Special Topic

The Relationship of Bacterial Biofilms and Capsular Contracture in Breast Implants

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Abstract

Capsular contracture is a common sequelae of implant-based breast augmentation. Despite its prevalence, the etiology of capsular contracture remains controversial. Numerous studies have identified microbial biofilms on various implantable materials, including breast implants. Furthermore, biofilms have been implicated in subclinical infections associated with other surgical implants. In this review, we discuss microbial biofilms as a potential etiology of capsular contracture. The review also outlines the key diagnostic modalities available to identify the possible infectious agents found in biofilm, as well as available preventative and treatment measures.

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Augmentation and reconstruction mammaplasty are among the most frequently performed cosmetic operations.[1] One relatively common sequela of breast augmentation and reconstruction is capsular contracture (CC). CC involves tightening of the collagen capsule that forms around the breast implant, which can be painful and very often distorts the breast. CC remains the most common cause of breast surgery revision. Various studies, including prospective studies that have been done with a considerable degree of follow-up have indicated CC incidences ranging from 5% to 74% of breast reconstructive surgeries.[2-12] Surgeons diagnose approximately 45,000 patients with CC annually.[9,13] The etiology of CC is not completely understood. Capsule formation itself is known to be a normal response to foreign bodies, however contracture is not. CC formation is likely a multifactorial process and several putative culprits have been proposed. These include placement of incision site, hypertrophic scarring, overactive inflammatory response, and foreign body reaction from powdered gloves, dust, or silicone gel leakage.[14,15]

Biofilms are microbial communities that are attached to a surface, including living tissue, implants, and medical devices. Infections related to microbial biofilms represent a significant number of all microbial infections in humans. These infections are difficult to treat, and as a result they become persistent and chronic. There is substantial evidence showing a correlation between the presence of microbial biofilms on various medical implants and persistent inflammation of the surrounding tissue.[16-19] It appears that microbial biofilms form on breast implants as well and might contribute to a chronic inflammatory response and thus formation of capsular fibrosis and subsequent contracture.[20-25] Investigations of biofilms on mammary implants begun by studying CC.[26-28] Virden et al[20] were among the first to demonstrate a correlation between biofilms on silicone shells and risk of CC.[20-24] Several additional studies have attempted to determine the pathophysiology and prognosis of biofilm-related CC, as well as potential prophylactic and therapeutic measures.

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Here we review key studies that have investigated the relationship between microbial biofilms and CC of mammary implants. Much of the data presented in this review derive from basic science, preclinical, and small case studies. This review is not a systematic review, but a survey of available and pertinent studies regarding the subject matter. We have included a table summarizing the experimental design and level of evidence for many cited studies (Table 1).

MECHANISMS OF BIOFILM FORMATION

Most bacterial species found in nature exist in two different forms, a free-floating form (planktonic), and an attached form (biofilm). The biofilm life cycle begins with planktonic bacteria that can form biofilm upon adhering to a solid surface anywhere in nature including tissue or a foreign material in the host.[16,18] The process takes place in three stages: attachment, maturation, and eventually dispersion (Figure 1).[29] The initial stage begins with the reversible interactions of the bacterial cells with a surface. These interactions are then reinforced by host and tissue-specific adhesions and ultimately result in the irreversible attachment of the planktonic cells to a surface.[29]

The next step of biofilm formation is maturation, which is defined by bacterial multiplication and the synthesis of extracellular polymeric substance (EPS).[30] EPS consists of proteins, polysaccharides, lipids, and nucleic acids. EPS fulfills several functions. It anchors bacteria to a surface and to each other, provides storage of nutrients, and provides a protective barrier for biofilms.[30-33] EPS also plays a role in biofilm-mediated antimicrobial resistance.[33] As adherent bacteria divide and secrete EPS, they form a highly structured microcolony, which is anchored to the surface and other microcolonies.[32]

As the biofilm continues to grow and mature, it becomes highly differentiated and complex. Different bacterial structures form and are intermixed with channels allowing the exchange of nutrients and waste products.[34] There are multiple microenvironments within biofilms that vary in pH, oxygen concentration, nutrient availability, and cell density. These microenvironments are characterized by a great deal of heterogeneity in metabolic activity among cells in different locations within the colony, making it difficult to target the entire biofilm with one type of therapy.[35-38] For example, metabolically inactive cells within the biofilm colony may be resistant to antimicrobial agents that target actively growing cells, such as penicillin.[35,36,39]

Detachment of planktonic cells from a biofilm and their subsequent dispersal into the environment comprises the final stage of the biofilm life cycle. As with the other stages of biofilm growth, detachment involves a myriad of environmental signals, bacterial signal transduction pathways, and their effectors. Detachment of planktonic cells facilitates bacterial survival.[40] Detachment also facilitates disease transmission.[40,41]

