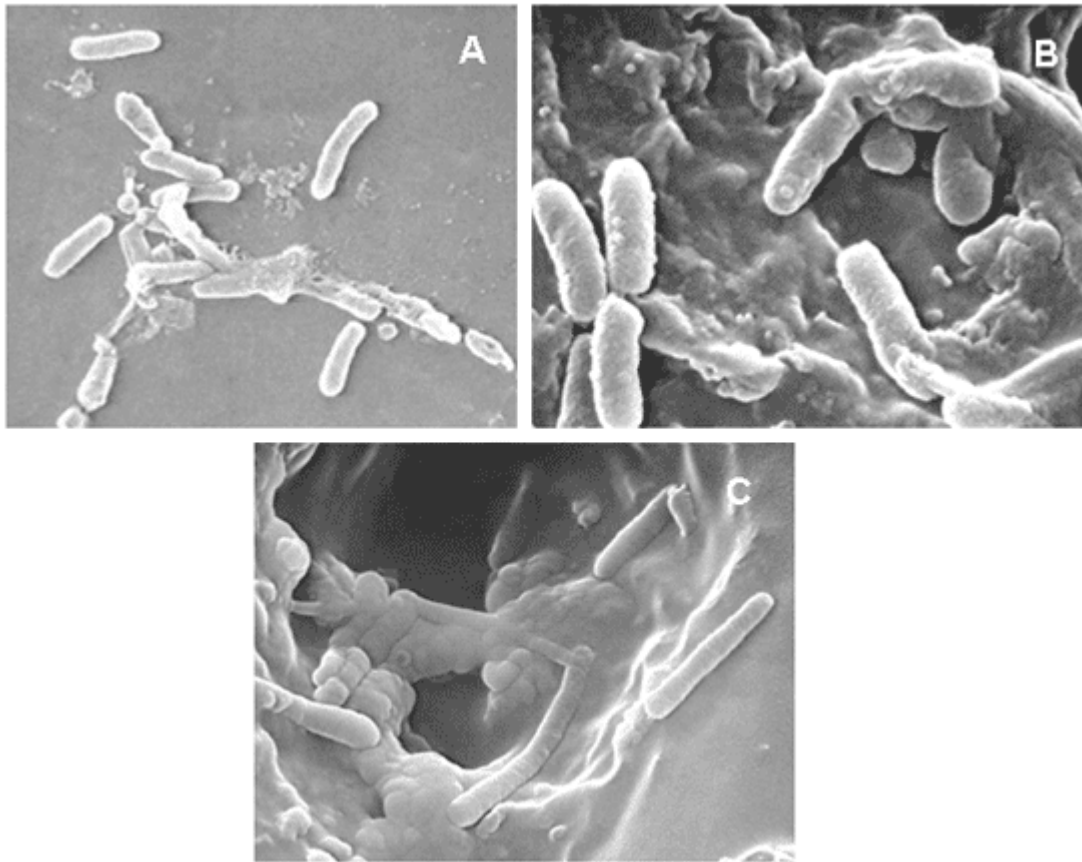


Figure 1. Scanning electron micrographs of *Pseudomonas aeruginosa* biofilm formation. A. Attachment to a surface. B. Attachment followed by phenotypic changes in the cell wall to induce production of adhesins. C. Further production of extrapolymer substances (alginate) embed the reproducing cells for microcolony and biofilm formation. Images from the CDC Public Health Image Library (<http://phil.cdc.gov/Phil/home.asp>).

