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Pharmacological Approaches for the Prevention of Breast Implant Capsular Contracture

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ABSTRACT
Capsular contracture is a common complication associated with breast implants following reconstructive or aesthetic surgery in which a tight or constricting scar tissue capsule forms around the implant, often distorting the breast shape and resulting in chronic pain. Capsulectomy (involving full removal of the capsule surrounding the implant) and capsulotomy (where the capsule is released and/or partly removed to create more space for the implant) are the most common surgical procedures used to treat capsular contracture. Various structural modifications of the implant device (including use of textured implants, submuscular placement of the implant, and the use of polyurethane-coated implants) and surgical strategies (including pre-operative skin washing and irrigation of the implant pocket with antibiotics) have been and/or are currently used to help reduce the incidence of capsular contracture. In this article, we review the pharmacological approaches—both commonly practiced in the clinic and experimental—reported in the scientific and clinical literature aimed at either preventing or treating capsular contracture, including (i) pre- and post-operative intravenous administration of drug substances, (ii) systemic (usually oral) administration of drugs before and after surgery, (iii) modification of the implant surface with grafted drug substances, (iv) irrigation of the implant or peri-implant tissue with drugs prior to implantation, and (v) incorporation of drugs into the implant shell or filler prior to surgery followed by drug release in situ after implantation.

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Introduction
Since the development and introduction of modern prosthetic breast implants in the 1960s, millions of women have undergone breast implant surgery to either adjust or enhance the breast shape and appearance (cosmetic surgery) or to restore function and normal appearance to the breasts following prophylactic or curative mastectomy due to risk or diagnosis of breast cancer (reconstructive surgery). The rising global incidence of breast cancer,13 continued interest in breast...
augmentation procedures, and various advancements in implant technologies will likely drive increased future demand for breast implants. According to a global survey conducted by the International Society of Aesthetic Plastic Surgery, ~1.8 million surgical procedures for breast augmentation (16% of all procedures conducted by plastic surgeons) were performed globally in 2019, a decrease of 3.6% over the previous year but a 21% increase over 2015. In the United States, the biggest market for breast implants, ~300,000 women underwent breast augmentation cosmetic surgery in 2019, an increase of ~45% compared to the number of procedures at the beginning of the millennium, while ~136,000 women underwent breast reconstruction surgery, representing an increase of ~75% since 2000.

As with all foreign devices implanted in the body, breast implants induce an immune response that can lead to rejection of the device. Over a typical 15-year period, ~50% women who undergo breast augmentation or reconstruction surgery will experience complications or implant failure, including asymmetric appearance of the implant, pain, and capsular contracture (CC), with ~10% of these complications occurring within two to 4 years following surgery. CC is defined as the formation of scar tissue—known as a fibrous capsule—around the breast implant during a heightened inflammatory response following surgery and is the second most common reason for follow-on operations. Although a detailed understanding of the causes leading to CC is still lacking, bacterial infection and development of microbial biofilms on the surface of implants are thought to be involved. Upon implantation of any medical device into the body, a “race for the surface” occurs in which host cells (including macrophages, fibroblasts and platelets) compete with bacteria for real estate on the implant surface. In addition to the host inflammatory response directed toward the implant, the gradual colonization of its surface by bacterial biofilms occurs over time, often leading to problems.

Various structural modifications of the implant device (including use of textured and polyurethane-coated implants) and surgical strategies (such as pre-operative skin washing, irrigation of the implant pocket with antibiotics, and submuscular placement of the implant) have been or are currently used as part of efforts to help reduce the incidence of CC. In this article, our primary goal is to describe the myriad of pharmacological (drug-based) strategies—including existing strategies used before, during or following surgery, and newer experimental strategies reported in the medical and scientific literature—for preventing or reducing the incidence of CC. However, to better place this topic in its wider context, we also provide summary descriptions of related background topics. Specifically, we provide: (i) an overview of breast implants and their manufacture (Breast implants and their manufacture), (ii) an overview of CC (Capsular contracture), (iii) a review of nonpharmacological strategies to prevent CC (Non-pharmacological strategies to prevent capsular contracture), and an extensive review of pharmacological strategies—both commonly practiced in the clinic and experimental—reported in the scientific and clinical literature aimed at either preventing or treating CC (Pharmacological approaches to reducing capsular contracture), including a review of the different types of drugs (Types of drugs); pre- and post-operative intravenous administration of drug substances (Pre-operative intravenous administration of antibiotics and Post-operative administration of antibiotics); systemic (oral) administration of drugs before and after surgery (Oral drug administration); modification of the implant surface with grafted drug substances (Modification of implant surface with grafted drug substances); irrigation of the implant or peri-implant tissue with drugs prior to implantation (Irrigation of implant/peri-implant tissue prior to implantation); incorporation of drugs into the implant shell or filler prior to surgery followed by drug release in situ release after implantation (Incorporation of drugs into the implant shell and Incorporation of drugs into the filler).

**Breast Implants and their Manufacture**

The first reported breast augmentation surgery was performed in Germany in 1895 by renowned surgeon Vincenz Czerny. He replaced the tumor found in the left breast of a 41-year-old woman with an apple-sized tumor found in her back. Although using one tumor to replace another does not make sense from the perspective of current knowledge, it was then pioneering to use a graft of autologous tissue. At the time, surgeons were using a diverse range of common materials to replace breast tissue, including paraffin, ivory, wool, sponges, ox cartilage, glycerin and even snake venom. However, use of these materials often led to infection, severe scarring, skin necrosis, pulmonary embolisms, and ultimately death.

Silicones (also known as polysiloxanes, which are synthetic polymers with a silicon-oxygen backbone) were developed in the 1930s and first considered for plastic surgery applications in the late 1940s. Although initially used as wound dressings due to their water-repellent characteristics, they quickly became the biomaterial of choice for intravascular tubing, catheters, pacemakers and artificial heart valves. In the early 1960s, Cronin and Gerow described the first breast implants comprising silicone elastomer (also referred to as silicone rubber) shells and silicone gel fillers. During the mid-to-late 1960s, drug delivery scientists were also beginning to exploit silicone elastomer materials for controlled release drug delivery applications, leading to the marketing of the drug-releasing contraceptive subdermal implant (Norplant) and development of various steroid-releasing contraceptive vaginal rings.