Biofilms are usually polymicrobial. Under certain conditions a few species may be overrepresented in the biofilm community. *Staphylococcus epidermidis* is a part of the microflora of the skin and the endogenous flora of the breast. It has been frequently identified on breast implants removed because of CC.[20,22,23,42,43] Another common organism found on removed breast implants is *Propionibacterium acnes,* a commensal species of the skin and gut. These bacteria could gain access to implants at the time of surgery, particularly when surgeons use peri-nipple-areola or trans-nipple-areola approaches.[44] Other bacteria implicated in the formation of biofilm on mammary implants include *Staphylococcus aureus,* and other Staphylococci, Streptococci, *Bacillus* species, *Escherichia coli, Mycobacterium species, Corynebacterium, and Lactobacilli.*[22,23,45-48]

Biofilms are highly resistant to antibiotics and multiple mechanisms contribute to this phenomenon. In addition to the already mentioned mechanisms of resistance, we highlight a few more here. Initiation of the biofilm mode of growth causes differential expression of numerous genes, including those involved in stress response, which allow biofilms to resist harmful conditions or chemicals, including antibiotics.[49] Multidrug efflux transporters are upregulated in biofilms and contribute to decreased antibiotic effectiveness.[50] The extracellular matrix of a biofilm provides several adaptive traits including accumulation of antibiotic-degrading enzymes such as β-lactamases which results in resistance to antibiotics such as penicillins, cephamycins, and carbapenems.[51] Additional information regarding antibiotic resistance in biofilms can be found in several excellent review articles.[52-54]

INFLAMMATORY RESPONSES TO BIOFILMS

All medical implants, including breast implants, are susceptible to bacterial colonization and biofilm formation.[18,55-57] Host response to implants can be divided into several phases: acute or chronic inflammation, foreign body reaction, and fibrous encapsulation.[18,58]

The immune host response consists of innate (immediate and short-lived) and adaptive immunity (long-lived). During the acute inflammatory phase, host cell damage triggers coagulation and plasminogen cascade which then activate the innate immune system.[59] The presence of pathogens also triggers innate immune response through various cell pattern recognition receptors (PRRs). These not only detect molecules released from damaged host cells, but also microbe associated molecules.[60] Activation of PRRs triggers production of cytokines and other inflammatory mediators that attract immune cells (such as neutrophils, dendritic cells, macrophages, and myofibroblasts) to the site of infection.[18]

Table 1. Summary of Capsular Contracture and Biofilm Studies

Study Topic	Author	Study Design (n)	Notes	Level of Evidence
Presence of Biofilms in Capsular contracture	Virden et al,[20]	Case-control (40 patients, 55 implants)	Culture and diagnostic SEM 17 of 27 devices developed CC before 12 months; range 2 mo to 5 yr	3
	Dobke et al,[21]	Case-control (87 pts, 150 implants)	Culture only	3
	Pajkos et al, 2003[22]	Case-control (16 pts, 27 capsules)	Sonication and diagnostic SEM	3
	Schreml et al,[23]	Case-control (45 pts)	Culture only	3
	Rieger et al,[24]	Case series (13 pts, 22 implants)	Culture only (sonication)	4
	Rieger et al,[24]	Case-control (84 pts, 121 implants)	Culture only (sonication)	3
Animal Models of biofilm and Capsular contracture	Shah et al,[42]	Animal Study (16 rabbits, 20 implants)	Experimental group inoculated with *S epidermidis*	5
	Kossovsky et al,[82]	Animal Study (10 guinea pigs, 20 implants)	Experimental group inoculated with *S aureus*, diagnostic SEM	5
	Tamboto et al,[83]	Animal Study (6 pigs, 51 implants)	Experimental group inoculated with *S epidermidis*, diagnostic sonication and SEM	5
Role of implant texture, biofilm formation, and CC	Wong et al,[6]	Systematic Review (6 RCTs; 235 patients, 470 breasts total)	Smooth implants more likely to undergo CC at 1, 3, and 7 yr	1
	Schreml et al,[23]	Case-control (45 pts)	Culture only, no difference in biofilm formation between textures; no follow-up time recorded	3
	Stevens et al,[100]	Sientra's prospective comparative study (2560 patients, 5109 implants)	Smooth implants more likely to undergo CC; 5 year study	2
	Spear et al,[103]	Allergan Core study (715 patients)	Smooth and textured implants had similar rates of capsular contracture over 10 year follow-up	2
	Namnoum et al,[101]	Allergan Core, 410 and 410 Continued Access prospective comparative study (4412 patients, 8811 implants)	Smooth implants more likely to undergo CC; mean follow-up 37 months	2
	Jacombs et al,[89]	Animal study (16 pigs, 121 implants)	Experimental groups inoculated with *S* epidermidis, Diagnostic sonication and SEM, no difference in biofilm formation or CC between textures; 16 weeks at explantation	5
	Liu et al,[102]	Meta-Analysis (16 RCTs, 2 case-control studies; 4486 pts, 8867 implants)	Smooth implants more likely to undergo CC, follow-up range 1-5+ yr	1
Role of Implant filler and CC	Schaub et al, 2010	Systematic review (16 studies)	Unable to draw conclusions based on available data	2
	El-Sheikh et al, 2008	Meta-analysis (4 prospective studies, 8 retrospective)	Pooled odds ratio = 2.25 for silicone implants developing CC; average scientific quality score range 5-9/14	2-3
Prevention	Wixtrom et al,[107]	Case series (32 patients, 63 samples)	6 month follow-up; 22 pts with shield + positive cultures→no CC; 3 pts with shield + neg. cultures → CC (1 was primary augmentation)	4
	Adams et al,[110]	Case series (335 patients)	Mean follow-up 14 months; 1.8% overall CC rate	4