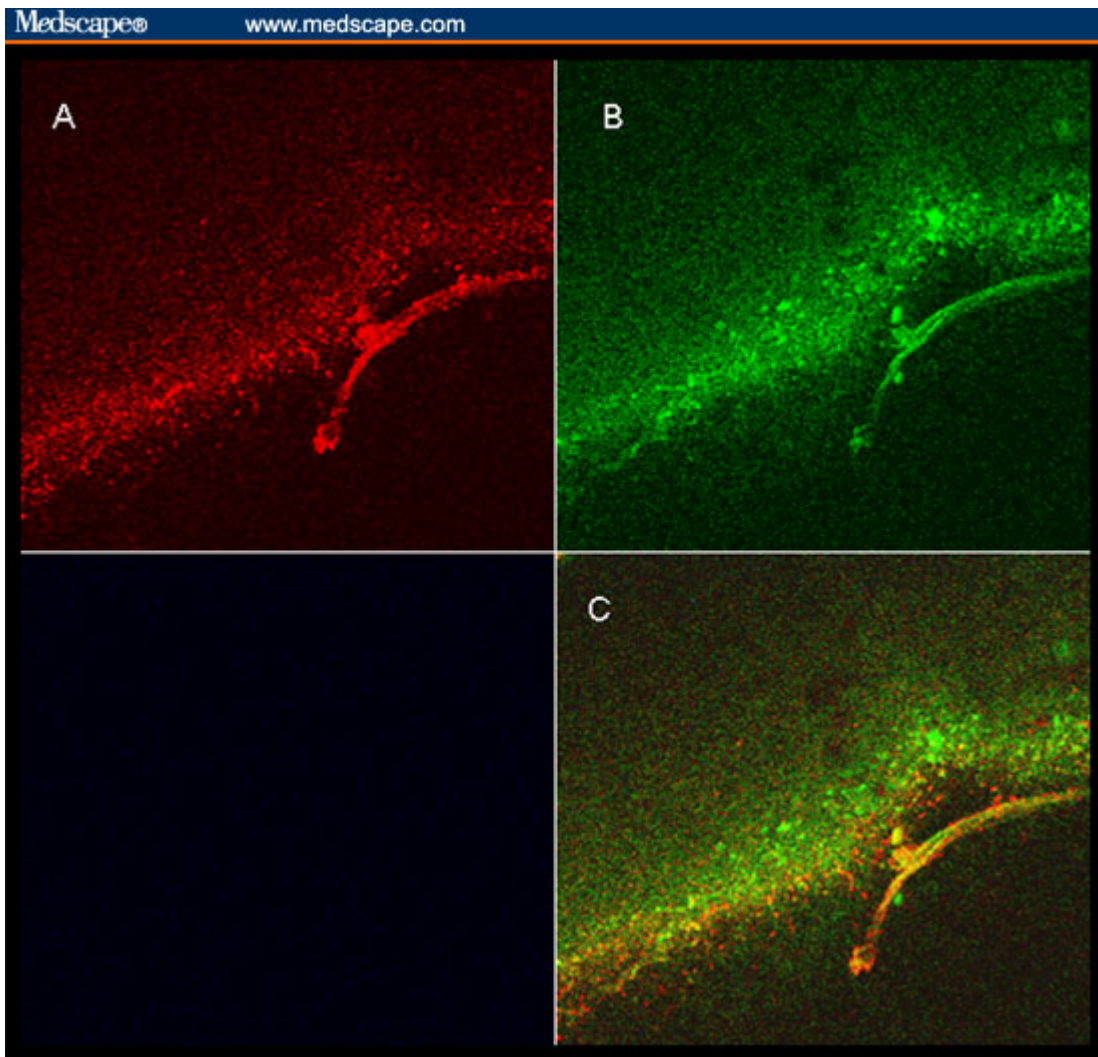


Figure 2. Confocal laser microscopy images of the stained intraluminal surface of a tunneled catheter removed from a pediatric patient at completion of therapy. Each picture represents a cross section of the continuous layer of biofilm along the catheter surface. A. Catheter section treated with a stain for extrapolymer saccharide (EPS) produced by the attached bacteria. B. The same catheter section stained for DNA. C. An overlay of A and B, with the EPS- and DNA-stained biofilm showing the dispersal of cells within the EPS.