Many different types of breast implants have been and are currently used, having different designs, surface textures (smooth, microtextured, macrotextured), shapes (round, teardrop) and filler materials. However, common to all modern implants is a multi-layered silicone elastomer shell filled with either a saline solution or a silicone gel. Silicone gel implants are currently the preferred option (used in 85% of surgeries in 2019), since they are reported to look more natural and are less likely to wrinkle than the saline implants. However, when early-generation silicone-filled implants ruptured, the filler leaked from the implant and spread, creating lumps in the surrounding tissues. By comparison, with saline-filled implants, any saline leaked from the implant is safely absorbed by the body. However, fewer problems have been reported with later generation so-called ‘gummy bear’ breast implants in which the silicone gel filler is chemically...
crosslinked such that it is more cohesive and less likely to leak when the shell ruptures.\textsuperscript{20}

Breast implants having textured surfaces were introduced in the 1980s as part of efforts to reduce the formation of scar tissue around the implants and the onset of serious CC.\textsuperscript{31} The pore size at the surface is known to influence tissue adherence to the implant, which in turn impacts its stability.\textsuperscript{52} Despite macrotextured implants having been shown to reduce formation of fibrous capsules around the implants and decrease the incidence of implant rejection,\textsuperscript{32,33} they also increase the risk of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL; a very rare type of blood cancer) compared to smooth and microtextured implants, causing withdrawal and recall of some macrotextured devices from certain markets. A thorough understanding of the mechanistic aspects around onset of BIA-ALCL has yet to be elucidated.\textsuperscript{34,35}

Surgeons choose to place breast implants either in a sub-glandular position (under the breast glands) or in a subpectoral position (under the pectoral muscle). As with implant texture and shape, the position of implant placement also impacts on the incidence and formation of a fibrous capsule; subpectoral placement may increase the implant encapsulation incidence by as much as 50\% compared to submuscular placement.\textsuperscript{36-38} In recent years, off-label use of acellular dermal matrices—surgical meshes derived from human or animal skin in which the cells are removed and the supportive reinforcing scaffold is left in place—has significantly increased for implant-based breast reconstruction. Where the implant is wrapped with an acellular dermal matrix, pre-pectoral reconstruction is preferred, since the pectoralis muscle is maintained in its natural position, leading to less surgical pain and avoidance of animation deformity (also known as dynamic breast deformity).

**Composition**

Generally, modern breast implants contain two main constituent parts—a multi-layer silicone elastomer shell and a filler material. Additionally, silicone-filled breast implants have a small—usually circular—silicone elastomer seal at the back of the implant through which the cohesive silicone (polydimethylsiloxane) filler is injected; the implant shell is then pre-filled during the manufacturing process. With saline-filled implants, the sterile saline (0.15 M; pH 7.2-7.4) is only injected into the shell after surgical placement of the implant in the breast pocket, via one or more ports/valves located on either the top or bottom of the shell. Globally, most implants contain silicone gel as the filler material, although saline solutions are also still widely used.\textsuperscript{39} Some multi-lumen implants contain both a silicone gel and saline filler.

**Manufacture of breast implants**

Breast implant manufacture involves three basic steps: (i) fabrication of the multi-layered silicone elastomer shell, (ii) sealing of the implant shell, and (iii) filling of the implant shell. Each step is briefly discussed here. An understanding of these manufacturing steps is particularly useful when considering options for incorporating drug substances directly into implants for sustained/controlled drug release following implantation, as a mean of preventing/reducing infection and CC.

**Fabrication of the implant shell**

Modern multi-layered breast implant shells are made exclusively from silicone elastomer formulations commonly referred to as ‘silicone dispersions’, since the components of the silicone elastomer formulation are suspended or dissolved in a solvent carrier. The components comprise (i) various vinyl and hydride-functionalized polysiloxanes for gel-filled implants or acyloxy-functionalized polysiloxane molecules for saline-filled devices, (ii) a silica-based reinforcing filler, and (iii) an organometallic catalyst based on platinum to initiate the curing reaction; these components are dispersed in a volatile organic solvent.

Each elastomeric layer of the implant device is produced by a chemical crosslinking reaction, either a platinum-catalyzed addition-cure reaction between the vinyl and hydride-functionalized polysiloxane molecules (referred to as ‘hydro-silylation’ reaction) or a moisture-initiated hydrolysis and condensation reaction. For gel-filled implants, the polysiloxane molecules comprise mostly dimethylsiloxane \([-\text{Si(Me}_2\text{)}-O-\text{]}\) units (Me = methyl group; typically 85\%-95\% mole percent) and a smaller fraction of diphenylsiloxane \([-\text{Si(Ph}_2\text{)}-O-\text{]}\) units (Ph = phenyl group; typically 5\%-15\% mole percent). Elastomeric layers containing higher concentrations of diphenylsiloxane units provide greater barrier properties than elastomers fabricated solely from dimethylsiloxane units, thereby reducing silicone gel bleed through the intact shell.\textsuperscript{20}

A reinforcing filler material—in the form of an amorphous silicon dioxide with particle size in the low nanometre range (also known as silica aerogel, fumed silica or precipitated silica)—is added to the elastomer (typically 21\%-27\% w/w) to improve its strength, as is common with all silicone elastomers. There can be some confusion with different uses of the term ‘filler’ here: the silica-based reinforcing filler used for fabrication of the elastomeric shell layers is quite distinct from the lightly crosslinked silicone gel or saline filler that is used to fill the implants; the two should not be confused.

Unlike most other silicone elastomer medical and drug delivery devices—which are commonly manufactured from nonsolvent-based high temperature vulcanized, room temperature vulcanized or liquid silicone rubbers (rather than solvent-based silicone dispersions) via automated or semi-automated extrusion or injection molding techniques—the shells of silicone breast implants are often prepared manually by trained operators using a dip-coating process (Fig. 1). The fabrication process differs depending upon the final surface texture required, but generally involves the following steps: (i) dipping of a plastic or coated metal breast-shaped mold (also known as a ‘mandrel’) into a de-aired low viscosity silicone elastomer dispersion formulation; this formulation most commonly comprises a two-part silicone dispersion formulation suspended or dissolved in a relatively volatile organic solvent (such as xylene), (ii) placement of the silicone-coated mandrel into a chamber for controlled evaporation of the organic solvent; (iii) multiple repetitions of the dipping and devolatilization steps to add further layers to the silicone shell, and (iv) curing of the elastomer at elevated
temperatures in the case of hydrosilylation crosslinked elastomers, or in controlled humidity chambers for hydrolysis and condensation crosslinked elastomers. Finished implant shells typically contain up to eight layers, each layer having a thickness of between 50 and 150 µm, and with a final shell thickness in the range 0.3-1.0 mm. Additional steps may also be included as part of the fabrication process. For example, to produce silicone elastomer shells having a textured surface, the mandrel can be dipped into salt or sugar granules (of well-defined particle size) immediately or shortly after applying the final layer of silicone. After curing, the salt/sugar particles are then either removed by washing with water leaving behind a surface pitted with indentations, or brushed from the shell surface to produce an ‘intermediate texture’ surface. Alternative techniques not involving a salt-loss process can also be used to generate surfaces of varying textures. Also, for implant shells destined to be filled with a silicone gel, at least one of the layers is commonly fabricated from a more highly phenyl-substituted silicone elastomer, which acts as an effective barrier to permeation of the gel components through the shell. Further details of the various fabrication techniques are described in the excellent 2011 review article by Barr et al.

Sealing of the implant shell
Once the silicone elastomer shell is fully fabricated, it is removed from the mandrel and inspected for quality, including for visual appearance, leak testing, and shell thickness. The large hole in the shell introduced to allow removal from the mandrel (Fig. 1) is then sealed with a pre-prepared silicone elastomer patch and a small channel or port created to permit filling of the shell, which is later sealed often using a condensation cure elastomer.