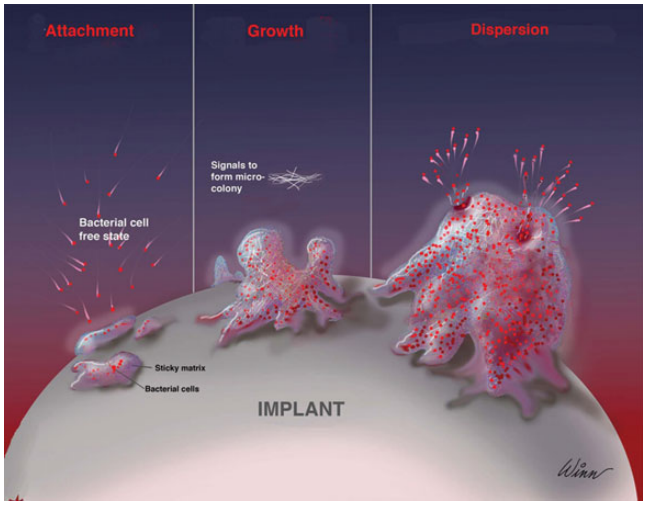

Figure 1. The three stages of the biofilm life cycle; attachment, maturation and dispersion. From Wixtrom et al.[107] Reprinted with permission from Oxford University Press.

Immune responses consist of multiple signaling pathways that are orchestrated by cytokines. Pro-inflammatory cytokines, such as interferons and interleukins, are released and activate their respective receptors to promote inflammatory responses. Upon killing and removal of pathogens and dead host cells, macrophages release anti-inflammatory cytokines which suppress inflammation and stimulate tissue remodeling, angiogenesis, and healing. Innate immunity activates adaptive immune response, which is highly specific, long lasting, and adaptable. During these processes, T cells, B cells, and plasma cells are predominant.[61,62] The adaptive immunity works in conjunction with the innate immunity to achieve an effective overall immune response. Both are essential to combat infection.

Medical implant biofilms are shown to induce a prolonged inflammatory response as the host attempts to eliminate the biofilms.[55,63-66] The host response contributes to the development of tissue destruction through continuous recruitment of pro-inflammatory cells such as macrophages and lymphocytes, release of inflammatory mediators, and proteases.[67] While proteases aid in dislodging biofilms, they also damage normal and healing tissue. Finally, microphages may form a fibrous capsule around an implant.[18]

Different types of fibroblasts, including myofibroblasts, have a very important role in healing. Their number increases in CC.[68,69] They are regulated by transforming growth factor beta-1 (TGF-β1) and mechanical stress, and are involved in wound repair.[68] However, if present in the wound for too long, they cause excessive fibrosis and scaring through matrix deposition and proliferation of connective tissue.[68] A recent study on patients with airway tracheal stenosis showed a correlation between bacterial biofilms and higher expression of TGF-β1 marker, which is consistent with myofibroblast activity and fibrosis.[70] Myofibroblasts produce collagen (types I and III) and a specific form of fibronectin[71] and may be involved in the formation of a contracted capsule around an implant.[72] Bacteria may also exploit this excessive collagen and fibronectin deposition because many bacterial species produce collagen- and fibronectin-binding proteins that mediate bacterial attachment to extracellular matrix components.[73-76] Once attached, bacteria multiply and form biofilms. Therefore, we speculate that the increased number and activity of myofibroblasts could contribute to biofilm formation and possible CC.

Biofilms also serve as one of several mechanisms microorganisms have developed to evade the immune system. It is not completely clear as to why the inflammatory response is not always successful in removing biofilms. However, it appears that biofilms are able to sense and manipulate host immune responses.[41,77,78] For example, one study documented that human leukocytes were capable of penetrating *S aureus* biofilms, but were not capable of phagocytizing these bacteria, suggesting that biofilms have developed mechanisms to prevent normal leukocytes responses.[79] Other research studies imply that the biofilms exposed to neutrophils release planktonic bacteria, and this presumably maintains the prolonged inflammatory response.[80]

The importance of biofilms in the chronic inflammation related to a variety of medical implants has been clearly demonstrated, thus it is reasonable to assume that biofilms may play a role in chronic inflammation and pathogenesis of CC.