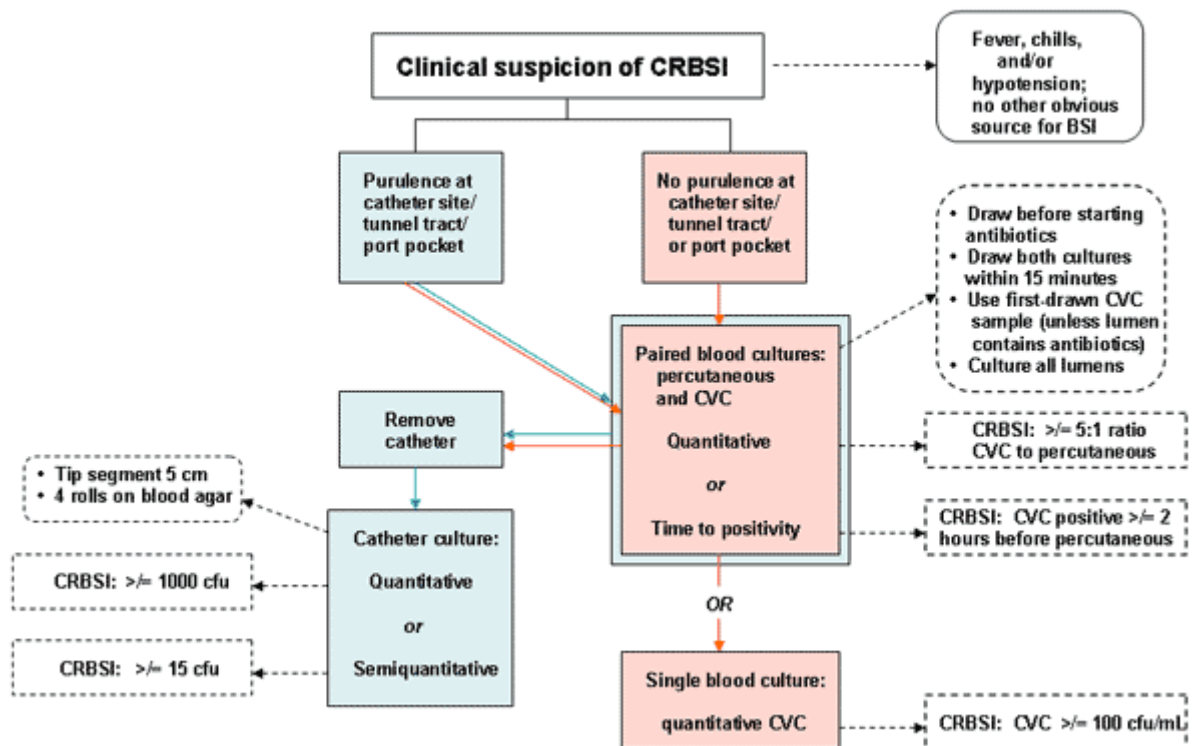


Figure 3.Diagnosis of catheter-related bloodstream infection.