Filling of the implant shell
The process of filling the shell varies depending upon the type of filler. Single-lumen implants are most common and are filled with either silicone gel or saline. Saline-filled implants are inserted empty into the breast pocket during surgery and then filled with sterile salt water once they are in place. By comparison, silicone gel implants are pre-filled with a lightly crosslinked silicone elastomer gel that is usually dispersed/swollen in a silicone oil. Once filled to the correct weight, the fill channel is then sealed, and the fully constructed implant
placed in an oven for several hours for a final cure process. Of course, the exact details of the fabrication method can vary significantly between manufacturers. Double-lumen implants—which are now exceptionally rare—have two shells, either connected or patched together, or floating freely one in the other. Double-lumen implants may have a silicone-filled core enclosed in saline filler to reduce the movement of the silicone from the inner layer and that can also act as a drug delivery device. Saline-filled cores in silicone lumens can also be found but are more rare.\textsuperscript{41,43,48} Less than 1 % of breast implants are of the triple-lumen variety, and are mainly used in reconstructive surgeries rather than cosmetic ones. These implants have a slightly overfilled silicone inner lumen, a slightly underfilled silicone middle lumen, and a saline outer lumen.\textsuperscript{49}

From a drug delivery perspective, there is potential to include dispersed or dissolved drug substances in the filler material prior to filling the shell with a view to releasing the drug slowly from the breast implant following implantation. According to well understood drug permeation mechanisms, drug release from such an implant can be considered as three discrete steps: (i) drug molecules diffuse to and partition into the hydrophobic silicone elastomer shell, (ii) the drug molecules would then transfer through the shell layers by molecular diffusion, and (iii) arriving at the implant surface, the dissolved drug molecules would then partition into and diffuse throughout the surrounding tissue. This entire process is driven by the drug concentration gradient established between the filler and the tissue, in accordance with Fick’s laws of diffusion.\textsuperscript{50} Although hydrophilic drugs would have relatively good solubility in saline solutions, they would have relatively poor solubility in the highly hydrophobic silicone elastomer shells, such that the rate of drug permeation through the shell would likely be limited. Silicone-type fillers would lend themselves better to incorporation of hydrophobic drug substances. Either way, a major challenge with this strategy of incorporating drug(s) in the filler is the relatively large drug amounts required to obtain drug concentrations in the filler sufficient to drive the permeation process across the shell, since, according to Fick’s first law of diffusion, the rate of permeation (or flux) of drug across a membrane is proportional to its concentration gradient across the membrane. With breast implants having fill volumes in the range 100-800 mL, multi-gram quantities of drugs per implant might be necessary.

**Silicone elastomer dispersions**

Different types of silicone elastomer dispersions are available for fabrication of the shells of silicone breast implants. These low viscosity dispersions are complex formulations. Consisting primarily of a mixture of various types and molecular weights of silicone polymers (also known as polysiloxanes; including dimethyl, dimethyl diphenyl copolymer, fluoro homopolymer or copolymer), reinforcing fillers, catalysts and solvents, they are specially formulated for ease and practicality of the dip-coating process (Fig. 1). The polysiloxane components of the dispersion formulations are usually based on so-called ‘two-part addition cure’ systems, whereby vinyl-substituted polysiloxanes in one part of the silicone elastomer system (Part A) react via a platinum-catalyzed hydrosilylation reaction with hydride-substituted polysiloxanes in the second part (Part B) (Fig. 2). These addition cure systems do not produce any by-products during their curing reaction. By judicious selection of the formulation components, the final dispersions can vary considerably in (i) viscosity (typically 60—3000 cP), (ii) solids-to-solvent ratio (20%-40% solid content is typical), (iii) solvent type (e.g., xylene, acetone, hexane), and (iv) post-cure mechanical properties (durometer hardness value typically ranges from ~25 Type 00 through to ~40 Type A).

**Capsular Contracture**

As with any implanted foreign body, breast implants induce a fibrous reaction in the surrounding tissue (Figs. 3 and 4). This fibrous capsule may contract with time, distorting the appearance of the implanted breast and causing pain. While inflammatory responses are common with all implanted devices, the term ‘capsular contracture’ is reserved to describe contracture phenomena associated with breast implants. Of course, complications caused by fibrous tissue growth are not unique to breast implants, and efforts have focused on addressing similar complication associated with other types of implantable medical devices.\textsuperscript{51}

Assessment of the extent of CC by surgeons is most commonly performed using the Baker classification system (BCS), which rates the firmness, thickness and visual impact of the newly formed capsule according to a four-point scale. A grade I breast looks and feels natural, while grade II breasts show minimal contracture and no clinical symptoms. Grades III and IV are clinically significant and symptomatic; grade III is associated with moderate contracture and some firmness is felt by the patient; with grade IV, severe contracture is observed and obvious symptoms experienced by the patient.\textsuperscript{52} Around 10% of cases classified as grade III and IV are identified as being due to CC, leading to further surgery for ~300,000 women every year and making CC the second highest reason for follow-on operations.\textsuperscript{14,16,17} However, identification and classification of CC using the Baker system is highly subjective, variable and unreliable, since it is dependent on the examiner.\textsuperscript{53} Use of durometers and other techniques (such as ultrasound elastography) can provide more objective and quantitative measurements of CC.\textsuperscript{54,55}

**The foreign body reaction**

Biomaterials used to fabricate implantable medical devices are intended to exist in contact with tissues of the human body without eliciting harm. Traditionally, the term ‘biocompatible’ refers to the material being nonirritant, nontoxic, nonthrombogenic, noncarcinogenic, etc.;\textsuperscript{56,57} essentially, the material was required to be ‘bio-inert’. However, more recent thinking around biomaterial performance places greater emphasis on bio-integration, tissue regeneration, or the desired modulation of biological processes. This introduces the concept of a dynamic host-material interaction within the microenvironment of the implant. Therefore, an ideal biomaterial would be able to reproduce the functionality of the natural extracellular matrix, providing an environment for the desired adhesion of an appropriate cell type and for the desired cellular function.\textsuperscript{56,57} A new
Fig. 2 — (A) Typical compositions of the Part A and B components of an addition-cure silicone elastomer dispersion formulation used to prepare the shell layers of a breast implant. Following mixing of the Parts A and B (B), the hydride and vinyl components of the silicone system cure via a platinum-catalyzed hydrosilylation reaction (C).

Fig. 3 — Representation of the initiation of the foreign body reaction and creation of a fibrous capsule around a breast implant after implantation. During the first step of the foreign body reaction, neutrophils are attracted to the surface of the implant and proteins are adsorbed onto its surface (A). This protein layer will then attract macrophages and monocytes which will start depositing a matrix layer around the implant (B) before merging into foreign body giant cells and attracting fibroblasts which will produce collagen I and III to encapsulate the implant (C).
The definition of biocompatibility—“the ability of a material to locally trigger and guide nonfibrotic wound healing, reconstruction and tissue integration”—has been proposed, whereas previous thinking on biocompatibility would be best considered as “biotolerability”, defined as “the ability of a material to reside in the body for long periods of time with only low degrees of inflammatory reaction”.

A major factor in determining the biocompatibility (or biotolerability) of an implanted biomaterial is its propensity to evoke an immunological and inflammatory reaction, commonly referred to as the foreign body response (FBR). The FBR describes the dynamic cascade of molecular and cellular events occurring after material implantation (Fig. 3). Inflammatory cells, such as macrophages, migrate to the peri-implant area, adhere to the biomaterial surface, and fuse to form foreign body giant cells (FBGCs). It is the presence of these large, multinucleated FBGCs that is the hallmark of the FBR. FBGCs express an armoury of potent enzymes and reactive oxygen species (ROS) that are released at the biomaterial/tissue interface during a process described as ‘frustrated phagocytosis’, and can result in considerable damage to both the structural and functional integrity of the implant.