ANIMAL STUDIES OF BIOFILMS AND CAPSULAR CONTRACTURE

Multiple animal studies have shown a correlation between biofilms and CC. These studies utilized the Baker Grading Scale in their evaluations.[81] Baker grade III or IV is usually defined as "capsular contracture."

The first animal model study that examined the role of biofilms in CC was a rabbit model.[42] All rabbits underwent bilateral silicone implant placement. Experimental implant pockets were inoculated with *S epidermidis* in varying concentrations. Baker grade III-IV CC was identified with the inoculated pockets, while control pockets were grade I-II, suggesting that *S epidermidis* biofilms may contribute to CC. Another study investigated *S aureus* biofilms and CC in a guinea pig model.[82] Animals underwent bilateral silicone implant placement. Experimental group implants were inoculated with *S aureus* culture overnight prior to placement. All surviving experimental animals had grade III CC, while none of the control animals did. Although these two studies used rodent animal models and a limited number of animals, their results suggest involvement of bacterial biofilms in CC.

Using a porcine model and an excellent study design, Tamboto et al[83] were able to successfully establish a causal

relationship between biofilms and the development of CC following augmentation mammaplasty. Submammary pockets were inoculated with *S epidermidis* or control (phosphate-buffered saline) prior to implantation of silicone prosthesis. Implants and intact surrounding capsule were removed after 13 weeks. Bacteria were then cultured from biofilms that formed on both capsules and implants. Presence of biofilms was confirmed by scanning-electron microcopy (SEM), which is currently the only direct method for biofilm conformation. Biofilms were detected on 72.2% of inoculated pockets. Of the inoculated implants, 77.8% had CC (Baker grade III/IV). Five of 15 control pockets developed biofilms from endogenous bacterial species, and four of these developed CC. Biofilm formation was associated with a 4-fold increased risk of developing contracted capsules.[83] Although microbial biofilms certainly are not the only cause of CC, these studies suggest a strong correlation between implant/pocket biofilms and development of CC.

CLINICAL EVIDENCE OF BIOFILMS IN CAPSULAR CONTRACTURE

Multiple clinical studies have demonstrated significant correlation between presence of biofilms/bacterial colonization and CC of breast implants.[20-22,24,25] All of these studies used an objective measure for CC, known as the Baker Grading Scale.[81] Typical appearance of CC grade III can be seen in Figures 2 and 3. A summary of these studies can be found in Table 1. The Wilflingseder histological classification is a rarely used but objective measure. The reader is referred to a following article for further reading regarding this classification.[84]

Virden et al performed one of the first studies to examine the link between CC and biofilms of breast implants.[20] Fifty-five silicone implants and tissue expanders were explanted due to CC after a follow-up ranging from 2 months to 5 years.[20] All implants were explanted with their capsules and examined. Biofilms were detected by SEM on approximately 56% of all implants.[20] In another study, Dobke et al examined 150 silicone wall mammary implants.[21] In this study, 76% of contracted capsules harbored bacteria. Unfortunately, SEM was not performed in this study. Although bacteria were detected on a large number of contracted implants, the presence of biofilm structures was not confirmed. In the third study, Pajkos et al evaluated 19 contracted and 8 non-contracted breast implants and capsules for bacterial presence.[22] Bacteria were detected in 89.5% of breast implants with CC out of which 57.9% had biofilms. Presence of biofilms was confirmed by SEM.[22] In contrast, bacteria were present in only two (10.5%) of the non-contracted implants.

These studies, despite some shortcomings, consistently show a significant incidence of bacterial colonization and/or biofilms in CC, suggesting correlation of CC and biofilms. Given the vast amount of clinical data supporting development of biofilm-related complications in other types of medical implants,[16-19] these pioneering findings warrant further research.

DETECTION OF BIOFILMS ON CONTRACTED IMPLANTS

There is no clinical standard for detection of biofilms on medical implants, including breast implants. Diagnostic modalities used investigationally include bacterial culturing with or without sonication of specimens, polymerase chain reaction (PCR) and/or 16S RNA sequencing for bacterial DNA identification, and SEM for direct visualization and conformation of the biofilms on samples. Future utilization