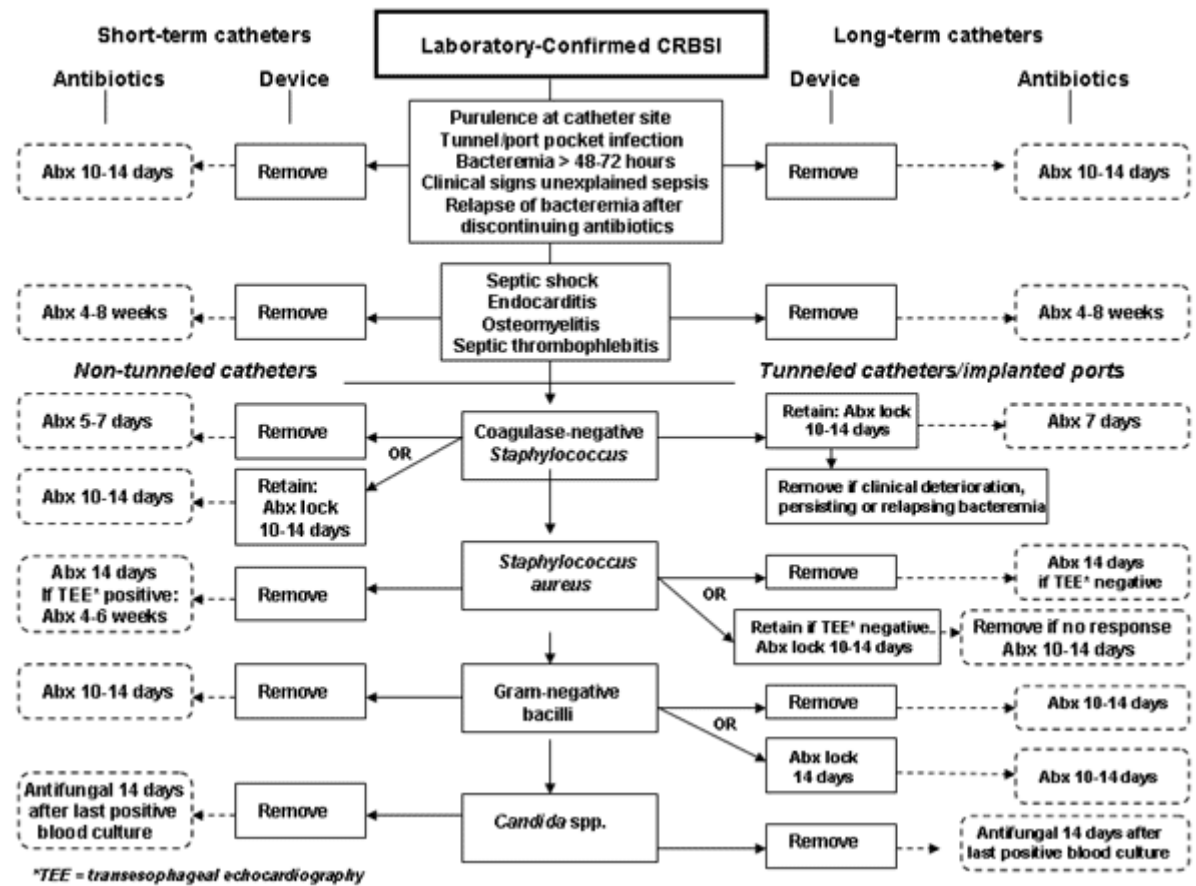


Figure 4. Treatment of catheter-related bloodstream infection. Adapted from Mermel LA, Farr BM, Sherertz RJ, et al. Guidelines for the management of intravascular catheter-related infections. Clin Infect Dis. 2001;32:1249-1272.

Table 1. Medical Devices Associated With Biofilm Infections

Catheters	Implants	Devices
Central venous catheters	Pacemaker and leads	Biliary stents
Hemodialysis catheters	Arteriovenous shunts	Mechanical heart valves
Pulmonary artery catheters	Spinal implants	Fracture fixation devices
Arterial catheters	Penile implants	Joint prosthesis
Urinary catheters	Breast implants	Vascular grafts
Peritoneal dialysis	Orthopedic prosthesis	Intrauterine devices
Enteral feeding tubes	Cochlear implants	Vascular assist devices
Gastrostomy tubes	Neurosurgical stimulators	Coronary stents
Nasogastric tubes	Middle ear implants	Vascular shunts
Endotracheal tubes	Dental implants	Ommaya reservoirs
Tracheostomy tubes	Voice prostheses	Intracranial pressure devices
Umbilical catheters	Implanted defibrillators	Intraocular lens
	Implanted monitors	Suture material
		Contact lens

Table 2. Chronic Biofilm-Related Diseases

Cystic fibrosis
Endocarditis
Otitis media
Prostatitis
Osteomyelitis
Chronic wounds
Myeloidosis
Tonsillitis
Periodontitis
Dental caries
Necrotizing fasciitis
Biliary tract infection
Legionnaire's disease

Table 3. CDC Definition: Catheter-Related BSI^[43]

Bacteremia/fungemia in a patient with an intravascular catheter with:

- At least 1 positive blood culture obtained from a peripheral vein;
- Clinical manifestations of infection (ie fever, chills, and/or hypotension); and
- No apparent source for the BSI except the catheter.

One of the following 3 (•) should be present:

Catheter culture

- A positive semiquantitative catheter culture >15 cfu/catheter segment or a positive quantitative catheter culture $>10^3$ cfu/catheter culture whereby the same organism (species and antibiogram) is isolated from the catheter segment and peripheral blood

Blood culture -- simultaneous blood cultures from CVC and peripheral site

- Quantitative blood cultures: $\geq 5:1$ ratio CVC to peripheral; or
- Differential period of CVC culture vs peripheral blood culture positivity of > 2 hours.

References for:

Catheter-Related Infections: It's All About Biofilm

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