Chemokines such as interleukin-1 (IL-1) are also expressed, attracting fibroblasts to the implant site and culminating in the laying down of a fibrous avascular capsule surrounding the implant and isolating it from neighboring tissues. While the pathogenesis remains unclear, CC of breast implants is thought to be the result of an excessive foreign body response toward the implant. While this fibrotic reaction does serve some purpose in keeping the implant in the correct anatomical position, excessive reaction can lead to pain and deformity of the breast. Histological examination of capsule composition suggests that the number of fibroblasts found at the implant-tissue interface correlates positively with the severity of capsule contracture. These fibroblasts produce the collagen that forms the capsule, while activated contractile fibroblasts, known as myofibroblasts, provide a contractile force whilst the collagen matrix remodels and stabilizes. Interestingly, myofibroblasts have been found to express estrogen receptors, with contractile forces increasing in response to circulating 17-β-estradiol concentrations.

Incidence of bacteria and biofilms

Following implantation of a breast implant, a “race for the surface” occurs in which host cells (including macrophages,
fibroblasts and platelets) compete with bacteria for real estate on the implant surface. In addition to the host inflammatory response toward foreign implanted materials, the colonization of the implant surface by bacterial biofilms is often problematic; bacterial biofilms serve as a reservoir of bacteria and are the source of chronic and/or sub-clinical infections. A possible etiological link between biofilm and CC has also been postulated.

Upon approaching the implant, bacteria experience Van der Waals, electrostatic and hydrophobic interactions with its surface, leading to initial adherence. This is followed by more permanent site-specific interactions when pili and fimbriae present on the bacterial cell begin to form attachments with the underlying biomaterial surface or its conditioning film. At this stage, the bacteria have transformed from their planktonic state to a sessile state. Biofilm formation proceeds with rapid proliferation, production of extracellular polymeric substances (EPS), and a shift in phenotype that contributes to the resilient nature of the biofilm mode of growth. Bacteria within the biofilm can communicate via a process known as quorum sensing, releasing signaling molecules to coordinate gene expression. It is also possible for biofilm bacteria to detach and revert back to their planktonic state, dispersing to colonize a new substratum. With breast implants, this could be another location on the implant surface or other tissues and regions of the body.

Many bacterial species produce binding proteins that are specific to collagen and fibronectin that form the fibrous capsule laid down around the breast implant. This may facilitate bacterial attachment and adherence to the capsule, followed by proliferation to form biofilms. Indeed, increased numbers of fibroblasts correlate with incidence of CC. Likewise, increased numbers of bacteria have been detected on contracted capsules compared to non-contracted capsules. A porcine model, devised by Tamboto et al., has highlighted that biofilm formation on and around breast implants is associated with a fourfold increased risk of developing CC.

The most common bacterial species detected on contracted breast implants are Staphylococcus spp., especially Staphylococcus epidermidis. These species are normal commensurate flora of the skin, suggesting contamination of the implant or the implant site during surgery (Fig. 4). Surgeons may use a “no-touch” aseptic technique to mitigate this potential source of bacterial infection. However, there is evidence to suggest that late CC (occurring months to years after surgery) may result from remote infection occurring in a distant region of the body with transient bacteraemia allowing bacteria and CC, bacteria have also been isolated on clinically benign, uncomplicated implants. This leads to the question of what mechanism triggers the conversion from a benign to a pathogenic state. It is possible that the degree of bacterial bioburden at the implant site may be a factor.

Studies that have investigated the presence of bacteria in CC have consistently detected more bacteria on pathogenic implants than benign.

Non-pharmacological strategies to prevent capsular contracture

As previously discussed, the fibrotic response around implanted biomaterials—referred to as CC in the case of breast implants—is one of the most widely reported causes of follow-on operation after a breast augmentation or reconstruction. Despite attempts by researchers to understand the mechanisms underlying CC, it is still not fully understood why inflammatory responses are sometimes so high despite the hydrophobicity of the implant surface, although the presence of biofilm is suspected. Also, inflammatory responses are known to be greater on hydrophobic surfaces due to the strong denaturing effect the surface exerts on adsorbed proteins; this occurs via hydrophobic interaction and is irreversible.

Various promising strategies to modify breast implants have been reported, including physical modification, chemical modification or incorporation and release of pharmacological agents. In this section, and to provide context for the forthcoming section reviewing the pharmacological strategies, we briefly review the various non-pharmacological strategies that have previously been used, are currently used in the clinic, or newer experimental methods reported in the literature.

Physical modifications to the breast implant

Polyurethane foam coatings

Historically, the surface characteristics of breast implants have been modified as part of efforts to disrupt the formation of scarring tissue around the devices. The first modified breast implants were coated with a polyurethane foam. Although this strategy resulted in fewer cases of CC, the coated implants were quickly removed from the US market when it was demonstrated that physical and chemical degradation of the polyurethane foam occurred under physiologic conditions to produce both foam fragments in women and 2,4-toluenediamine—a probable genotoxic carcinogen—in mice. However, this molecule was never demonstrated to be carcinogenic in humans. Currently, a new generation of polyurethane-covered breast implants is approved for use in many countries. Studies are underway to assess their effectiveness in preventing CC relative to other textured implants.

Breast implants with textured surfaces

In the 1980s, manufacturers and researchers focused on implants with textured surfaces, produced by various methods: (i) dipping the silicone-coated mandrel into a powdered salt or sugar material and then removing the salt/sugar particles after cure (the ‘salt-loss’ technique) by dissolution in water, (ii) brushing salt onto the pre-cured silicone surface with subsequent washing to remove the particles after cure, and (iii) negative-contact imprinting with a polyurethane foam. Shells were initially produced with various pore sizes,
and pore size was deemed critical for good tissue adherence to the implant. However, there was no evidence of correlation between pore size and incidence of CC. Later, it was observed that macrotextured implants could decrease the risk of formation of the fibrous capsule around the implant, and, in turn, reduce the incidence of CC. However, macrotextured implants are no longer widely marketed following studies showing that they increase the risk of BIA-ALCL compared to smooth and microtextured implants; the mechanism behind this reaction is not yet known.

Biological matrices
Various surgical scaffold materials—including synthetic materials (adsorbable polymeric meshes) and acellular dermal matrices (ADMs; biological meshes)—are now routinely used in breast reconstruction/augmentation to help provide tissue support. While these meshes are not direct adoptions of the breast implants themselves, their placement around the implant is intended to increase biocompatibility, encourage rapid host revascularisation and cell repopulation, and limit the extent of interactions between the silicone and the host tissues, thereby facilitating improved surgical outcomes.

In some cases, surgeons use autologous fat as filler for the breast. Two different techniques are commonly used: lipofilling, involving taking fat from one part of the body and injecting it into the implantation site; and fat grafts placed around a half-sized implant during the initial surgery. Outcomes appear to be favourable with both strategies. Indeed, when such techniques were previously used, no major complications were observed, and only grade I CC could be found after a follow-up period of 17 mo. Other investigators have studied the influence of decellularized porcine matrices placed around the implants to reduce the incidence of CC. After 1 y, the results were promising, showing a decrease in incidence of Class III and IV CC.

Although these techniques appear promising, long-term studies are required to determine whether the addition of matrices around the implants prevents CC or simply delays its occurrence.