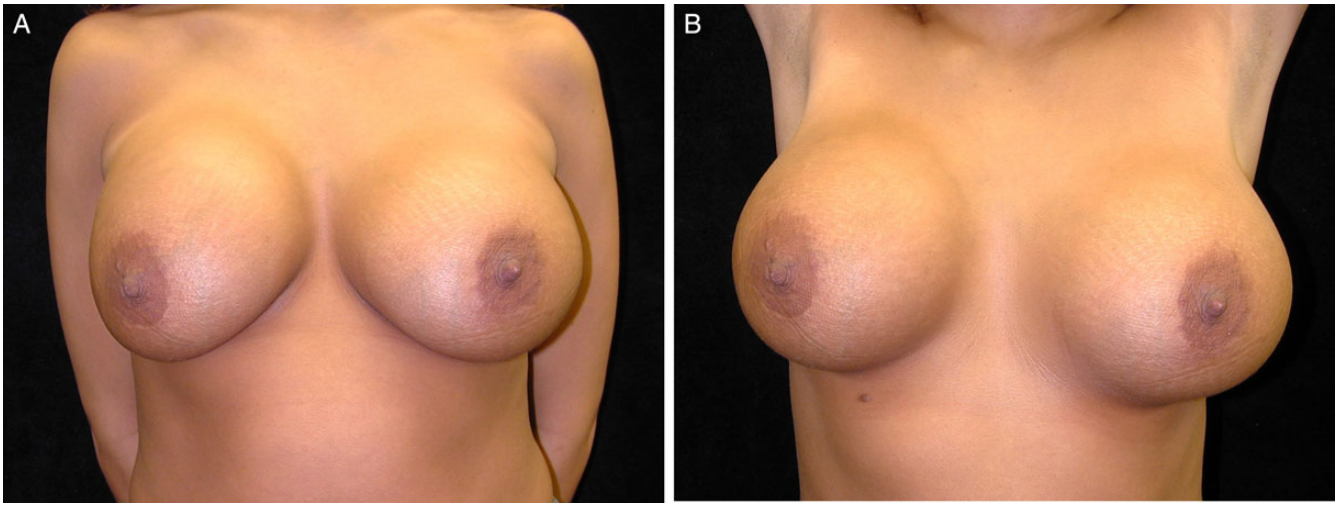

Figure 2. (A, B) A 24-year-old woman with capsular contracture in the right breast (Baker grade III). Patient had 350 cc saline implants placed in the subglandular plane 1.5 years prior to presentation. The implant is displaced laterally, and the implant margin is clearly demarcated. Palpation demonstrated firmness of the breast. Photographs courtesy of Christopher Salgado, MD.

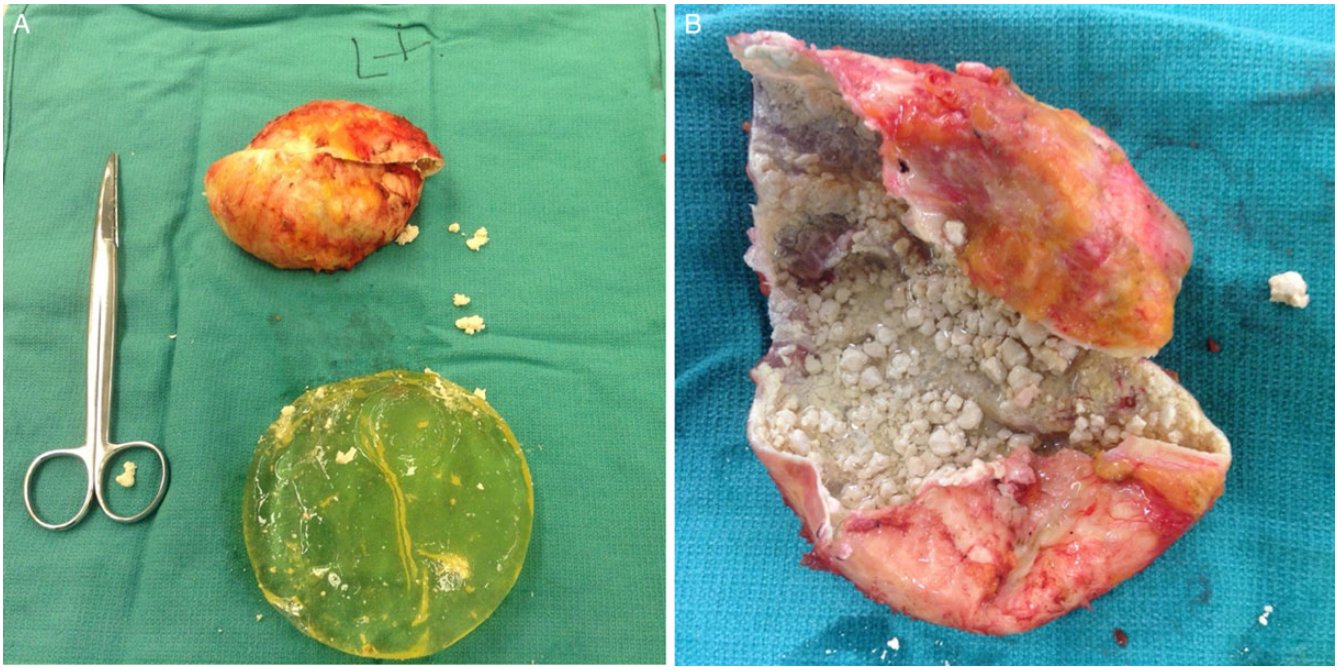

Figure 3. (A) Breast implant with Baker grade IV capsular contracture after explantation and capsulectomy. The patient was 54-years-old at the time of removal; augmentation had been performed 30 years prior. Manufacturer information was unavailable. (B) Capsule has been incised, exposing the interior surface. Photographs courtesy Zubin Panthaki, MD.