Synthetic meshes
As with biological meshes, polymeric adsorbable synthetic meshes—such as those constructed from Vicryl (a lactide/glycolide copolymer) and TIGR matrix surgical mesh (comprising two polymeric fibers, one produced from a copolymer of glycolide lactide and trimethylene carbonate, and the second from a copolymer of lactide and trimethylene carbonate)—are intended to degrade slowly by bulk hydrolysis following implantation. Nonabsorbable meshes are also used, such as the titanium-coated polypropylene mesh (TiLOOP). These meshes may be associated with lower rates of infection, skin necrosis and explantation.

In an effort to add a pharmacological function to synthetic meshes, Huh et al. described the wrapping of silicone breast implants in drug-loaded polyurethane nets to provide sustained release of the glucocorticoid triamcinolone to prevent fibrosis. The highly elastic drug-loaded mesh was prepared via electrospinning. Sustained release of triamcinolone occurred over 4 wk and exhibited a significant anti-fibrotic effect when implanted in rats.

Other meshes have been prepared from spider silk in a bid to increase the biocompatibility of implants, and have been reported to significantly reduce the agglutination of collagen and the formation of capsules around breast implants by acting like a shield around the implants preventing the adsorption of unspecific proteins. Zeplin et al. reported that breast implants homogeneously coated with a micrometer thin layer of eADF4(C16)—a recombinant spider silk protein of the European garden spider Araneus diadematus—inhibited fibroblast proliferation, collagen I synthesis, and significantly reduced both post-operative inflammation and capsule thickness.

However, in the context of CC, the biocompatibility of the implant is not the only issue that needs to be addressed; the presence of bacteria on the implant also undoubtedly induces strong inflammatory responses. Use of polypropylene meshes impregnated with the antibiotics minocycline and rifampicin drastically reduced in vivo the appearance of grade III and IV CC, even when S. epidermidis was inoculated next to the implants.

Thus, the addition of meshes and matrices around the breast implants is now a routine strategy approach to reduce the incidence of CC, although it does require an additional component to be fitted to the implant before or during surgery.

Zwitterionic polymers
Zwitterionic polymers are molecules possessing an equal number of cationic and anionic moieties while maintaining a global neutral charge. Their potential as biomaterials with promising biocompatibility has been realized within the last decade, as studies have highlighted their ability to modulate the FBR. The superior hydrophilicity of these polymers means they are able to resist fouling and the adsorption of proteins and inflammatory cells. Zwiterionic hydrogels have been shown to prevent the FBR and fibrous capsule formation for at least 3 mo in mice.

The conjugation of phosphoserine, an immune-signalling molecule, to uricase has been shown to actively modulate and reduce any unwanted immune response; these results could also be applied to trimethylamine N-oxide derived zwiterionic polymers and poly(carboxybetaine methacrylate) which also promoted angiogenesis in surrounding tissues. Consequently, the addition of such hydrogels to the implants could possibly lead to a reduced FBR and incidence of CC.

Surgical techniques and practices
It is now accepted by most plastic surgeons that subpectoral placement of breast implants leads to a reduced incidence of CC compared with subglandular placement (grade III/IV CC occurred in 2.8% and 8.6% of implantation cases, respectively). However, manipulation of the implants and the surgical procedures employed may also lead to variations in the incidence of CC. Indeed, the use of the areolar rather than the inframmary route is associated with a fivefold increase in grade III and IV of CC. Bacterial parenchyma contamination of the implants—principally with S. epidermidis, coagulase-negative staphylococci and Propionibacterium acnes—shows the importance of limiting the contact between
the implant and the skin of the patient. To this end, new “no touch” techniques have been widely introduced combining best clinical practice and use of insertion funnels (e.g., Keller funnels) to minimize bacterial contact once the implant is removed from the sterile packaging.64,75,80,107

**Pharmacological Approaches to Reducing Capsular Contracture**

The ‘exogenous hypothesis’ postulates that CC is caused by bacterial contamination during surgery, and therefore seeks to reduce incidence of CC by promoting surgical practice methods aimed at minimising bacterial contamination around the implant.108-110

With physical modifications to breast implants offering few practical and reliable advantages, attention is now turning to pharmacological approaches (where drugs are administered either directly to the implant site during surgery or incorporated and released from the implant itself; Fig. 5) and other surgical techniques. Results of a 2016 online survey studying attitudes and practices in breast augmentation among members of the American Society of Plastic Surgeons indicated that 3.5% of the 1067 surgeons who responded always used pharmacological agents for CC, 35.6% upon first onset, and 8.4% as a first option in treating established CC; 52.3% of surgeons never used pharmacological agents.111 This divergence of practice is clearly due to differences in opinion as to the efficacy of pharmacological strategies—only 9.3% opined that pharmacological approaches were always effective, 14.3% if started early, 47.5% were unsure, and 29.1% considered such approaches to be ineffective. When asked to identify specific non-surgical methods effective for treating capsular contracture, only three of the nine responses reported were pharmacological strategies—leukotriene inhibitors (39%), papaverine (1.5%) and Cox-2 inhibitors (6.1%); the largest response was for massage (54.9%).

Here, we briefly outline the different classes and types of drugs that are either commonly used or have been investigated for potential use in preventing or treating CC, before then reviewing the evidence reported in the scientific literature for the different methods of drug administration, including intravenous prophylaxis, oral administration, modification of implant surface with grafted drug substances, irrigation of implant/peri-implant tissue prior to implantation, and incorporation of drugs into either the implant shell of the filler.

**Types of drugs**

Various types of drug molecules—administered at different times before, during or after implantation surgery (Fig. 5)—have potential application in reducing the incidence of CC and other post-surgery complications. Given the non-infectious and infectious mechanisms commonly proposed to account for CC,112 it is not surprising that pharmacological approaches have focused on targeting anti-inflammatory, anti-fibrotic and antibacterial mechanisms. Many of the reported drugs exhibit a combination of activities.

**Anti-inflammatory/immune modulating drugs**

Although a detailed understanding of the pathogenesis of CC remains elusive, it is widely considered to be a multifactorial process involving an initial inflammatory response followed by a fibrotic reaction in the tissue surrounding the implant.64,105 Therefore, a rational strategy to reduce the incidence of CC is to target the inflammatory response using anti-inflammatory drugs. Various classes of anti-inflammatory drugs are used clinically, including glucocorticoids, antihistamines, amino-salicylates, disease-modifying anti-rheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), and leukotriene receptor agonists (LTRAs).

Glucocorticoids, a sub-type of corticosteroids, bind to the glucocorticoid receptors present in the immune cells commonly associated with the foreign body response, including macrophages, neutrophils, and lymphocytes. As such, they decrease the production of both pro-inflammatory cytokines and collagen, and boost the production of anti-inflammatory cytokines.113,114 Dexamethasone, a common potent glucocorticoid drug, has previously been reported to significantly reduce fibrous tissue growth when incorporated into the silicone elastomer of the electrode arrays of a cochlear implant.51 The drug has also been administered intravenously during breast implant surgery to reduce scar formation.115 More recently, perioperative administration of dexamethasone—either via single intravenous injection only or single intravenous injection plus 10-d intraperitoneal administration post-surgery—in mice implanted with silicone implants demonstrated the role of toll-like receptor (TLR) activation on CC and indicates that dexamethasone may be useful in preventing or minimising CC.116 Another glucocorticoid, triamcinolone acetonide, has been incorporated into an elastic drug delivery nanofiber net.97

The LTRAs zafirlukast and montelukast (Table) have been used to treat asthma since the 1990s.149 Their mechanism of action involves inhibition of cysteinyl leukotrienes—potent inflammatory mediators derived from arachidonic acid and synthesized by a variety of cells, including mast cells, eosinophils, basophils, and macrophages150—and inhibition of the contractile activity of smooth muscle. Studies have also investigated LTRAs as a treatment strategy for CC where the effect is likely mediated through the suppression myofibroblast contraction.141-146 Significantly increased levels of leukotriene receptor activity have been seen in patients with severe CC compared with controls where no capsule was present.147 These findings support the role for LTRAs in the treatment and prevention of CC. It should be noted that zafirlukast antagonises the effects of three different leukotrienes (C4, D4, and E4), whereas montelukast inhibits only D4. It is yet unclear if C4 and D4 are important mediators in the pathogenesis of CC, and therefore more research is required to characterize any differences in potency between these two LTRAs.147

NSAIDs are among the most frequently prescribed drugs in modern medicine. Their primary effect is to inhibit the enzyme cyclooxygenase (COX), of which there exists two isozymes, COX-1 and COX-2. Both isozymes are membrane bound proteins that act in the biotransformation of arachidonic acid to prostaglandins, lipid compounds that are
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<td>Histamine H&lt;sub&gt;2&lt;/sub&gt; receptor antagonist</td>
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involved in many inflammatory processes. The NSAID drug diclofenac, a COX-2 inhibitor, has been demonstrated to reduce the severity of CC in 86% of patients presenting with grade II to grade IV CC. However, this was a small study involving only 19 women.

Anti-fibrotic drugs

Fibrosis is a major cause of CC; an abundance of fibroblasts is positively correlated with the severity of CC. Therefore, an obvious pharmacological approach is to administer anti-fibrotic drugs that target transforming growth factor (TGF)-β, tyrosine kinases, and peroxisome proliferator-activated receptors (PPARs). TGF-β plays a major role in activating fibroblasts; tyrosine kinases are a group of “molecular switches” that can trigger or suppress biological responses; and PPARs are a family of receptors that act directly on DNA to suppress the gene encoding molecules that promote fibrosis. Some anti-fibrotic therapies target immune system molecules, such as interleukin-6 (IL-6) and interleukin-1 (IL-1) as well as immune system cells such as B and T-cells. Anti-fibrotic drugs that have previously been considered for prevention/treatment of CC include pirfenidone and halofuginone.

Pirfenidone (Table), a drug used for the treatment of idiopathic pulmonary fibrosis, has well-established anti-inflammatory and antifibrotic properties, although the exact mechanism of action remains unknown. It has been shown to reduce production of inflammatory mediators in both cultured cells and isolated human peripheral blood mononuclear cells. Oral administration of pirfenidone for 8 wk in rats following submammary implantation with silicone gel implants significantly reduced capsule thickness, proliferation of fibroblasts, and recruitment of inflammatory cells, and may therefore be useful in in human mammary implantation surgery.

Halofuginone is traditionally an antiprotozoal agent used for treatment and prevention of coccidiosis in veterinary medicine. It is known to exhibit antifibrotic activity via inhibitor of collagen type I synthesis. It also inhibits the development of T helper 17 cells, immune cells that play an important role in autoimmune disease, but does not affect the other types of T cells involved in normal immune function. When chemically grafted to the surface of a silicone implant via a silane-coupling reaction and submuscularly embedded in rats, significant decreases in foreign body responses and capsular thickness were observed after 3 mo implantation.
Antibacterial drugs

Surgical site infections associated with breast implants surgery are mostly due to staphylococcal species associated with the skin flora. However, other gram-positive cocci, gram-negative species, and anaerobes may also be involved; several studies have reported that up to 25% of implant-related infections involve gram negative bacteria. The incidence of methicillin resistant staph aureus is increasing, and many infections may be polymicrobial. Fungal and mycobacterial infections are rare but increasing in incidence. Various anti-bacterial drugs targeting these microorganisms have been previously reported for use in breast implant surgery, including cephalixin, cephalotin, povidone iodine, cefazolin or gentamicin (Table), administered either orally, intravenously, or for irrigation of the implant or the surgical site.121,117 The administration of antibacterial drugs is discussed further below.

Miscellaneous drugs

Roxatidine is a histamine H2 receptor antagonist (Table) used in the treatment of gastric disorders, including ulcers, acid reflux and gastritis. It inhibited production of pro-inflammatory cytokines in macrophage and fibroblast culture media stimulated with silicone implant samples, and reduced both serum concentrations of transforming growth factor-β and the number of fibroblasts around the implant in implant-bearing mice administered roxatidine orally.135

Simvastatin (Table) belongs to a class of drugs known as hydroxy-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, better known as statins. As with other statin drugs, simvastatin is primarily used as a cholesterol-lowering agent by catalysing the rate-limiting step of the cholesterol synthesis pathway in liver and other tissues, and thereby reducing cholesterol levels and improving serum lipid profiles. However, simvastatin also exhibits other pleiotropic effects, including anti-inflammatory and anti-oxidative activity.136,135,154 Although previous studies in rats have shown simvastatin able to induce heme oxygenase-1 (HO-1) expression in the periprosthetic capsule surrounding a silicone shell implant (which could explain its antioxidant and anti-inflammatory activity), oral administration (2 mg/kg/d) in rats failed to reduce common markers of inflammation.157 In a later study testing higher oral doses of simvastatin in rats (15 mg/kg/d), radiation-induced capsular fibrosis around silicone implants was significantly reduced compared with a control group.138

Pre-operative intravenous administration of antibiotics

Patients undergoing implant-based breast reconstruction now commonly receive preoperative prophylactic systemic administration of antibiotics targeted at those microorganisms most likely to cause infection, typically a first or second-generation cephalosporin (such as cefazolin) targeted at susceptible staphylococci or vancomycin/gentamicin for patients allergic to penicillins.117,155,156 According to a study by Ballard et al. assessing trends and changes in breast augmentation surgery, administration of preoperative antibiotics increased dramatically between 2011 (3.8%) and 2015 (98.7%).5 In many instances, the intention here is to prevent immediate post-operative wound infection. Generally, a single dose administered immediately prior to surgery is sufficient, although a second dose is often given for prolonged procedures or in the event of significant blood loss. In patients undergoing implant-based breast reconstructions, Townley et al. reported that a single pre-operative dose of intravenous antibiotic (1 g cefazolin or 600 mg clindamycin) was as effective as the same regimen coupled with continued post-operative oral administration of cefazolin (500 mg three times daily until drain removal) in preventing immediate infection.157 The authors were careful to note that the antibiotic regimen used in the study were too short to allow evaluation of CC formation caused by subclinical infection.