of some or all of these methods in clinical practice may help identify a cohort of patients who would otherwise undergo multiple revisions for recurrent CC secondary to lingering biofilm.

Bacterial Culturing

"Conventional/traditional" bacterial identification is defined as bacterial growth on a selective media (on agar plates or in the liquid media). Additionally, biochemical tests can be used for bacterial identification. However, these methods have poor sensitivity for detection of biofilms. In the study by Virden et al, standard plating culture techniques detected bacteria in only 3 out of 27 implants with CC. However, using an experimental culturing protocol with prolonged broth incubation, detection increased to 56% (15/27). Presence of biofilm was confirmed with SEM in all 15 positive specimens. This demonstrated the importance of exploring alternate culturing methods in identifying biofilms in CC.

Sonication

Sonication has been used experimentally to improve the sensitivity and specificity in detecting biofilms on implanted devices and prostheses.[24,85-87] Biofilm matrix encases bacteria present on the surface of implanted devices, making conventional culturing on selective media difficult.[85] In sonication, each implant is exposed to high frequency sonic energy, which releases the bacteria from the biofilm matrix.[85] Bacteria are then grown aerobically or anaerobically on blood agar plates and enumerated. Currently, sonication is not routinely performed clinically. However, given the ease of the technique, sonication followed by culturing may become standard in detection of subclinical infection in prosthetics such as breast implant capsules.

PCR-Identification of Bacterial DNA

Rapid detection and identification of the surgical implant biofilms can be done using molecular biology methods such as PCR. PCR is a very sensitive method that involves amplification of a few copies of bacterial DNA using bacteria-specific primers or universal broad-range primers that can recognize any bacteria present in the sample.[88] Tissue specimens and/or sonication treatment of explanted prosthesis is usually required to obtain adequate DNA for PCR. PCR can detect bacterial DNA in the samples that failed to show positive results using conventional bacterial identification.[88] Furthermore, PCR is a rapid process, taking 2 to 4 hours to complete.

Sonication followed by culturing and PCR detection of microorganisms in biofilms is currently utilized in numerous research laboratories, but only in selected clinical/hospital microbiology laboratories. Future utilization of some or all of these methods in clinical practice may help identify a cohort of patients who would otherwise undergo multiple revisions for recurrent CC secondary to lingering biofilm.

IMPLANT TEXTURE, BIOFILMS, AND CAPSULAR CONTRACTURE

The role that breast-implant texture plays in biofilm formation and CC is not completely clear. Scherml et al found no quantitative difference in the bacterial colonization on smooth and textured implants.[23] In contrast, Jacombs et al reported a 72-fold biofilm increase in textured implants compared to smooth implants in vitro after 24 hours incubation with bacteria.[89] This outcome was similar to the several other in vitro implant studies.[90-93] However, the in vivo (porcine-model) portion of Jacomb's study demonstrated very little difference in development of CC on smooth (82.6%) and textured (83.7%) implants after approximately 19 weeks following inoculation of implant pockets with *S epidermidis*. Interestingly, initial bacterial attachment was 20-fold higher on textured implants, which is not surprising since numerous in vitro studies have shown enhanced bacterial adhesion and biofilms development on rough surfaces.[94-99] Therefore, it is reasonable to conclude from a number of studies that implant texture would affect initial biofilm growth.[90-93] Once mature biofilms are formed, difference in implant texture may be negated. This could explain why both smooth and textured implants had no statistical difference in biofilm formation in Jacomb's study.[89]

The findings explained above are somewhat contradictory to several clinical studies. Stevens et al studied risk factors of CC in smooth and textured implants in Sientra's 5-year prospective study.[100] After a follow-up of 5 years, incidence of CC was significantly higher in smooth implants vs textured implants (odds ratio 2.3, $P < 0.0001$). No attempts were made to detect biofilms on these implants. Other studies have shown similar results.[6,101,102] Spear et al reviewed CC rates for patients enrolled in Allergan's 10-year Core study.[103] Risk of CC was not significantly different between surface texture types.