Post-operative administration of antibiotics

There is currently no consensus among surgeons around use of post-operative antibiotics for preventing infection following breast implant surgery.157 Some studies have reported significant increases in surgical site infection following policy changes to preclude post-operative administration of antibiotics,158 while others have concluded that no benefit in post-operative antibiotics beyond 24 h.159 The current lack of supporting evidence, coupled with concerns over cost, hypersensitivity reactions and antibiotic resistance, means that continuation of antibiotics after surgery is generally discouraged unless there is a strong clinical rationale.160

Oral drug administration

Oral administration of drugs is the most common route for drug delivery in modern medicine. It is often preferred due to its convenience, non-invasiveness, and patient compliance. Many of the drugs discussed previously are administered orally for the treatment or prevention of CC. Notable examples are the oral tablet formulations of zafirlukast (Accolade) and montelukast (Singulair).148,159 Likewise, many NSAID drugs and simvastatin are routinely administered by the oral route. While the oral route is convenient, various factors limit the use of oral administration for certain drugs, including poor solubility and mucosal permeability, poor stability in the gastrointestinal tract, first-pass metabolism and low bioavailability, and systemic side effects. For this reason, targeted site-specific drug delivery strategies could prove useful, particularly for a localized pathology such as CC. Examples of such strategies are discussed in the following sections.

Modification of implant surface with grafted drug substances

The ‘endogenous hypothesis’ postulates that CC is caused by an exaggerated foreign body response resulting from contamination of the implant surface with the normal flora of the external breast and nipple tissues.108,109,161,162 Although there only limited clinical evidence to support the endogenous hypothesis,161 methods to modify the physical or chemical characteristics of the breast implant surface so as to increase
its biocompatibility/hydrophilicity and reduce protein adsorption have been widely reported.\textsuperscript{153}

Although grafting of various moieties—including zwitter-ionic molecules\textsuperscript{164}—onto the surface of implants has been widely explored, there have been relatively few articles reporting the grafting of pharmacological agents. Zeplin et al. described surface modification of miniature textured silicone implants via preactivation of the silicone using a reactive silane followed by dipping the preactivated implants into a saturated aqueous solution of with halofuginone lactate (a type I collagen synthesis inhibitor that interferes with the TGF-β signaling pathway).\textsuperscript{125} In this manner, the halofuginone is permanently bonded to the silicone surface.

Copper ions are known to have antibacterial properties and various articles have described their use in medical devices.\textsuperscript{165,166} Model silicone elastomer breast implants—having their surface chemistry modified by the grafting of multiple chitosan layers and then immersed in aqueous solutions of copper acetate (containing Cu\textsuperscript{2+} ions)—have been shown in vitro to (i) provide controlled release of copper ions over 8 wk, (ii) reduce initial adherence of Staphylococcus epidermis to the implants (the first step in biofilm formation), and (iii) have a direct antibacterial effect.\textsuperscript{167} S. epidermis is widely implicated in post-operative infections and CC.\textsuperscript{75,76,82,84,99} While this strategy is interesting and warrants further research, it would be complex, costly and impractical to implement from a commercial manufacturing perspective given the need to chemically modify the silicone elastomer surface and incorporate the copper ions.

Recognising that the hydrophobic surface of silicone elastomer breast implants encourages absorption of proteins and bacterial adhesion, Joo et al. described a method to introduce surface hydrophilicity by chemical modification using a crosslinked hydrogel containing hyaluronic acid and gelatin.\textsuperscript{168} As with any surface-grafting strategy, introduction of such a method into an industrial manufacturing process would be complex and lead to increased costs, at least compared to current manufacturing methods; the surface modification step would need to be completed after manufacture of the breast implant shell, and would involve exposing the shell to oxygen plasma treatment, reaction of the resulting silanol groups with a silane, and then final conjugation of the hydrogel system. Nonetheless, the data indicate that the method is useful in improving hydrophilicity and biocompatibility, effective in reducing bacterial adhesion following implantation in mice, but only moderately effective at reducing capsule thickness.

Kang et al. reported a method for modifying the surface of silicone elastomers by immersing the implant for 1 min in a solution (containing the monomer 2-methacryloxyethyl phosphorylcholine, a crosslinking agent and a free-radical initiator), followed by UV (15 min) or heat-induced (16 h, 70°C) polymerisation in situ.\textsuperscript{164} A significantly thicker and more effective MPC-grafted surface was achieved using the heat-induced method, although both methods resulted in significant increases in surface hydrophilicity. Following 24-wk implantation in pigs, the heat-induced implants also showed significant reduction in capsular thickness and inflammatory markers in surrounding tissues compared to non-grafted implants. Moving forward, issues that will need addressed include removing residual peroxides, and long-term mechanical integrity and safety of the grafted polymer coating.

**Irrigation of implant/peri-implant tissue prior to implantation**

Irrigation of the breast implant pocket, and/or the implants themselves, with various sterile or drug solutions is both widely reported and practised as part of efforts to reduce the rate of CC and for mitigating the risk of BIA-ALCL.\textsuperscript{117,164,118,169-172} Commonly administered solutions include sterile saline,\textsuperscript{115,173} a triple antibiotic solution (such as bacitracin, neomycin and polymyxin b),\textsuperscript{115} and triamcinolone acetonide (Table).\textsuperscript{139} The results to date have been mixed. Results of several studies support the use of a triple antibiotic solution,\textsuperscript{117} while others caution against its use pending more robust evidence of efficacy.\textsuperscript{174}

In other circumstances, such as during a mastectomy, surgeons may use compounds like methylene blue to detect sentinel lymph nodes for the diagnosis of early stages of BIA-ALCL. However, studies show that the use of this compound before the placement of an implant increased the risk of CC by 75%, regardless of the concentration used.\textsuperscript{175}

Treatment of the implantation site with a local application of drugs has proven to also impact the occurrence of CC. For example, irrigating the area with antiseptics such as Povidone-iodine has proven to reduce the occurrence of grade III/IV CC, with an increased effect when antibiotics such as cefuroxime and gentamicin are also administered intravenously.\textsuperscript{121,176} A topical application of antibiotics only (e.g., cephalotin, cefazolin, gentamicin and/or bacitracin) halved the risks of infection and seroma but did not significantly modify the risks of CC occurrence.\textsuperscript{169,177} These results show that irrigating the pocket with antibiotics and antiseptics is important to reduce the risks of CC but not mandatory.

In a 55-patient prospective cohort study limited to just two surgeons, a comparison of pocket/implant irrigation with triple antibiotic solution versus saline showed no significant difference in the incidence or severity of CC.\textsuperscript{115}

In a prospective cohort study involving 335 patients and a single surgeon, a triple antibiotic irrigation solution (comprising bacitracin + gentamicin + cephalaxin) was associated with a relatively low incidence of CC, compared to previously reported data.\textsuperscript{117} The authors acknowledged that the lack of a prospective, double-blind, randomized trial design was a weakness of the study, and highlighted the potential of future implants containing antibiotics impregnated within their shell for optimal control of the bacteria.

Nguyen et al. reported no significant differences in surgical site infection with post-mastectomy pocket irrigation comparing triple antibiotic solution to 0.05% chlorhexidine gluconate in 85 patients undergoing bilateral immediate breast reconstruction.\textsuperscript{123}

Ngaage et al. assessed in vitro the ability of different antimicrobial irrigation solutions (10% povidone-iodine, Clorox decid, Prontoan, triple-antibiotic solution, and normal saline) to reduce bacterial adherence/load of meticillin-resistant *Staphylococcus aureus* and *S epidermidis* with silicone implant discs.\textsuperscript{178} Povidone-iodine was the most efficacious of the irrigation solutions.
Jeon et al. described spray coating of model silicone implants with low and high dose acetone solutions of the synthetic corticosteroid drug triamcinolone acetonide as part of efforts to develop implants providing local sustained drug release for the prevention of fibrosis. In vitro drug release testing was performed into 5 mL pH 7.4 PBS (shaking incubator, 37°C, 125 rpm), with periodic sampling and complete replacement of the release medium. Since acetone is known to permeate into and swell silicone elastomers, it is assumed that the triamcinolone acetonide penetrated beneath the surface of the implants, helping to sustain release over ~30 d; drug release beyond this time was negligible.