"Smooth" and "textured" are somewhat arbitrary designations, as all breast implant surfaces show irregularity on microscopic scales. Barr et al examined surfaces of 5 implant types.[104] The "smooth" surface shell, Allergan Smooth surface (Allergan Medical Corporation, Santa Barbara, CA), contained parallel surface ripples measuring 5 µm. Studies have shown that parallel grooves measuring 5 µm or less facilitate fibroblast migration and organized collagen deposition.[105,106] Thus, this may be one of the reasons why smooth surface implants are correlated with higher incidence of CC. The four "textured" implants' grooves ranged from 200 to 500 µm. These grooves are much larger than the approximate diameter of a fibroblast (25 µm), and they presumably interfere with fibroblast migration and the orientation of collagen deposition, which may result in lower incidence of CC.

Biofilm formation is favored when the average roughness of a surface is greater than 0.2 µm.[94] This suggests that both "smooth" and "rough" implant surfaces provide enough roughness for biofilm formation. These data further suggest that, while topographic features of all types of breast implants most likely allow formation of biofilms, "smooth" implant surfaces may further contribute to CC by promoting enhanced collagen deposition. The degree to which these factors contribute to CC remains a topic of investigation. Biological advantages of textured implants, including better tissue ingrowth and a potential reduction in long-term incidence of CC, need to be balanced by the increased risk of bacterial attachment and initial biofilm development.

PREVENTION AND TREATMENT OF BIOFILM-RELATED CAPSULAR CONTRACTURE

Multiple preventative techniques that may contribute to lower CC incidence have been described. We have summarized these in in Table 2. Wixtrom et al used Tegaderm (3 M, Two Harbors, MN) nipple shield to reduce implant contamination from endogenous breast flora.[107] After a 6 month follow-up, three of the 32 patients developed CC despite nipple shielding. Wixtrom et al did not correlate the incidence of CC with the presence of a positive nipple culture. However, of those three, two had undergone multiple revisions for CC. This suggests that one possible cause of CC may be incomplete biofilm removal from previous operations. Breast pocket irrigation with antibiotics and/or antibacterial agents has been practiced and recommended for many years. Due to the implication of polymicrobial infections associated with CC, finding the optimal broad-spectrum irrigation remains unsettled. In 2000, Adams et al conducted a study comparing the most commonly used breast pocket irrigations in vitro.[108] At a lower concentration compared to other solutions tested, betadine, gentamicin,

Table 2. Summary of Preventive Strategies Suggested by Authors for Minimizing Risk of Biofilm

Phase of Procedure	Recommendation
Implant adjuncts	Antibiotic mesh
Aseptic preparation	Nipple shield
	Irrigation of breast pocket with antibiotic solution
Preoperative IV antibiotics	Standard prophylaxis for surgical site infections (cefazolin, ampicillin-sulbactam, clindamycin); no benefit in CC vs placebo in 12 months[112]
Surgical Technique	Avoidance of peri-nipple-areola incision, especially with subglandular implant placement
	Atraumatic technique
	Meticulous hemostasis
	"no touch" technique with Keller Funnel

and cefazolin solution was 100% effective against bacteria. Due to concerns that betadine-caused implant deflation, the US Food and Drug Administration banned immersion of breast implants in betadine solution in 2000. This prompted testing for alternative broad-spectrum solutions. Adams et al reported use of bacitracin, cefazolin, and gentamicin solution.[109] After a mean follow-up of 14 months (range 6 to 75 months), incidence of CC was 4- to 5-fold less for breast augmentation compared to manufacturer pre-market approval data.[109] Breast pocket irrigation alternatives for patients allergic to antibiotics are presented in Table 3.[110]

Prophylactic intravenous (IV) antibiotics have also been studied. Arad et al conducted an animal study using rats and IV vancomycin.[111] This treatment was more efficacious against immature biofilms and soft-tissue infection. It had limited efficacy against mature biofilm. Preoperative antibiotics in prevention of CC have also been evaluated clinically.[112] After a 12-month follow-up, there were no statistical differences between control and antibiotic groups regarding prevalence of CC (47% and 53%, respectively). Presence of biofilm was not assessed. These data suggest that local treatment with antibiotic irrigation is more effective in prevention of bacterial colonization and initial biofilm formation compared to systemic perioperative antibiotics. Additionally, irrigation may decrease selection of antibiotic-resistant bacteria compared to IV prophylaxis.

Jacombs et al used a porcine model to examine the effectiveness of antibiotic impregnated mesh in the prevention of biofilm formation and CC. Researchers implanted a total of 28 prostheses into 5 pigs. All 28 implants and their pockets were inoculated with *S epidermidis* isolated from a human patient with CC. Fourteen implants were inserted with antibiotic mesh (treatment) and the other 14 were untreated (control). All untreated implants developed Baker grade III/IV CC. In contrast, all treated implants were Grade I/II after 16 weeks, ($P < 0.001$).[113] Specimens with CC had at least 10-fold higher bacterial counts. Bacterial colonization of mesh-covered implants was typically single-layered, if present. In contrast, multilayered biofilms were detected by SEM in all untreated implants.[113] This study highlights that prevention of biofilm formation in its early stage using antibiotic coating of implants, rather than treating biofilm related infections, would be more desirable in clinical settings. However, due to the rise of antibiotic resistance, additional approaches are also needed. Alternative antimicrobial or anti-adhesion coating agents currently used for other medical implants should be studied as novel preventative solutions.[114,115]

Table 3. Recommended Alternative Solutions for Breast Irrigation for Substitution of the Bacitracin-Cefazolin-Gentamicin Triple Antibiotic Solution Components

Allergen	Recommended Alternative Irrigation Solution
Cephalosporin or penicillin	Gentamicin (80 mg), providone-iodine solution (250 mL), normal saline (250 mL)
Bacitracin	Cefazolin (1 g), gentamicin (80 mg), providone-iodine solution (50 mL), normal saline (50 mL)
Gentamicin/aminoglycoside	Providone-iodine (250 mL) and normal saline (250 mL)
Iodine	Bacitracin (50,000 units), cefazolin (1 g), gentamicin (80 mg), normal saline (500 mL)

Moyer et al conducted a cadaver study to assess the amount of skin contact and skin and breast parenchyma contamination with standard implantation compared to delivery via the Keller Funnel (Keller Medical Inc., Stuart, FL).[116] The funnel is composed of rip-stop nylon and a hydrophilic inner coating and is designed to facilitate implant placement without skin contact. Bacterial transfer from the breast parenchyma to implant surface with the funnel was 37.5%, while with the standard implantation technique it was 62.5%. Since this was a cadaver study, no long-term data regarding CC could be determined.

Surgical technique may also affect implant contamination with microorganisms.[15] A retrospective study by Wiener demonstrated the effect of the incision on the development of CC in over 400 patients. Patients who had an inframammary incision had a 0.59% incidence of CC compared with 9.5% in patients who had a peri-nipple-areolar incision. Peri-nipple-areola approach transects ducts near the nipple, which harbor the greatest amount of bacteria. These ducts can continue to release bacteria until they have scarred, healed, and sealed. Thus this approach increases the potential for bacterial contamination and biofilm formation. On the other hand, the intramammary incision is in a plane deep to most of the ducts, hence there is less risk of exposure to endogenous bacteria.[117] Pocket location also appears to have an impact on development of CC. Incidence of CC is higher in implants placed in the subglandular vs subpectoral plane.[100,101] This is also likely due to proximity to bacteria harbored by mammary ducts.

Gold standard treatment of CC is total capsulectomy with implant removal and replacement. Using a new implant when treating the CC is imperative, due to possible presence of biofilm and their notorious antibiotic resistance. Change in pocket location could also be considered at the time of revision.[15]

Other non-surgical modalities have been considered for patients with established contracture. These include vitamin E, steroids,[118] nonsteroidal anti-inflammatory drugs (NSAIDs), and leukotriene inhibitors.[15] Findings from studies by Scuderi et al suggest that zafirlukast, a leukotriene receptor antagonist (LTRA), may reduce pain and breast capsule distortion.[119,120] More recently, Mazzocchi et al also studied the effects of zafirlukast on CC. They found a significant reduction in mammary compliance values and severity of CC. However, mammary compliance values gradually increased after drug withdrawal.[121] The efficacy

of anti-inflammatory drugs (such as steroids or leukotriene inhibitors) in treatment of CC supports the hypothesis that inflammatory processes, including biofilm-induced inflammatory processes, are involved in the genesis of CC.

CONCLUSIONS

All medical devices, including breast implants, are susceptible to microbial attachment and formation of biofilms. Development of CC is most likely multifactorial. However, many experimental studies demonstrated a significant link between biofilm infections and increased incidence of CC. In addition, several clinical studies suggest a clinically relevant causal relationship.

Detection of biofilms remains one of the greatest challenges of biofilm infections. New molecular methods should be introduced in the practice. These innovative methods are expected to provide a more sensitive bacterial enumeration and detection that would contribute to more complete picture of microbial biofilm infections encountered in plastic surgery, especially CC.

Biofilm infections are difficult to treat with conventional antibiotics, and this treatment is further hindered due to the increase of antibiotic resistance. Therefore prevention, rather than treatment, of possible biofilm-related CC might be a better strategy. Future implants may be manufactured with antimicrobial or anti-adhesion coating, which could limit risk of CC. At this moment associated risk factors can be minimized through meticulous surgical technique, proper aseptic preparation, and minimal skin contact. Delivery systems such as the Keller funnel hold promise, but studies reporting long-term outcomes and cost effectiveness are lacking. With regards to implant characteristics, there is no clear evidence regarding shell texture or implant type and development of biofilm-related CC.

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