Baker et al., demonstrated that model silicone breast implants pretreated with a solution of doxycycline (a tetracycline-type antibiotic drug) in ethanol significantly reduced bacterial colonization of the implants with methicillin-resistant S. aureus and Pseudomonas aeruginosa (both administered into the implant pocket before closure) following subcutaneous implantation in mice, compared to implants treated only with ethanol, doxycycline administered intraperitoneally, and irrigation of the pocket with a triple-antibacterial wash. The implants were dipped into the doxycycline solution at a rate of 2 mm/s. However, the duration of immersion and the final amount of doxycycline in the implants were not reported. Instead, doxycycline was confirmed present on the surface of the implants by infrared spectroscopy, mass increase of the implants was noted, and doxycycline concentrations were measured via a zone of inhibition assay method. In line with expectations for applying drugs to implants via simple coating methods, the doxycycline appears to be exhausted from the implants with ~48 h, such that release is not sustained for longer periods of time.

Silicone implants inserted in rats showed significantly decreased capsule thickness and number of inflammatory cells after 12 wk compared to controls when the implant pocket was inoculated with rifampin (an antibacterial drug) and S. epidermidis prior to implant insertion. In an in vitro study evaluating the activity of various marketed antimicrobial ointment/cream products against biofilm formation by S. epidermidis following their application to the surface of punch biopsies taken from smooth and textured silicone breast implants, Van Heerden et al. reported that many of the products showed a significant antibacterial and anti-biofilm effects, with Fucidin (fusidic acid), Terramycin (oxytetracycline), and Chloramex (chloramphenicol) ointments performing particularly well. This localised strategy is similar to that of Betadine (povidone-iodine), which was previously restricted by the FDA for use with breast implants due to concerns that it could degrade the silicone elastomer shell. These localised approaches may offer a simple alternative to systemic administration of antibiotics or anti-septic washing of the implant/pocket. It is likely that the product type (creams are emulsion-based formulation having approximately equal proportions of oil and water, while ointments have much greater oil concentrations), the physicochemical properties of the active agent (e.g., molecular volume, lipophilicity, aqueous solubility, etc.) and the rheological characteristics of the product would effect retention of the product on the implant and the extent of absorption of the antimicrobial substance into the implant. It should also be noted that products having high oil content can be detrimental to silicone elastomers.

Most of the pharmacological strategies directed toward reducing or preventing CC involve use of low molecular weight drug molecules, typically less than 1000 Da (Table). However, many of the recent advances in drug therapies have been driven by developments in large molecular weight bio-molecules, such as proteins, nucleic acids (e.g., DNA and RNA), and carbohydrates. Lee et al. have reported that botulinum neurotoxin A—a neurotoxic protein produced by the bacterium Clostridium botulinum—significantly reduces capsular thickness around silicone devices subcutaneously implanted in mice 30 d when instilled into the implant pocket. Based on data obtained from supporting in vitro studies to help elucidate the mechanism of action, the authors concluded that the botulinum neurotoxin interrupts the differentiation of fibroblasts to myofibroblasts, most likely by blocking the TGF-β 1 signaling.

Incorporation of drugs into the implant shell

Despite the ease and prevalence of incorporating solid crystalline drugs into other types of silicone elastomer drug delivery systems during the manufacturing process (e.g., subdermal implants, vaginal rings, intrauterine devices) and the potential clinical benefits in reducing the incidence of CC, there have been no reports describing this strategy as part of the manufacture of drug-releasing breast implants. This is most likely due to very significant challenges associated with integrating drug handling capacity into current breast implant manufacturing protocols, the impact of drug incorporation on the performance of the breast implants, and additional regulatory hurdles. However, some researchers have considered an alternative strategy, involving the incorporation of drug substances into the silicone elastomer shell (and presumably also the filler material) via a molecular permeation method. Although details of the ‘impregnation’ method are lacking in the article, Darrouiche et al. describe incorporation of the antibacterial drugs minocycline and rifampin into the silicone shell of custom miniature saline-filled implants for testing in rabbits. Since silicone elastomers are relatively permeable to low molecular weight hydrophobic drug molecules, placement of the preformed implants into a concentrated solution containing the two drugs would certainly permit some degree of drug ingress. However, an obvious disadvantage of this approach is that only relatively small quantities of the drugs could be incorporated, since these hydrophobic drugs would have relatively low solubilities in both the silicone elastomer shell and the saline filler. With relatively low drug loadings, duration of release might be expected to be limited to just a few days post implantation, although zone of inhibition studies with implants removed from rabbits showed similar antibacterial activity out to 4 wk.

Nonetheless, it may be feasible to dissolve one or more hydrophobic drugs in one or both parts of, for example, a xylene-based silicone elastomer dispersion formulation, and then dipcoat and cure the shell layer in the usual fashion. Depending upon their solubility characteristics in the cured silicone elastomer, it is possible that the drug(s) would precipitate to form small particle size crystals in the silicone layer.
after evaporation of the solvent. The presence of these solid drug crystals would provide much higher drug loadings and offer sustained release over prolonged time periods; different drugs could even be incorporated into different shell layers, providing additional control over drug release kinetics. However, a disadvantage with this strategy is that the presence of drug(s) in the shell layers would cause the implant to be opaque white in appearance rather than translucent.

**Incorporation of drugs into the filler**

To date, only one study has reported the incorporation of drugs directly into the gel component of breast implants. Solutions of Keflin (active agent cefalotin, Table) or Garamycin (active agent gentamicin, Table) were instilled into the gel of silicone breast implants and their release over time was shown to be effective against the development of fibrous capsules around the implants. Unfortunately, no further studies have been reported. Instead the surgeons in charge of the experiment selected to apply a Betadine irrigation around the breast implant during surgery.

**Conclusions**

Here, we have highlighted the various pharmacological approaches that are already being used before, during, and after surgery to prevent/treat CC, and various new experimental pharmacological strategies that have been reported in the literature. It is clear that existing pharmacological approaches are not widespread among surgeons and that robust supporting evidence for their efficacy is still lacking. Nonetheless, given the extent of infections and clinical complications associated with breast implants, the development of newer and more effective strategies is both timely and necessary. The last 50 y have witnessed an explosion of knowledge around the incorporation and sustained/controlled release of drugs from polymeric materials, and silicone elastomer drug delivery devices have often been at the forefront of these developments, with numerous products having reached market. Many of the newer pharmacological strategies discussed here for preventing CC associated with breast implants leverage established knowledge derived from the drug delivery field. This cross-fertilisation of concepts and ideas is to be encouraged as we seek to develop the next generation of breast implants.

**Author Contributions**

EG, LC and RKM conceived the topic of the review article and EG, LC, BD, JML, EH and RKM contributed significantly to writing different sections of the manuscript. EG, LC, BD, JML, EH and RKM contributed to reviewing and editing the manuscript. All authors approved the final version of the manuscript for submission.

**Declaration of Interest**

None to declare.

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